The Effect of a Source Change for an Active Pharmaceutical Ingredient (API) or Excipient on the Finished Drug Product

by

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Author’s Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The global cost of health care is increasing year after year, and one of the ways governments and health care providers are looking to reduce cost is by reducing the cost of drug products. The generic industry is under tremendous pressure to remain competitive in the market place by reducing the cost of their product, with the main cost factor being the active pharmaceutical ingredient and some of the excipients used in the manufacture of the drug product. These companies are expected to follow the required guidelines set out by the international regulatory authorities and more specifically of the countries they intent to market their product in if they are planning to change the source of the material. These regulatory guidelines are general in nature with a focus on safety and efficacy and the evaluation of an alternate source of material by pharmaceutical companies varies greatly from company to company. The evaluation is conducted mainly on the basis of chemical and physical data from the Certificate of Analysis comparing the current and alternate source to determine equivalency. Differences in process and critical processing parameters of the material can have significant impact on the behavior of the chemical, which may not be detectable through evaluation of the Certificates of Analysis. It is, therefore, critical to study properties that are not captured on the Certificate of Analysis, such as polymorphism, melting point, solubility, particle shape, packing tendencies among other aspects of the material that are important for the performance of the material in the drug product formulation and manufacturing process. The differences in these properties can have significant impact on the unit operations during the manufacturing process as well as the critical quality attributes and the stability of the drug product. The evaluation is conducted by utilizing various tools of analytical and process testing to determine the physical performance, physicochemical evaluation, chemical evaluation and functional performance evaluation for the active

pharmaceutical ingredient and excipient. The evaluation of the Certificate of Analysis will also need to be more in depth, and go beyond the alternate source meeting the specifications as there can be significant differences with the results obtained even though they meet specification. It is important to identify these differences earlier in the evaluation stage and to assess the impact, if any, on the manufacturing process and the drug product prior to introducing the change.

This study was conducted with active pharmaceutical ingredients selected based on the processing unit operations, such as direct compression process (metformin HCl), dry compaction (gabapentin), and hot-melt process (fenofibrate). The selection of the excipients was based on their functional properties, such as binders (copovidone NF/EP) and super disintegrant (croscarmellose Sodium NF/EP), allowing for evaluation with respect to differences in functionality if any, from the different sources. Additionally, the copovidone NF/EP is the binder in the gabapentin USP tablet formulation while the croscarmellose Sodium NF/EP is the super disintegrant in the fenofibrate EP/BP tablet formulation.

An example of this challenge is that the evaluation of Certificate of Analysis for the materials supplied from two companies and two sources revealed differences in tests required for the two materials and a significant difference in some of the results obtained; however, both materials met their respective Certificate of Analysis specifications. Several tests beyond the Certificate of Analysis were performed and significant differences were also observed in many of these as well. The two sources were evaluated with respect to the compression process and the alternate source of material did show significant challenges during the tablet compression process and did not meet some of the in-process critical quality attributes test. The in-vitro performance for both sources were comparable, however, the recommendation will be not to proceed with the alternate source. There were many differences between the sources of all the

materials evaluated including differences in particle size, morphology, moisture, manufacturing process and residual solvents among others. The impact on the manufacturing unit operation varies from no impact for the fenofibrate EP/BP materials, to not meeting the critical quality attributes for metformin HCl tablets with the new source of the active pharmaceutical ingredients.

This study indicates the importance of a systematic evaluation of a material from an alternate source with respect to the performance of the manufacturing process, drug product, and their critical quality attributes; understanding the impact of these changes to the material and having the ability to correlate these to potential issues with the manufacturing process and drug product critical quality attributes prior to introducing an alternate source of material is critical.

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Dedication

To my wife Rehana, my two daughters Amila and Safiyah, my mother Mrs. Doreen Chan and my father Mr. Mohamed Chan (deceased) for their endless love and encouragement.

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List of Abbreviations

ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
AV	Acceptable Value
BCS	Biopharmaceutical Classification
BET	Brunauer–Emmett–Teller
BP	British Pharmacopeia
BRT	Below Reporting Threshold
cc	Cubic centimeter
CW	Clockwise
CCW	Counter clockwise
cGMP	current Good Manufacturing Practice
C of A	Certificate of Analysis
CQA	Critical Quality Attribute
CV	Coefficient of Variation
DoE	Design of Experiments
DSC	Differential Scanning Calorimetry
EMA	European Medicines Agency
EP	European Pharmacopeia
FDA	Food and Drug Administration
FT-IR	Fourier Transform-Infrared
g	Gram
HC	Health Canada
HPLC	High Pressure Liquid Chromatography
ICH	International Conference of Harmonization
IP	In Process

IR	Immediate Release
Kp	Kilopound
kN	Kilo Newton
LOD	Loss on drying
mg	Milligram
mL	Milliliter
mm	Millimeter
ND	None Detected
NF	National Formulary
NMT	Not More Than
NLT	Not Less Than
ppm	Parts Per Million
QbD	Quality by Design
RC	Related Compounds
SEM	Scanning Electron Microscopy
Spl	Samples
STDEV	Standard Deviation
T_g	Transition glass temperature
TGA	Therapeutic Goods Administration
TPD	Therapeutic Products Directorate
µm	Micrometer
USP	United States Pharmacopeia
WHO	World Health Organization
°C	Degree Celsius

Chapter – 1: Introduction

1.1 - Market Overview

The global pharmaceutical industry is worth close to $1 trillion dollars today, with the generic industry representing approximately one third, or $350 billion. Over the next five years the industry is expected to grow by an additional $200 - $250 billion with most of the growth coming from the generic industry. In addition the value of the drug products with their patent expiring over the next several years is over $100 billion[1]. This, combined with the double digit growth in the industry itself, presents significant opportunity for the generic industry over the next several years. There are other major drivers for the generics industry, these include the efforts of government and health care providers around the globe to substitute brand product with generic product, continued price pressures, too few products expiring for too many generic companies, and emerging possibilities for bio-generics[2].

There is significant pressure from governments and health care providers globally to try to reduce the mounting cost of health care by reducing the cost of generic drugs in addition to generic substitution of the branded product. The Ontario government went as far as to introduce a law to cap the price government will pay for a generic equivalent of a drug at 50% of the brand price if there are two competitors on the market. As one of the largest customers of the generic industry in Canada, this puts significant pressure on the industry to be cost competitive. In many drugs the Active Pharmaceutical Ingredients (API) is the largest contributor to the cost per dosage, representing between 50 – 90 % of that cost. It is therefore no surprise that one of the main drivers to reducing the cost per dosage is to find less costly sources of the API. Different companies take different approaches, or a combination of approaches, to achieve a reduction in the cost of the API. Many of the larger pharmaceutical companies such as Teva, Mylan, and

Sandoz are vertically integrated and therefore have the ability to control their cost internally. A vertically integrated company is one that has developed the capability to manufacture most of its API required for drug product manufacturing internally. Some companies look to their sources of the API to reduce the cost, while others look at a combination of the two approaches. Regardless of the approach used, one element that is common in all cases is the need to reduce the cost of the API over the life cycle of the product. There are significant advantages for a generic company to be the first on the market at patent expiry, and companies are usually aggressively pursuing the development and approval of their products such that they can be the first to market. This also means that they will likely develop the drug product using a single source of API and will pay for the opportunity to be the first to market. However, it typically takes less than a year for a product to have 80% market penetration and to reach marginal cost after patent expiry[3] due to generic competition. The need for cheaper API means that companies, regardless of if they are vertically integrated or not, look to their process to eliminate waste and to reduce cost as much as possible soon after they launch the product to the market for them to remain competitive in the market place. One way this is achieved is to change the manufacturing process and/or the intermediates used in the manufacture of the API. This is usually achieved by going to another (cheaper) source, which today is mostly from South Asia; namely India and China.

There are several guidelines that specify the various requirements for an API manufacturer to comply with; however, the guideline to change a source or process is vague in terms of the physiochemical properties of the API. Materials may vary as to the legal definition of an API depending on the different jurisdictions across the world. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it

should be manufactured according to the guidelines laid by the appropriate regulatory authorities[4].

1.2 - Regulatory Guidelines

The United States Pharmacopeia initiated a program referred to as the "USP Drug Substance Verification Program" or "Program" to several public health industries[5]. The participation of the API manufacturers in this program is voluntary, but is open to all manufacturing units making APIs for use in pharmaceutical products[5]. The program covers drug substances used in the manufacture of pharmaceutical products and it includes:

- Evaluation of participants' quality systems through an audit of each manufacturing site for compliance with current Good Manufacturing Practices (e.g., ICH Q7 current *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*)[6],
- Review of the manufacturing and quality control documents for each drug substance submitted for verification, including review of the characterization, stability, and release data for compliance. The review also includes labelling of the product, Certificate of Analysis (C of A) claims as well as compliance with USP-NF or any other monographs as applicable,
- Laboratory testing for drug substance samples from selected lots for compliance with labeling and/or C of A claims and program requirements,
- The Certification Mark is only granted upon full adherence and confirmation that all of the Program requirements are met,
- Post-verification surveillance testing of drug substances bearing the Certification Mark,
- Post-verification audits,
- Periodic re-validation of the manufacturing process,

- Reporting by participants of any major changes to the manufacturing or testing of drug substances bearing the Certification Mark.

The use of the distinctive Certification Mark is granted for API manufacturers that successfully meet the Program requirements. This mark indicates that verification of the API quality and the adequacy of the participant's quality systems and controls by a trusted and established authority are completed and it will provide the assurance that:

- The participant has established and is following a quality system that helps to ensure that the drug substance evaluated meets it's labeling or C of A claim for identification, strength, purity, and quality, and is consistent in quality from batch to batch,
- The participant follows accepted manufacturing practices in producing the subject drug substance,
- The tested drug substance samples meet requirements for acceptable limits of contamination and impurities.

The extension of current Good Manufacturing Practices (cGMP) to API manufacturing has increasingly been recognized as a necessary element in ensuring the overall quality and consistency of marketed drug products[6, 7]. This requirement resulted in the formation of a working group in 1997 to develop cGMP guidance for API manufacturing. This group (and their resulting guidance document) is referred to as the International Conference on Harmonization (ICH). This document also includes the Canadian requirements, which were finalized and signed by the ICH Steering Committee in November, 2000. Health Canada (HC), like its other counterparts around the world is charged with implementing and enforcing regulation governing drug products adopted by the ICH Q7 guidance initially on a voluntary basis. It (HC) has now implemented internationally aligned regulatory cGMP requirements for APIs destined for human

use[8]. To encourage the use of alternative sources for the API in the manufacture of Drug Products, the World Health Organization (WHO) developed guidelines for the submission of applications for prequalification of the Multi-source (Generic) Finished Pharmaceutical Products (FPPs) for the treatment of HIV/AIDS, Malaria and Tuberculosis. The guidelines were developed based on WHO document WHO/DMP/RGS/98.5 "Marketing Authorization of Pharmaceutical Products with special Reference to Multisource (Generic) Products: a Manual for a Drug Regulatory Authority (DRA) [9]" and on the International Conference on Harmonization (ICH) guideline "The Common Technical Document for the Registration of Pharmaceuticals for Human Use: M4Q: Quality; Module 2: Quality Overall Summary (QOS); Module 3: Quality[7].

The use of alternative source of APIs to manufacture a drug product at a lower cost is welcome by the generic drug manufacturing organizations as a way to keep pace with increasing demand to lower the cost of treatment by various Governments and health care providers around the world. In an effort to make the process more effective and efficient, and to ensure that the end product using an alternate source of API is of the same Quality, Efficacy and Safety, there is now a guidance document issued by the Food and Drug Administration (FDA). This guidance is intended to describe the Office of Generic Drugs' (OGD) policy on the use of alternative sources of the API in an unapproved abbreviated new drug application (ANDA). This guidance describes the circumstances under which an alternative source can be used prior to the approval of an abbreviated new drug application. This guidance is intended to decrease the regulatory burden on industry and the regulatory body, and to provide a more consistent approach to pre- and post-approval changes in API sources[10].

1.3 - Product Development

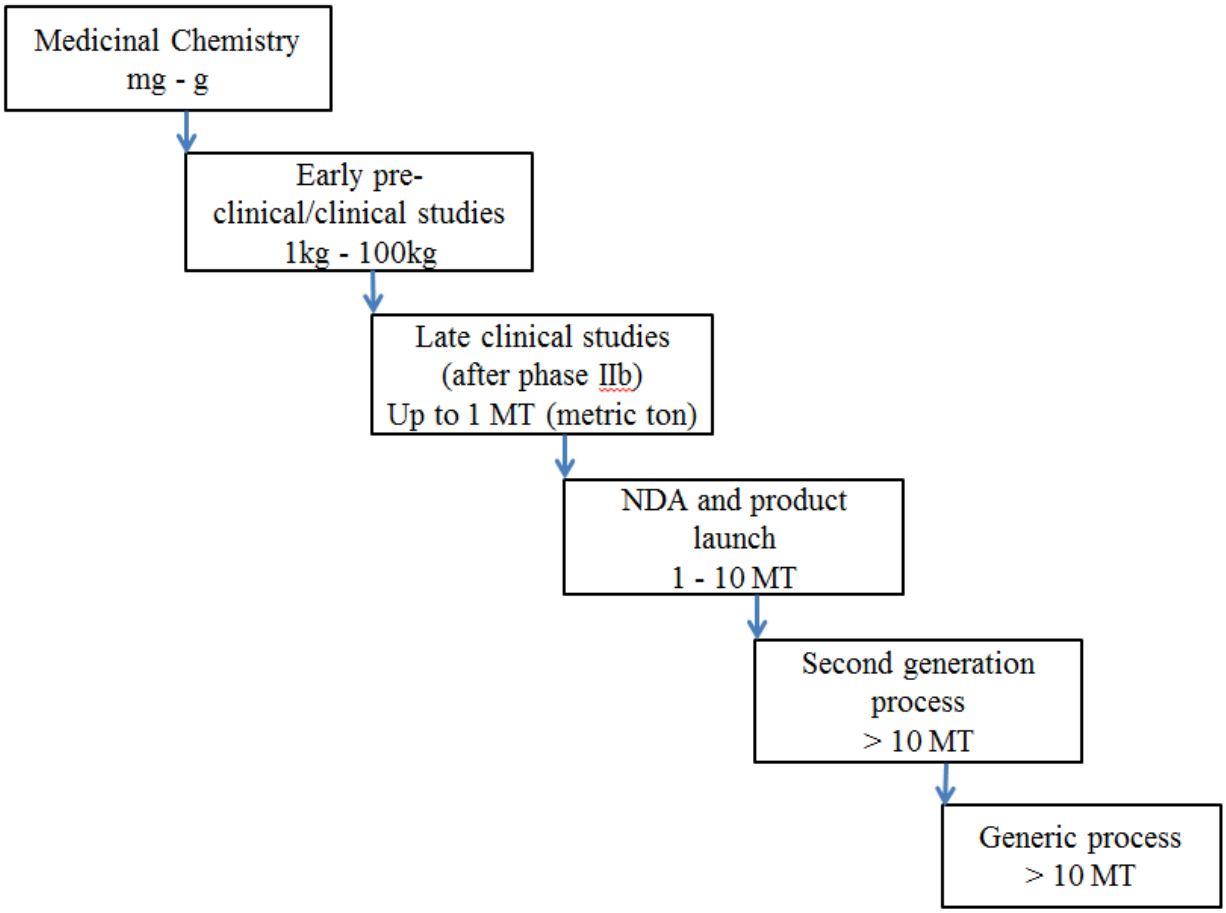
Drug substances, also known as Active Pharmaceutical Ingredients (APIs), generally exist as crystalline powders, amorphous powders or as viscous liquids. Historically in pharmacy practice drug substances were dispensed as such in powder or mixtures of powders to the patient. This practice is virtually unknown in the pharmacy world today with the advent of modern technology to present drug substances to patients in the form of drug products. These drug products can exist in several dosage forms such as oral, parenteral, topical, etc. There are significant advantages to presenting a drug substance in specific dosage forms; these include patient compliance, taste masking, varying release profiles, different route of administrations, etc. While the advantages are numerous, the actual performance of the drugs in clinical practice is known to be greatly affected by the method of presentation of the drug to the patient. Several factors that impact the most appropriate from of presentation include[11]:

- the portal of drug entry,
- the physical form of the drug product,
- the design and formulation of the product,
- the method of manufacture of the drug product,
- various physicochemical properties of the API and excipients used in the manufacture of the drug product,
- physicochemical properties of the drug product,
- control and maintenance of the location of the drug product at the absorption site(s),
- control of the release rate of the drug substance from the drug product.

New drug molecules are marketed in various dosage forms suitable for patients to ingest with ease. The most common dosage forms developed for use are tablets, capsules, oral liquid or oral suspensions, while some of them are also marketed as injections. The intravenous route of administration is generally required during the toxicity, metabolic, bioavailability and clinical studies to provide precise drug and dose disposition. The development of a drug product starts and ends with the API. The major challenge for API development is the design of the appropriate physiochemical properties with regards to the route of administration. The process of developing an API is a long and challenging one and starts long before the drug product is first tested in humans. The goal for the First in Human milestone of a drug product is to "deliver a safe, scalable, reproducible and robust protocol for API manufacturing" [12, 13].

The development of the API over the life cycle of the drug product development will continue to evolve[14] and at the end of the drug product development cycle the physicochemical properties are expected to be fully characterized. However, at this stage neither the API nor the drug product is commercially viable and both require scale up to meet the commercial demand. As the development of an API moves from pilot scale to large scale manufacturing it becomes more challenging to maintain the physicochemical properties[15]. There are several factors that can contribute to this including changes in the batch size and/or equipment during scale up resulting in changes to the processing parameters. There could also be changes to the synthetic route to improve the purity and yield of the batch as the drug product development move through the different stages. The impacts of some of these changes are discussed in detail in section 1.4 of this chapter. Once the API is available it is then required to be formulated into a desire dosage form(s) for use by patients. There are several challenges associated with the development of a drug product, including stability, compatibility, and the manufacturing process.

The innovator company usually has several patents covering both API and the resulting drug product, and is very protective of its Intellectual Property. The patents not only cover the drug substances and drug products but in most cases also extend to the manufacturing process, intermediate material, formulations, etc. The Innovator and Generic companies usually develop a drug product using API from a single source which can either be supplied from internal synthesis, or from an external source. The material available for development is usually from the small scale manufacturing plant of the API source. The process characterization and Critical Quality Attributes (CQAs) of the API and the drug product are then established as part of the development process. At the time of submission for approval the brand companies will have carried out API and process characterization of their scale up material, although not at their second generation scale, which is equivalent to the generic scale. As can be seen below (Scheme 1.1), there are several stages in the development of an API during the innovators development process; as the drug product moves through different phases of its development so does the API. As a result the physical and chemical characteristics of the API are evolving at the same time as the formulation and process development of the drug product is evolving. This provides significant advantages to the innovator as the CQAs of the API are well known and characterized at the time of launch. As a result of the time and money invested, the brand company does not disclose any of the CQAs or any unique characteristics of its API so as to maintain their competitive advantage. The generic industry operates on a significantly different model, both in terms of cost and time. The cost of developing a generic equivalent of an innovator product is approximately $2 - $3 Million, which is less than 1% of the estimated $868 million to develop a new drug product[3].



Scheme 1.1: The API – life cycle, illustrating the approximate volume of material at the different stages of the API and drug product development process[14]

The search for a generic equivalent source of API starts years before a brand patent is due to expire and the length of time the generic product is kept on the market is dependent on the number of competitors and if the generic company can remain competitive. In most cases that competitive advantage is dependent on a generic company finding a much cheaper source of an API, or if vertically integrated, a cheaper way to make it. There are over 340 experienced API manufactures of which approximately half are vertically integrated into a finished dose[2]. As a result there are a significant number of source changes and process changes for API manufacturers as both API manufacturers and drug product manufacturers look at ways to reduce cost.

The API is the main ingredient of any drug product; however, most APIs lack the physical and chemical properties to form a drug product on their own. As a result many pharmaceutical ingredients are available or are being developed to facilitate the product and process development to transform the drug substance into the desired finished drug product. Excipients play a critical role in the performance of a drug product, roles that include (but are not limited to) enhancing solubility, bioavailability, stability, maintaining pH, release profile etc.[16] , and any change to their physical and/or chemical properties can have as a significant impact on the product and/or process as would a change in the API. While the API cost of any formulation is the most significant contribution to product cost, another substantial contribution can arise from the excipients used in the formulation of the drug product. As drug product manufactures look beyond API to reduce cost, excipients are starting to gain focus. While traditionally excipients have not been a major driver to reduce cost, excipients are becoming a more common approach to cost reduction today. There are two approaches used; one is to maximize the utilization of excipients that are already in use as this will give the manufacturing companies buying power and therefore the ability to reduce price and the other is to procure excipients from new and cheaper sources[17 - 20]. As stated above, one of the main drivers to reduce the cost of a generic product is to source cheaper APIs from sources such as those found in India and China. The lower cost of the API is not only associated with lower labor costs, but also to changes in the manufacturing process that can contribute significantly to the lower cost. In addition to cost there are other factors that may influence a company to change the current source of their material. These include

- Having multiple sources,
- Intellectual Properties,

- Quality of current supplier.

There are several guidelines that deal with the change of sources, FDA, EMA, TGA, TPD, and ICH among others. The primary criteria of all of these guidelines are the assumption that if the product meets the monograph then it can be considered like for like and therefore can be substituted. The regulatory requirements also vary greatly from a submission of comparable C of A, to the requirement to have six months of stability data on drug product manufacture with the new source of API. The change in source or process for an excipient is even less stringent and does not require any form of stability or notification to the regulatory bodies. Again the assumption is that if all of the C of A specifications are met then the API and excipient are assumed to be equivalent. In order to assess the impact of any change in the manufacturing process to the resulting material it is first important to understand the process by which the material is manufactured. There are two types of material, crystalline and amorphous, and the differences in the manufacturing process and materials are discussed further in the next section.

1.4 - Active Pharmaceutical Ingredients

1.4.1 - Crystalline Material

The brand and generic industry can both point to numerous instances where a change in API or excipient source or process has had a negative impact on their drug product, although the opposite is also true[21 - 23]. The impact can vary significantly in how it propagates itself and can be observed as early as during the powder dispensing process, in-vitro testing, or worse during the long term stability studies of the drug product. One of the main reasons for recall of drug product from the market is due to failures on stability. Most stability programs are initiated due to changes made to the drug product, including changes made to the manufacturing process, specifications, API or excipient sources, or significant changes made to the manufacturing

process of the API or excipient. The starting material for the API is also an important consideration as this can also go through changes to process or source affecting the physical and chemical properties of the API [24]. New drug molecules are more potent today and with complex physical properties changes are much more difficult to characterize.

Pharmaceutical materials exist mainly in two forms, either as crystalline or as amorphous particles. Crystalline material can exist in three forms; polymorphs, solvates, and hydrates and co-crystals. The crystalline material has a more definite shape, while amorphous material is more random. Amorphous material also differs from crystalline material in that they do not have precise melting points. Some material can exist in more than one crystalline form (different crystal structure) although they are chemically identical[25, 26]. These different structures are referred to as polymorphs and can result from differences in temperature, pressure, moisture, salts and/or solvent used in the synthetic process. The different polymorphs can have significant impact on the physico – chemical properties as well as the stability of the API and subsequent drug product. Polymorphs can differ significantly in crystal properties that include solubility, dissolution, melting point, density, hardness and stability. From a clinical perspective these differences can potentially lead to a difference in the bioavailability of the drug and therefore can have an impact on the safety and efficacy of the drug product [13, 25, 26]. As an example phenobarbital, primarily used as a treatment for seizures is known to have 11 different polymorphs, each with a different melting point ranging from 112°C to 176°C[26.] They can each exhibit different physicochemical properties at given conditions, with Form A reported being the stable form and is present in the drug product[26, 27]. However, over time the unstable polymorphs, referred to as metastable polymorphs, will convert to the stable form. The amorphous and metastable polymorphs are usually more soluble than the stable polymorphs. This is important

in the pharmaceutical industry as polymorphisms have been the source of numerous litigations and patents. It is also important to understand the crystalline form that you are working with to ensure that conversion from a metastable polymorph to the stable polymorph does not occur over time in your manufacturing process, storage or during drug product stability. There are several challenges associated with inadequate characterization of the crystal properties of an API. These include unexplained challenges during the manufacturing process, precipitation in liquid formulations, poor stability, and poor in vivo and in vitro performance[13]. There are several methods used to evaluate the physical and chemical properties of an API including dissolution, X-Ray Diffraction, Infrared Analysis, Thermal Analysis, Hot – Stage Microscopy and Scanning Electron Microscopy[13, 28]. There is no one method that is superior or more reliable in identifying the crystalline form of a material and it advisable to use a combination of methods during evaluation. Typically X-Ray diffraction is used in the pharmaceutical industry to identify if different crystalline forms exist within a sample of material or between two different samples. This is a critical test during the evaluation of a different source of material as the material can be chemically identical; however, they can be different polymorphs.

There are several properties that can impact the performance of the drug substance, drug product or the manufacturing process. These properties, however, rarely have an impact based on a single factor. What are obvious from the physical and chemical characteristics described are the interdependencies of these properties with each other. As a result a change to one of these characteristics can impact one or several other properties; these can be either positive or negative[25]. While there is no requirement to test for all of these physical properties, it is important to assess which is critical and which is not so that an evaluation can be done prior to the introduction of an alternate API or excipient.

The primary method of producing APIs is solvent based crystallization and recrystallization; however, new methods are being developed with the goal of identifying all possible solid states of a molecule. These include: laser induced crystallization, capillary crystallization, sonocrystallization, non-solvent based recrystallization and recrystallization through solid state transitions and transformation of polymorphs[25]. There are several factors that can impact the properties of an API during the API manufacturing process. The impact can vary significantly and can impact purity, polymorphism, particle size and the physical properties of the crystals. The particle size and crystal properties are more likely to impact the manufacturing process and performance of the drug product while the purity and polymorphism are more likely to impact the stability and physicochemical properties of the API and drug product[25, 26].

1.4.1.1 – Impact of crystallization process and parameters on the material

The crystallization process is a long and complex one that involves many steps as described in figure 1.1[29]; however, the three main process steps that control the properties of the crystal are supersaturation, nucleation and crystal growth[25, 26]. There are several factors that can effect nucleation and crystal growth such as concentration, temperature, solvent, agitation, interfaces, surfaces, impurities etc[25]. Changes to the crystallization method can influence the shape and size of the resulting crystals; a few examples are described below:

- Degree of supersaturation: Greater saturation produces needle shaped crystals due to more growth in one direction. This is due to significant solute – solvent interaction resulting in the rate of nuclei formation being greater than crystal growth which causes more growth in one direction. Lower saturation produces plate-like crystals due to insignificant solute – solvent interaction[25, 26],

- Nature of crystalizing solvent: A solvent having higher affinity for the crystallizing solute results in symmetric crystals as nuclei formation is delayed. Interactions of certain functional groups between solute and solvent can impact the crystal growth at the crystal surface and to produce well shaped crystals requires a high ratio of crystalizing solute and solvent. The opposite is true when the solvent has less affinity for the crystallizing solute, where crystal growth is rapid as nuclei is formed immediately and produces larger crystals. Also, it requires low ratio of crystalizing solute and solvent to produce well shaped crystals[25, 26],
- Temperature of crystallizing solvent: At high temperatures nuclei formation is delayed resulting in fine symmetric crystals. At low temperature irregular shaped crystals are produced due to rapid nucleation resulting from spontaneous decrease in saturation level. Temperature also has other secondary but inter related impacts such as on solubility and therefore on supersaturation[25, 26],
- Agitation/mixing: At high agitation the crystallizing solid is distributed more evenly on the nuclei and produces elongated crystals with small particle size. At low or zero agitation the crystallizing solid is deposited on selected crystal face resulting in large platy crystals. Stirring can also impact the chiral symmetry of the molecule[25, 26, 29],
- Rate of cooling: Symmetric crystals are produced from slow cooling due to a decrease in the rate of crystal growth while rapid cooling results in asymmetric thin plate – like crystals due to the rapid crystal growth [25, 26],
- Crystallization equipment: There are generally three type of reactors used in the crystallization process, glass line reactor, alloy reactor or glass lined metal reactor[30 - 32]. There are also three types of agitators used:

1) Three blade retreat curve agitator with a glass line reactor where the agitation speed is moderate to high,

2) Anchor agitator with a glass plus metal line reactor, where agitation speed is slow,

3) Turbine agitator with an alloy reactor can also be used with glass line reactor where agitation speed is high.

The type of reactor used generally does not impact the drug substance properties; however, a change in agitator can impact the drug substance physical properties. As discussed earlier, this is due to variation in agitator speed[25, 33 - 35].

There are other factors such as pressure, moisture, humidity, additives and impurities which can have differing impact and can either inhibit or cause excessive growth of certain crystal faces[25, 26, 36].

The possible changes in the crystallization process or process parameters can impact the crystals in many ways such as different polymorphic forms, impurity levels and in the physical attributes such as particle size, particle shape, surface morphology, surface area and porosity. These differences can in turn have an impact on both the drug product and the manufacturing process of the drug product. These include bulk flow properties, compressibility, dissolution rate and stability. Reactive impurities such as iron and peroxide can impact the stability of the drug product resulting in failures over time and may not appear for months or years. Nonvolatile impurities with low melting point may influence sticking/picking, during the compression stage of the drug product manufacturing, based on drug content in the formulation, formulation composition and drug product manufacturing process[25, 26].

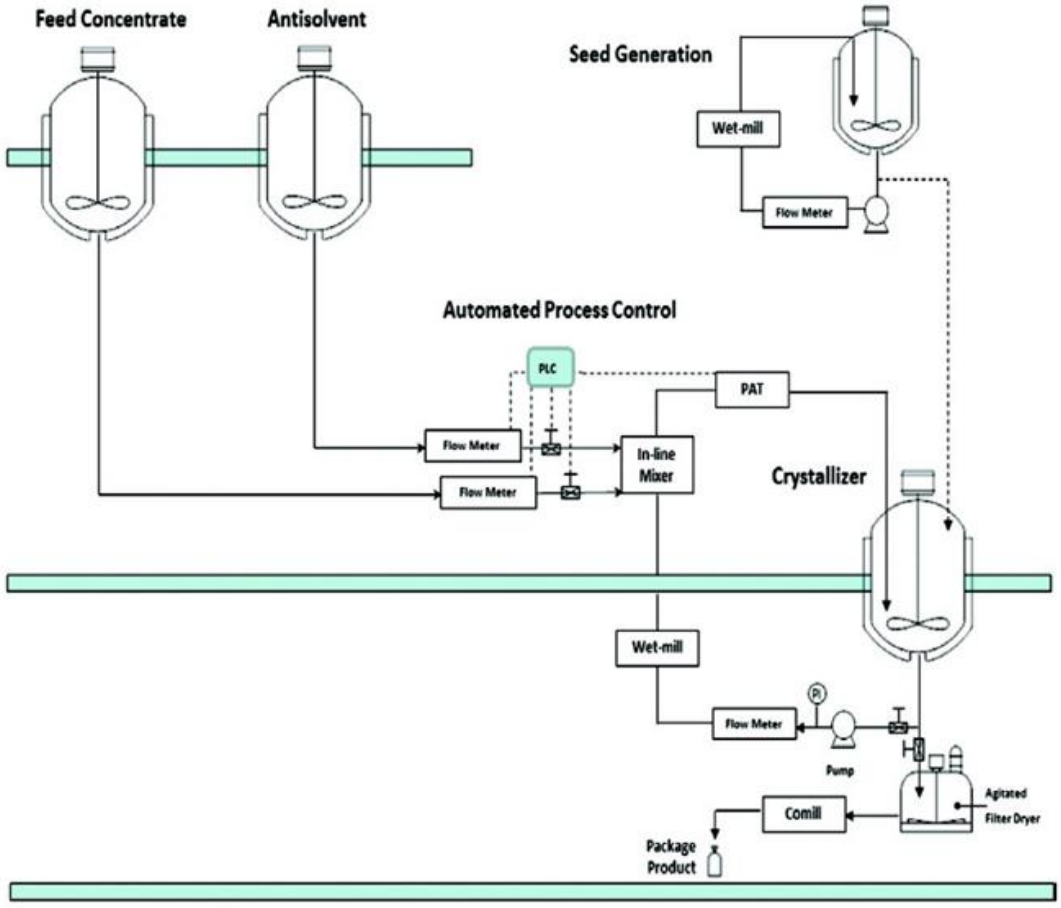


Figure 1.1: A process flow diagram depicting a typical equipment layout for a crystallization process use in the manufacture of APIs and Excipients.[29]

1.4.2 – Amorphous Material

Amorphous solids are described as any non-crystalline solid in which the atoms and molecules are not organized in a definite lattice pattern; examples of amorphous solids include glass, plastic, and gel[37]. The crystalline state of material has historically been the desired state for pharmaceutical materials due to the low free energy of this state when compare to amorphous material. This desire was due mainly to the fact that crystalline materials are more stable under a given set of conditions; also when there are multiple polymorphs, it is known that the one with the least energy will be the most stable and over time other polymorphs will transform to the lowest energy form[26]. Amorphous material is known to contain more free energy and is

therefore less stable than crystalline material and will convert to the more stable crystalline form during storage and handling. The difference in free energy can also lead to differences in the physicochemical properties of the material such as stability, solubility, dissolution and impact on the drug product manufacturing process[26, 38, 39]. The amorphous form of an API typically has higher solubility and using the amorphous form of an API is increasingly seen as a method to overcome low bioavailability of many poorly soluble and permeable drugs. While enhanced physicochemical properties is the main driver for the use of amorphous form of a drug and pharmaceutical materials, there are other consideration that can also play a role such as patent and commercial reasons[26, 40 - 42].

Potentially any material can be made amorphous if the rate at which the material solidifies is faster than the rate at which they can align into a crystal lattice structure[26]. There are several methods and techniques used in the manufacturing of amorphous material, which can be classified into two general categories, solution based or solid state methods[43]. The solution based method can be further divided into three different methods; vapor condensation, super cooling of melt, and precipitation from solution[38]. The solid state techniques include melt quenching, ball milling, cryogrinding, lyophilization, spray drying, super cooling, dehydration, etc. of which the most common is lyophilization (freeze drying) [43 - 45]. The amorphous material is characterized by the glass transition temperature (T_g) as they do not have distinct melting points[26]. At temperatures below T_g the material remains brittle while at temperatures above T_g the material becomes moist, sticky, and cold to the touch. The technique used to prepare an amorphous material will depend on the physical properties of the molecules; melt quenching will be appropriate for heat stable molecules, grinding or milling will be appropriate for physically stable molecules, spray drying will be appropriate for organic solvent soluble molecules, and

freeze drying for water soluble molecules. Many of these techniques (such as ball milling) are rarely used commercially to manufacture materials; however, when used can impact the drug molecule and ultimately the drug product [39 - 42]. There is also evidence to show that amorphous material of the same molecule prepared by different techniques will exhibit different physical properties and chemical stability[43].

1.4.2.1 – Impact of manufacturing process and parameters on the material

The amorphous state of a molecule is thermodynamically metastable; as a result, the focus must be to prevent conversion and/or degradation of the drug substance to the thermodynamically stable form. Therefore, it is critical to control the manufacturing process of the amorphous solids as any changes in the manufacturing process may impact the characteristics of amorphous powder. Each amorphization technique has its own set of critical processing parameters, with the main goals of preventing the formation of crystalline material and maintaining the stability of both the amorphous material and the resulting drug product over its shelf life. Changes to the amorphization process can influence the properties of the resulting material; a few examples are described below:

- Rate of Cooling: One of the common parameters that could result in the formation of crystals during solution based method of amorphization is the rate of cooling, if it is too slow then crystalline material can form[43],
- Temperature: The transition glass temperature (T_g) is critical to the amorphous material and can result in significant challenges. If the T_g is below the processing temperature then the probability of crystals forming is increased[46]. T_g can impact the manufacturing process of the material, as well as any subsequent processing to convert the material into the desire drug product. The rubbery nature of the material at temperatures above T_g can

affect flow properties, handling, and cleaning of the material[43]. Temperature has also been shown to influence the material properties during milling. Milling above T_g results in different polymorphs while milling at temperatures below T_g results in the creation of amorphous material[43],

- Degree of supersaturation: The viscosity, solubility, solvent, and solute are all inter related and can all impact the degree of amorphization. It has been shown that some materials become stronger as solute concentration decreases, while in other cases they become more fragile[38]. As an example, high viscosity combined with low temperature is used to prevent crystal formation in sugars. These factors can also impact process parameters such as spray rate and atomization, which can also impact the properties of the resulting material[46],
- Time: As stated above the amorphous state is known to be thermodynamically metastable and has a tendency to revert to its more stable crystalline form. It has been shown that this conversion can occur at temperatures above and below the T_g, although it is expected that the rate will be much faster at temperatures above T_g[47]. Time is also a significant factor in the milling process technique of making amorphous material. Milling is generally used for size reduction purposes which require milling for a short period of time. The conversion of crystals to amorphous material, however, requires several hours of intense milling resulting in the continuing buildup of crystalline defects[43],
- Milling: Milling is one of the techniques used to produce amorphous material; however, factors such as time of milling, co-milling with excipients, and temperature are known to impact the rate and extent of amorphization[43]. Milling can also impact the particle size, particle shape, T_g, and the chemical stability of the material[43].The manufacturing process

utilized in the production of a drug product often also includes milling of the materials; however, due to the relatively small time involved, this is not expected to have any noticeable conversion to amorphous material. Where milling can have a significant impact is if amorphous material is able to absorb water that can then act as a plasticizer. This can also lead to increased degradation to levels that can be detected and quantified as impurities[38],

- Impurities: Impurities such as degradation products, residual solvent, and moisture can act as plasticizers, thereby lowering T_g, resulting in some of the challenges described above. Increases in moisture have also been shown to increase the rate at which a material converts to the crystalline form. In some cases, for example polymer coating, a lower T_g is usually desirable to facilitate the effective layering of the polymer[43, 46, 47].
- There are other factors such as solubility, viscosity, pressure etc. that can impact the process. It was noted that process temperature and pressure have little or no effect on particle size, morphology, or water content of the material[38, 43, 46, 48].

The possible changes in the amorphization process, much like the crystallization process, can impact the material in many ways such as extent of amorphous material, impurity levels and in the physical attributes such as particle size, particle shape, surface morphology, surface area and porosity. These differences can in turn have an impact on both the drug product and the manufacturing process of the drug product[49, 50]. The processes described above are mainly in relation to APIs; however, excipients can also be produced in a similar way as they can be crystalline, amorphous, partially amorphous, or partially crystalline. The role of the excipient and its impact on the manufacturing process and drug product are discussed in the following section.

1.5 – Excipients

Drug products are made up of the API and excipients, where the type and number of excipients present is typically dependent on the dosage form. While, the therapeutic effect of the drug product is delivered by the API, the excipients play many critical roles in the design of the drug product formulation. These include[51, 52]:

- support a consistent and robust manufacturing process resulting in physically stable product over time,
- administration by intended route to patient,
- improve patient compliance,
- enable/enhance bioavailability and stability,
- control drug delivery, etc.

There are several types of excipients use in the manufacture of an oral solid drug product; some of the common ones are diluents, binders, disintegrants, glidants, lubricants, coating agents and coloring agents[51, 53]. Ideally excipients should have no pharmacological activity and should not react chemically, physically or biologically with the API. These excipients can be functional, for example as antioxidants and plasticizers, or non-functional, such as diluents and glidants. Table 1.1 provides a list of typical excipient types along with examples[51, 53]. The list in table 1.1 is not exhaustive, and represents excipients commonly used in the manufacture of solid oral dosage forms. There are numerous other classes of excipients, used in the preparation of other dosage forms (liquids, ointments, etc., and in some cases also solid oral) such as suspending agents, viscosity increasing agents, antimicrobials, complexing agents[54, 55], and solubilizers[55 - 59]. Newer APIs are generally less soluble and less permeable with less than 10 % classified as high solubility and high permeability[55] and many functional excipients such as cyclodextrins[50],

plasma protein[56], lipids[57] and surfactants[58, 59] are used to enhance their solubility, permeability and bioavailability[54, 60 - 62]. It is worth noting that not all inactive ingredients are completely inactive and patients can have allergic reactions or other adverse effects to these so-called "inactive" ingredients.

Table 1.1: A List of different excipient types and examples use in the Pharmaceutical industry to formulate APIs into drug products

Excipients Type	**Examples**
Diluents/Fillers	Lactose, microcrystalline cellulose, sugars
Binders	Starch, polyvinylpyrrolidone, methylcellulose
Disintegrants	Sodium starch glycolate, crospovidone, croscarmellose sodium
Glidants	Colloidal silicon dioxide, talc
Lubricants	Magnesium stearate, stearic acid, polyethylene glycol
Anti-adherents	Talc, corn starch, sodium dodecylsulfate
Film coating agents	Hydroxypropyl methylcellulose, hydroxypropyl cellulose
Modified coating agents	Methacrylate polymers, hydroxypropyl ethylcellulose, ethylcellulose
Colorants	Iron oxide, natural pigments
Flavor modifiers	Mannitol, aspartame, vanilla
Adsorbent	Activated charcoal
Antioxidant	Ascorbic acid, butylated hydroxyanisole, sulfoxylate
Plasticizer	Glycerin, tributhylcitrate, diethyl phthalate
Surfactant	Polysorbate 80, sodium lauryl sulfate, nonoxynol 10
Polishing agent	Carnauba wax

The regulatory bodies, such as the FDA and EMEA, approve the thousands of excipients that are used in the manufacturing of pharmaceutical drug products. The specific function of an excipient can vary significantly depending on the formulation and manufacturing process of the drug product and therefore it can be very difficult to establish acceptable specifications to cover a wide range of potential functions. As a result, the focus of the regulatory bodies and the excipient monographs is on purity and safety of the material; meeting the monograph requirements does not assure that batches are necessarily equivalent. The source of excipients

can include plant, animal or can be synthetic and as a result the individual excipients are expected to have variation from batch to batch. There needs to be a clear understanding of how this variability will affect the drug product formulation and manufacturing process; such understanding will most likely be on a product by product basis[63]. This was demonstrated in studies where super-disintegrants from different suppliers were found to have no effect on one formulation, while affecting another formulation. A study of five different brands of croscarmellose sodium in a placebo tablet containing lactose, dicalcium phosphate and magnesium stearate illustrated that two brands were almost identical in the disintegration time observed; two had slightly higher disintegration times while one was significantly different with a higher disintegration time. In addition three superdisintegrants, Crospovidone, Croscarmellose Sodium and Sodium Starch Glycolate, supplied by the brand companies and a generic equivalent were evaluated at different concentrations in an orally disintegrating tablet formulation for Domperidone containing Pearlitol, Avicel PH 101, Aspartame, Orange flavour, Aerosil and Sodium stearyl fumarate. In all three instances the disintegration time of the tablets using the branded product were lower than the disintegration times of the tablets using the generic equivalent irrespective of the concentration used. In addition both suppliers of Crospovidone exhibited significantly lower disintegration times than the suppliers of Croscarmellose Sodium and Sodium Starch Glycolate[64 - 66]. This problem could extend further if there is a change to the manufacturing process or source of the material resulting in a change in the physical or chemical properties of the excipient.

The drug product is made up of the API and at least one excipient, but typically a tablet formulation will consist of a diluent, binder, disintegrant and a lubricant. The excipients can sometimes make up to 99.9 % of the drug product; however, on average they account for

approximately 90% of the drug product[51]. Excipients are generally amorphous in nature and many exist as fully amorphous (such as amino acids) or partially amorphous material (such as spray dried lactose and microcrystalline cellulose) [38]. As a result the excipients, like the API, can have a significant impact on the physical and chemical properties of the drug product. The mechanical properties of both the API and excipients are critical in the manufacturing of the drug product. The crystalline material is known to be more elastic and brittle when subjected to external stress, while the amorphous materials exhibit more viscoelastic properties, depending on T_g. These properties are critical during the manufacturing of a drug product as they can induce flow and provide mechanical strength to the dosage form[38].

1.6 - Drug Product

The required dosage of a drug substance can range from micrograms (10^{-6} g) to approximately one gram, but is typically in the milligram (10^{-3} g) range. The average customer is not likely to be in a position to accurately weigh this small quantity of material directly from the pure API, as a result dosage forms were developed[67]. The drug product formulation must have the desired *in vivo* and *in vitro* performance, and must not be impacted by any changes in the manufacturing process, API or excipient for the formulation designed[53]. This is a diversified process that requires a systematic approach to gather a full and detailed understanding of the material properties, formulation, manufacturing process, and their interactions, and to also satisfy the regulatory authorities that the drug product is completely understood. The approach must provide sufficient justifications and support, based on research and experimentation, to ultimately provide a dosage form that is physically, chemically, and therapeutically stable for the shelf life of the drug product. A proper experimental design can define the operating boundaries for the materials as well as for the manufacturing processes to ensure the quality of the drug

product. Information from various categories such as properties of API and excipients, interactions between materials, unit operations, and equipment use are required[68]. Figure 1.2 illustrates the relationship between the API and the excipients in the formation of a drug product.[53] Figure 1.3 illustrates the complexity of the relationship between material, manufacturing process and equipment in the development and understanding of a drug product[68].

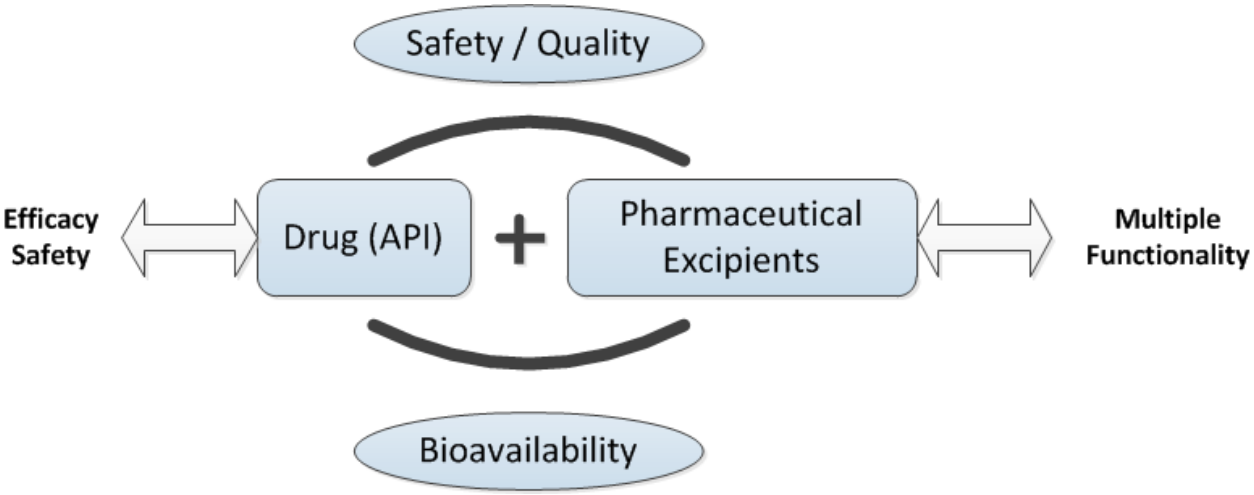


Figure 1.2: A schematic of the relationship between API and excipients which are combined to produce a drug product with the desired pharmacological effect in a safe and effective manner[53].

Design of Experiment (DoE) and statistical methods are now being used extensively in the formulation and process development in pharmaceutical manufacturing, to optimize the formulation, manufacturing process, and equipment parameters[69 - 72]. The role of statistical analysis also extends into the validation study and subsequently to the Product Life Cycle Management. The final drug product and the manufacturing process for that product are required to be validated according to the regulatory requirements and guidelines. In general the validation process is used to verify the quality attributes of the dosage form, which for tablets would include disintegration, dissolution, friability, hardness, weight, assay, blend uniformity, and dosage uniformity; however the specific quality attributes can vary depending upon the type of

dosage form been manufactured. The validation batches also undergo stability evaluation over the drug product shelf life to ensure no effect from the scale up of the process or any other changes, including material changes that may have occurred. Any significant change to any of the starting materials of the formulation will require revalidation of the product and manufacturing process, which is expensive in both cost and time[53].

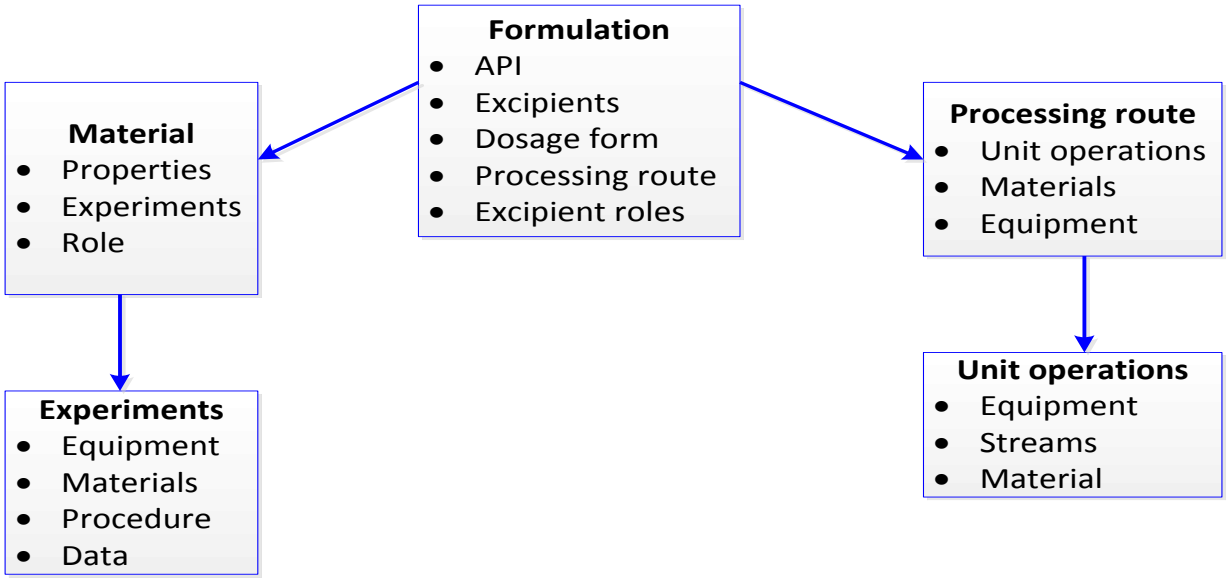


Figure 1.3: Schematic describing the complexity of the relationship between material, manufacturing process and equipment; clearly illustrating that a change in the property of one impacts the others[68].

There are several dosage forms such as capsules, patches, injections, liquid etc.; however, the most common dosage form in the pharmaceutical industry is the tablet. The manufacturing process for a tablet most often includes mixing, milling, granulation (dry or wet), and compression into a tablet (which can be then followed in some cases by film coating). A tablet is formed by eliminating the void spaces in between particles, and reducing the volume of a powder mix resulting in the formation of a solid mass[73]. The process involves "particle rearrangement, elastic, viscoelastic and plastic deformation of particles, fragmentation of particles and formation

of inter particulate bonds"; see figure 1.4 as an example[73, 74]. There are several factors to consider leading up to the formation of the final dosage form, the selection of excipients, physical and chemical compatibility of drug and excipient, characteristics of the individual materials, characteristics of the physical blend and finally the characteristics of the final tablet[53]. The selection of the appropriate excipient and their relative concentration in the formulation is also critical for the success of the manufacturing process of the dosage form. The selection of an appropriate excipient is based on the intended function, drug-excipient compatibility, type of dosage form, and the manufacturing process and parameters. Drug-excipient incompatibility, whether physical, chemical or therapeutic, is a very important issue before and after dosage form preparation with respect to the product stability and the requirement to meet the intended shelf-life. The incompatibility can be chemical (such as hydrolysis, which is most common), oxidation or physical such as cross linking with gelatin[52, 53, 75 - 77]. It is important to understand the chemistry of the API so that an appropriate excipient can be selected. It is also critical to understand the excipients as many of the incompatibilities do not result directly with the excipient but with the impurities present in the excipient material. These impurities, such as peroxides and heavy metals, can catalyze many of the reactions leading to the degradation of the drug product[53]. Any change to the excipient resulting in an increase in these impurities, while within the compendia specification, can ultimately lead to degradation and potential failure of the drug product.

1.6.1 Tablet Manufacturing Process

The API and excipients are required to be mixed together for a predetermined time to produce a blend that meets two main objectives; (1) homogeneity of the materials in the blend, and (2) the ability of the blend to flow; both objectives are expected to be maintained for the time

of processing to the final drug product. The blend of the drug product formulation contains the API and the desired excipients, each having their own physical and chemical characteristics. As a

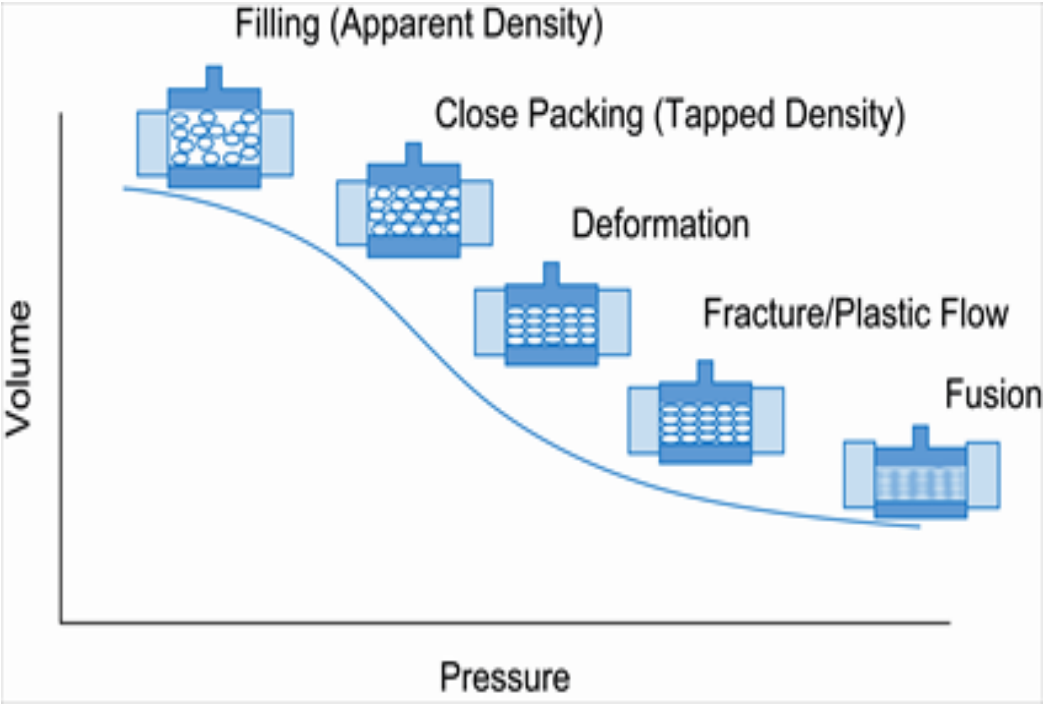


Figure 1.4: The various stages of powder compaction during tablet formation on a compression machine, indicating a decrease in the powder volume with a corresponding increase in pressure[74].

result this can lead to differences in particle size, particle shape, surface area, flowability, density, porosity etc. of each material, and of the resulting blend[53].The factors that affect the desired properties of the blend are generally interdependent; blends that are not homogenous can lead to several challenges including segregation of material, non – uniformity of the drug substance in the drug product, and erratic flow. There are other factors such as humidity, temperature, blender speed and blending time that can also affect the blend [53, 73]. Any single property or a combination of these properties can be impacted by a change in any of the individual materials in the blend. The root cause of segregation in a blend is mostly due to differences in particle size, shape and density. Materials are milled during processing with the

intention of ensuring all agglomerates and particles are reduced to a similar size; however, the key is to select excipients with particle sizes that are as close to the same size as possible compared to the API particle size. The shape of the particle can also cause segregation as spherical particles flow well, while needle - like particles do not. The adhesive forces between particles in a given material can affect the flow properties of the blend if the material is present in a sufficiently large volume. Materials that are very cohesive do not flow well, affecting both blending and discharging of the material in a negative fashion. The opposite is true for low cohesive material[73]. Depending on the batch size of the blend it may be subjected to compressive forces (due to the overall weight and volume of the blend) that can cause partial rearrangement[78]. A common tool used to evaluate changes to the properties of the materials is to measure their bulk density (or apparent/pour density) and tapped density (see figure 1.4). The bulk density of the blend is related to the cohesiveness of a powder while the bulk density and tapped density together can be used to calculate the Housner ratio (a measure of flowability) and the Carr Index (a measure of the compressibility) for the blend[53].

The powdered blend of API and excipient does not always possess the require properties for the direct compression into tablet or capsule dosage form. In some cases it is necessary to further process the blend to form denser granules. This can be due to several reasons including prevention of segregation, prevention of API migration, or prevention of API loss during processing. Granulation is a process where the primary powder particles are made to adhere to form larger, multi - particle entities called granules. This process is normally initiated after the initial mixing of the necessary powdered ingredients, particularly if they have flow or segregation issues or there is a difference in each component particle size granulation. Granulation of the mix can be achieved either by wet granulation, by adding liquid binder, or by

dry granulation, involving the dry compaction of the blend[79]. The compaction process for granulation, much like the milling process, may change the crystal structure into a different polymorphic form. To understand the compaction behavior of a material, it is necessary to be able to quantify much of the same properties as with the blend, such as elasticity, plasticity, and brittleness.

A good granulated blend can be converted successfully into a tablet dosage form and to perform this various properties should be considered, including drug-excipient compatibility, flowability, lubricity, appearance, dissolution, and disintegration. The compression process is made up of four distinct stages; pre-compression, main compression, relaxation and ejection[80].The pressure or compression force is applied to form a lucid mass and is directly interrelated to the resulting tablet hardness and used as a surrogate for the weight of the tablets on the completely automated compression machines[81]. The compression machine does not have the capability to weigh every tablet during the compression run but is equipped with a strain gauge on each punch that can measure the compression force use to produce each tablet. As a result the compression machine monitors the weight of the tablets throughout the compression run by monitoring the compression forces at each punch. Compression force is considered one of the main critical processing parameters during the manufacturing of a tablet; however, several other factors such as press feed system, paddle feeder, fill cam, ejection cam, press speed, dwell time, punch depth and the tablet press Operator can all impact the quality of the tablet[82]. The formed tablets must meet the quality attributes according to the monograph and generally the weight of the individual tablet, weight variation, dosage uniformity, thickness, hardness, friability, disintegration, and dissolution should be the CQAs characterized for the validation of the process. The tablet dosage form has to undergo several physical processing unit operations

and must maintain product integrity as several physical characteristics are required to be met at the end. The mechanical strength of tablets is an important aspect and it is required to be controlled in the manufacturing process. This has been described by various terms such as friability, hardness, fracture resistance, crushing strength, flexure, or breaking strength[83 - 85]. Tablets require a certain amount of strength, or hardness and resistance to mechanical stress, to withstand the rigors of handling in manufacture, packaging, and shipping of the drug product. A sufficient amount of tablet hardness and resistance to prevent friability is a necessary requisite for consumer acceptance, while immediate-release tablets should readily disintegrate in the stomach as rapid as possible. This makes the relationship of hardness and disintegration important to achieve the required dissolution of the drug. These factors need to be controlled to achieve the CQAs of the drug product in the end[53, 86].

1.6.2 - Disintegration

Once the tablet is taken orally a process that is almost the reverse of that for manufacturing the tablet takes place, in order to make the drug substance available to the circulation system and tissues. The tablets will have to break down into granules or powder and go into solution for absorption and distribution to take place. Figure 1.5 illustrates the pathways that a drug substance, presented as a solid dosage form can take in order to be absorbed into the circulation system and tissues[53]. If the tablet dosage form is designed to release the drug substance immediately after ingestion then the tablet should readily disintegrate in the stomach, or in the case of an orally disintegrating tablet, should disintegrate within seconds under the tongue in the mouth. As a result the disintegration test is an integral part of the in-process testing during the compression process of tablets. There are many mechanisms by which a tablet can disintegrate depending on the disintegrant and excipients used. These mechanisms include

swelling, porosity and capillary action, deformation, and particle repulsive forces, of which swelling is the most common[87]. There are several physical factors that can affect the disintegration time including water penetration, disintegrant content in the formulation, disintegrating fluid, and compression force. In addition, excipients within the formulation such as diluents, binders, surfactants and lubricants can all effect the disintegration time. There is some correlation between these factors and any change to any of the material property can ultimately have an impact on the disintegration time[88 - 90].

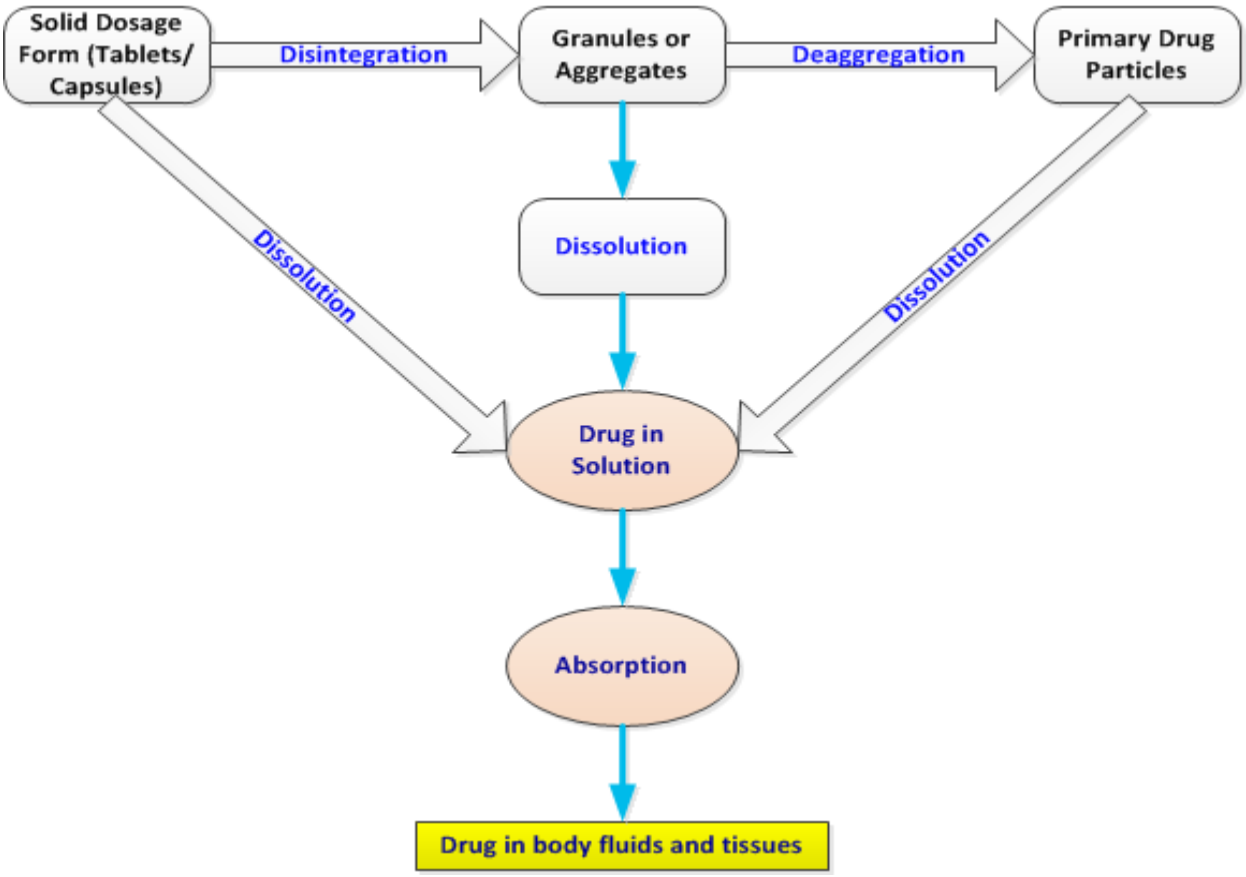


Figure 1.5: The pathways of a solid dosage form to disintegrate and dissolve for the absorption of the drug substance in the body[53]

1.6.3 - Dissolution

Clinical studies by the Innovator are performed on many batches of product, while the bio – equivalency study for the generic product is usually done on a single batch of product. It would

be both cost and time prohibitive to perform an in-vivo study on every batch of product in order to prove efficacy, and as a result the *in-vitro* dissolution test is use as a surrogate for *in-vivo* studies, to release each batch of drug product for use by patients. The basic premise of this is that there is a correlation between the *in-vivo* results and *the in-vitro* result and a passing *in-vitro* result will ensure the bio availability of the drug in the body. The dissolution test is a measure of the rate and extent of the release of the API and is a CQA for a number of reasons, including;

- to evaluate the potential effect of material, formulation and process variables on the bioavailability of a drug;
- to ensure that the drug product complies with product specifications;
- to indicate the performance of the drug product under *in-vivo* conditions.

There are several factors that can affect the dissolution of a drug product including material properties, formulation, process parameters, the testing equipment, and the testing parameters. It is well documented that lubricants and mixing times can change dissolution behavior and any variation of either can lead to variation in the dissolution[91, 92]. The material properties that can impact the dissolution have already been introduced, and include particle size, particle shape, particle density, surface area, surface tension, polymorphism, amorphous state, wetting, humidity, and solubility. Changes to these properties can occur as a result in changes to the raw material manufacturing process or the drug product manufacturing process. There is also inherent variability with any manufacturing process which can result in batch to batch variability of any material. Finally, many of these factors are also interdependent; for example the particle size of a material can be changed due to milling in the manufacturing process, leading to a change in the surface area of the material. The surface area of the drug substance will likely

impact the dissolution and absorption for the drug product with an increase in surface area resulting in an increase in dissolution rate[91].

1.6.4 – Impact of particle size on drug product and manufacturing process

While a number of material properties have been introduced that can have direct or indirect impact on the manufacturing process and the resulting properties of the drug product, particle size can perhaps have the largest single impact on the CQAs of the material, drug product and processing of a drug product[93]. CQAs such as blend uniformity, dosage uniformity, dissolution, hardness, bio–availability, etc. can all be impacted, while the impact on process can include variations in flow properties, granulation properties, compressibility, etc. The other aspect directly related to particle size is that of particle shape, which can similarly have a significant impact on the bulk properties of material[53]. Despite its criticality, the impact of particle size on the product and process is not studied extensively during development, or during the life cycle of the product. The particle size specification is usually set during the development process, as it is a required part of the submission dossier. This is usually done on small scale batches with data available only from a small number of batches. Particle size is examined in greater detail often only as a result of an abnormal event. As a result during scale up of the API manufacturing process it is usually very difficult to meet these specifications and in many instances changes in the particle size specification must be made. The impact of such a change is not always adequately evaluated as it is done at or close to the time of launch of the product. This can also be a challenge for the drug product manufacturer when the source of the API or excipient is changed. The new source may meet the specification requested; however, if they are using different test equipment and/or test method, the material can still fail when tested at the drug product manufacturer site. Pharmaceutical powders, API and excipients, usually range in

size from 0.01 micron to 1000 microns. The majority of APIs typically range in particle size from 1 to 100 microns; however, newer molecules have been prepared with particles sizes in the nanometer range[94]. There are several challenges associated with particle size testing and the results using the same material can vary greatly depending on the method and instrument used to perform the test. There are several methods used to test particle size including microscopy, sieving, electrical sensing, light scattering, and photon correlation spectroscopy[13]. It is critical to establish a correlation between the supplier test and result and that of the drug product manufacturer, so that the appropriate specification can be set such that good batches are not rejected and bad batches are not accepted.

The ultimate challenge for the Formulations Development Scientist in the twenty-first century is to achieve a true understanding of material properties and material science and the impact of any change or variation. Those who can conceive a compatible, functional formulation will be irreplaceable as large companies shrink their Research and Development resources and the public sector demands better efficiency.

Chapter – 2: Hypothesis and Objectives

2.1- Overview of the project

The objective of this research is to understand how the physical and chemical characteristics for APIs and excipients may be critical for the success or failure of alternative source/process even though the given molecule is deemed to be equivalent. The main focus of most alternate API or excipient source change is on the physical properties that can impact either the manufacturing process and/or performance of the drug product (refer to table 2.1). The impact will vary depending on the material characteristics, such as attractive forces, particle shape, particle size, surface morphology etc. Initially three current sources of API and one current source of excipient were selected for a parallel evaluation with an alternate source/process of the same material leading to a total of eight batches. During the execution of the batches, an additional excipient that is used in one of the API formulations was added, bringing the total to ten batches. The C of A for each material was then evaluated and the differences were highlighted. Additional tests were performed (beyond the C of A), these include DSC, X-ray diffraction, bulk density, tapped density, particle size, volume weighted mean diameter, surface weighted mean diameter and specific surface area, where applicable.

2.2 - Research Question

Variation of Product Quality and manufacturability generally arises from two sources, either the raw material, or processes involved in manufacture of the product[95]. This research seeks to understand how the physical and chemical properties of an API and excipient obtained from an alternate source/process can impact the material properties, manufacture processing, drug product performance and their CQAs. The manufacturing process is known to impact the

final quality of any product and the confidence in ensuring that the final product will meet its quality attributes is dependent on the robustness of the manufacturing process. While APIs and excipients from the currently approved source and from the alternative source appear similar, they may exhibit significantly different physical behavior during processing and testing of drug product. The extent of this difference is not always adequately captured in the C of A for the API or excipient. Chemical differences are often due to the synthetic impurities, related compounds and degradation products generated during processing or storage and can all lead to drug substance and/or drug product failures. In a similar manner, that it is cost and time prohibitive to perform an in-vivo study on every batch of product, the expectation was not to perform all of these tests for every lot of APIs or excipients received, however, these tests should form the basis of the evaluation to introduce an alternate source of material.

The tests to be completed as part of the evaluation on the impact on the processing, CQAs and drug product performance are described in table 2.1.

Table 2.1: Tests to be completed for the processing, CQAs and drug product performance to evaluate the impact of a source/process change for an API and/or Excipient

Processing	**Critical Quality Attributes (CQAs)**	**Drug Product performance**
Hausner Ratio	Weight	Dissolution
Carr Index	Hardness	Assay of API content
Sieve Analysis	Thickness	Dosage Uniformity
Flow Index	Friability (4 minutes and 20 minutes)	
Bulk Density	Disintegration	
Tapped Density		
Compression force		

2.3 - Hypothesis

The comparability of the two C of As of an API or excipient supplied from different sources/processes will not demonstrate equivalency in the properties or behaviors of the materials.

2.4 - Specific Objectives

The specific objectives of this study are:

1. Determine if the raw materials meet all C of A specifications,
2. Determine if the two sources differ with respect to the tested C of A specifications,
3. Determine if the two sources differ with respect to the tests beyond the C of A,
4. Determine if the two sources differ with respect to Process testing (see Table 2.1),
5. Determine if the two sources differ with respect to CQA and Drug Product Performance (see Table 2.1).

Chapter – 3: Materials and Methods

3.1 - Rationale for selection of APIs and Excipients

All materials used in this thesis were graciously provided by Apotex Inc. (Canada), who also provided access to the tablet manufacturing facilities, analytical methods and testing equipment's.

The experimental plan for this study was based upon an examination of 3 API materials (metformin hydrochloride USP, gabapentin USP, and fenofibrate EP/BP), and 2 excipients (copovidone NP/EP and croscarmellose sodium NF/EP), with each material being obtained from two different sources; an exception was the copovidone experiments, where materials from the same supplier but different manufactured batch sizes were examined. A brief description of the formulations and processes used is provided below:

1. Metformin hydrochloride USP API is supplied as crystalline metformin HCl Form A. Metformin HCl tablets are prepared using a direct compaction method, is available from an alternate supplier using an alternate manufacture process, and is present as 84% w/w active concentration in the composition of the drug product;
2. Gabapentin USP API is supplied as crystalline gabapentin USP Form II. Gabapentin USP tablets are manufactured using a dry compaction process, is available from an alternate supplier using alternate manufacture process, and is present as 69% w/w active concentration in the composition of the drug product;
3. Fenofibrate EP/BP API is supplied as crystalline Fenofibrate Form I. Fenofibrate EP/BP tablets are manufactured using a hot melt technology where the resulting solid mass is pulverized using a hammer mill, is available from an alternate supplier using an alternate

manufacture process, and is present as 55% w/w active concentration in the composition of the drug product;

4. Copovidone NF/EP is used as a binder in most formulations and is used in the gabapentin USP tablets prepared in this study. There is no change in supplier or in the manufacture process for copovidone; however there is a change in the scale of manufacture and manufacturing equipment;
5. Croscarmellose Sodium NF/EP is the only excipient used in the fenofibrate EP/BP formulation other than the API; is present as 45% w/w composition of fenofibrate EP/BP tablets, is a super-disintegrant, but is also being used as both a disintegrant and as a binder in this formulation and is available from an alternative supplier.

3.2: The APIs, Excipients and their suppliers used in each batch

The APIs and excipients tested for each batch are provided in table 3.1, along with the supplier information. The actual materials used in the preparation of each batch of tablets, including both the test APIs, test excipients, along with any other materials (excipients) required for the tablet formulation (held constant across experimental batches) are listed in section 3.3.

The metformin hydrochloride API for the metformin HCl tablets were supplied by two different companies, the API used in batch 1 was supplied by company A while the API used in batch 2 was supplied by company B.

The gabapentin USP API for the gabapentin USP tablets were supplied by two different companies, the API used in batch 3 and batch 5 was supplied by company X, while the API used in batch 4 and batch 6 was supplied by company Y.

The excipient copovidone for the gabapentin USP tablets was supplied by company D; two different materials were supplied based on the scale of the manufacturing equipment used by the

supplier. The two materials are identified as copovidone NF/EP 35 which was used in batch 3 and batch 4, and copovidone NF/EP 20 which was used in batch 5 and batch 6.

The fenofibrate EP/BP API for the fenofibrate EP/BP tablets were supplied by two different companies, the API used in batch 7 and batch 9 was supplied by company J, while the API used in batch 8 and batch 10 was supplied by company K.

The excipient croscarmellose sodium NF/EP for the fenofibrate EP/BP tablets were supplied by two different companies, the croscarmellose sodium NF/EP used in batch 7 and batch 8 was supplied by company G, while the croscarmellose sodium NF/EP used in batch 9 and batch 10 was supplied by company H.

Table 3.1: The batch numbers, materials used and their suppliers for each batch during the execution of the batches to test the hypothesis of this research

Batch #	**API**	**API tested**	**Excipient tested**
1	Metformin HCl BP	Company A	N/A
2	Metformin HCl USP	Company B	N/A
3	Gabapentin USP	Company X	Copovidone NF/EP 35
4	Gabapentin USP	Company Y	Copovidone NF/EP 35
5	Gabapentin USP	Company X	Copovidone NF/EP 20
6	Gabapentin USP	Company Y	Copovidone NF/EP 20
7	Fenofibrate EP/BP	Company J	Croscarmellose Sodium NF/EP (Company G)
8	Fenofibrate EP	Company K	Croscarmellose Sodium NF/EP)Company G)
9	Fenofibrate EP/BP	Company J	Croscarmellose Sodium NF/EP (Company H)
10	Fenofibrate EP	Company K	Croscarmellose Sodium NF/EP (Company H)

3.3 – Formulation, process maps and target in-process CQAs for each product

Metformin HCl – Batches 1 and 2

The specific ingredients used in the formulation of the metformin HCl tablets are listed in table 3.2. In addition to the two sources of metformin HCl listed in table 3.1, methylcellulose USP A15LV and polyethylene glycol NF 8000 were supplied by The Dow Chemical Company, microcrystalline cellulose NF M102 was supplied by Mingtai Chemical Co. LTD., colloidal silicon dioxide NF was supplied by Cabot Corporation, and magnesium stearate NF was supplied by Peter Graven. A flow diagram of the process used for the preparation of metformin HCl tablets is provided as figure 3.1, below. The targets in process CQAs for the compression process are listed in table 3.3.

Table 3.2: Composition of the metformin HCl tablets listing the API and excipients used in batches 1 and 2

Item #	Material Name
1	Metformin HCl BP/EP
2	Methylcellulose USP A15LV
3	Microcrystalline Cellulose NF M102
4	Polyethylene Glycol NF 8000
5	Colloidal Silicon Dioxide NF
6	Magnesium Stearate NF

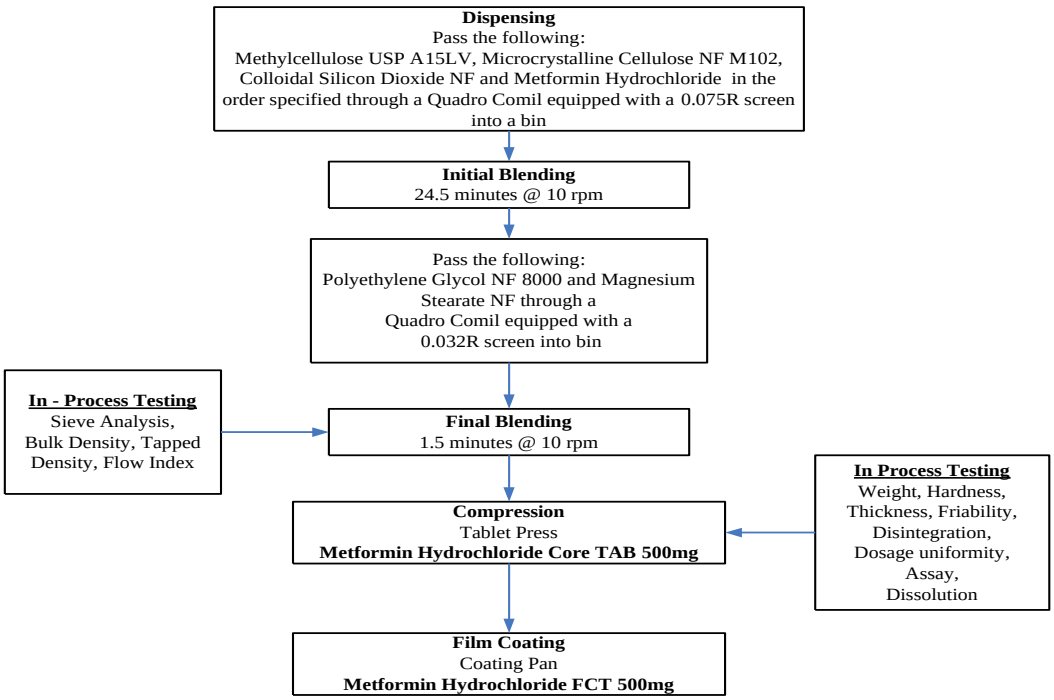


Figure 3.1: Process flow diagram describing the direct compression process for the preparation of metformin HCl tablets in batches 1 and 2.

Table 3.3: The target in process CQAs during the compression process for batches 1 and 2 (metformin HCl tablets).

Dies:	0.3125" x 0.6145"
Upper punches:	Capsule shaped. Standard cup, unscored, imprinted "APO 500"
Lower punches :	Capsule shaped. Standard cup, unscored, imprinted "MET"
Individual core tablet weight:	Target: 596mg, Range 566mg to 626mg
Weight of 10 core tablets:	Target: 5.96g, Range 5.78g to 6.14g
Hardness:	Target 7 kp, Range 5 kp to 10 kp
Thickness:	Target 0.216 inch, range 0.209 inch to 0.224 inch
Friability:	NMT 1% after 100 revolutions (4 minutes at 25 rpm)
Disintegration:	NMT 30 minutes (without disc)*
Description:	White to off-white, capsule shaped, unscored cores imprinted "APO 500" on one side and "MET" on the other side

* The total time for the six tablets in the disintegration apparatus to completely disintegrate and pass though the mesh screen must not exceed 30 minutes.

Gabapentin USP /Copovidone – Batches 3 to 6

The specific ingredients used in the formulation of the gabapentin USP tablets are listed in table 3.4. In addition to the two sources of gabapentin USP (batches 3 and 4) and the two types of copovidone (batches 3 and 4 as compared to batches 5 and 6) listed in table 3.1, magnesium stearate NF was supplied by Peter Graven. In all 4 batches executed for gabapentin USP, copovidone (copovidone NF/EP 35 and copovidone NF/EP 20) was obtained from Company D. A flow diagram of the process used for the preparation of gabapentin USP tablets is provided as figure 3.2, below. The targets process parameters and CQAs during the compaction process are listed in table 3.5, while the targets in process CQAs for the compression process are listed in table 3.6.

Table 3.4: Composition of gabapentin USP tablets listing the API and excipients used in batches 3 – 6.

Item #	Material Name
1	Gabapentin USP
2	Copovidone NF/EP
3	Magnesium Stearate NF

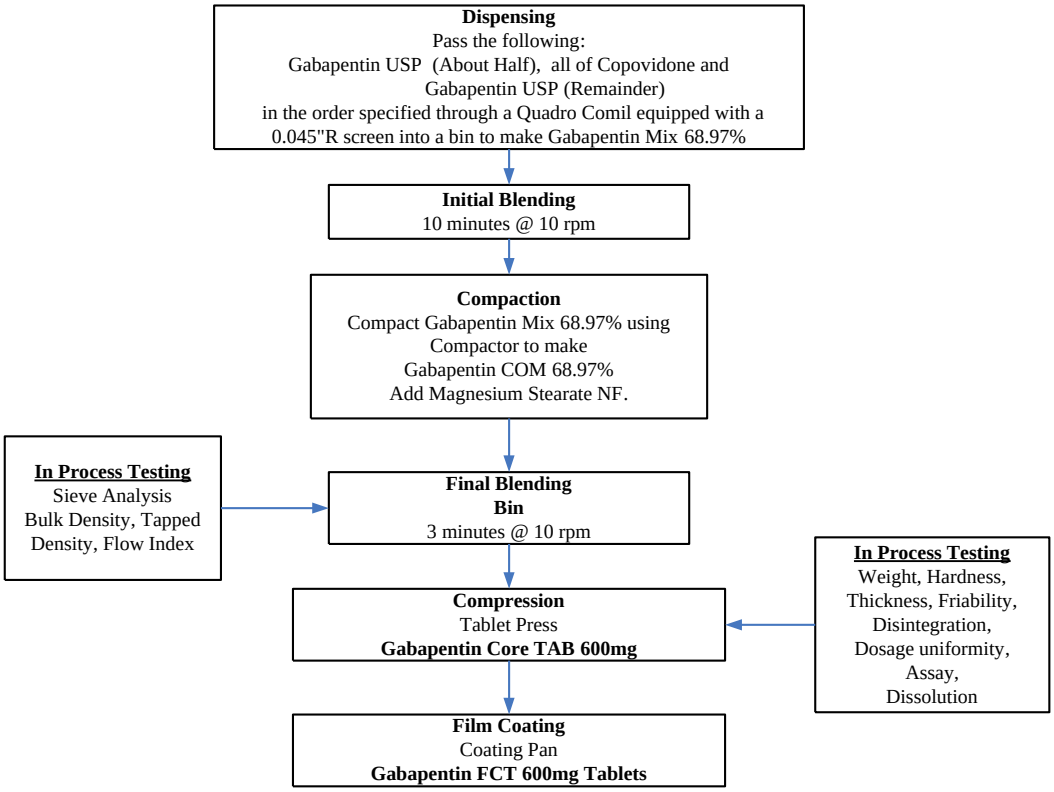


Figure 3.2: Process flow diagram describing the compaction process for the preparation of gabapentin USP tablets in batches 3 –6.

Table 3.5: The target process parameters and CQAs during the compaction process for batches 3 – 6 (gabapentin USP tablets)

Process Parameters	**Settings Operating Range**
Screen size	1.5 mm
Granulator Wheel	Open-faced angular
Roller Type	Knurled
Roller Gap Width (mm)	3.3 mm
Compaction force	9.0 kN/cm
Compaction Roller Speed	6.0 rpm
Granulator Speed	75 rpm CW
	75 rpm CCW
Granulator Angle	180 CW
	270 CCW
Sieve Analysis	Operating Range
20 mesh (12+20 mesh) (%)	11-61
80 mesh (40+60+80 mesh) (%)	24-46
Fines (100+200+ Fines mesh) (%)	5-53
Bulk Density (g/cc)	0.45-0.65
Tapped Density (g/cc)	0.65-0.85

Table 3.6: The target in process CQAs during the compression process for batches 3 – 6 (gabapentin USP tablets)

Dies:	0.3440”x0.6875” Oval
Upper punches:	Modified concave, oval, Embossed “GAB” over Partial bisect “600”
Lower punches:	Modified concave, oval, Embossed “APO”
Individual core tablet weight:	Target: 870mg, Range 826mg to 914mg
Weight of 10 core tablets:	Target: 8.70g, Range 8.44g to 8.96g
Hardness:	Target 19 kp, Range 11.5 kp to 26.0 kp
Thickness:	Target: 0.258” (Range 0.240” to0.275”)
Friability:	NTM 0.8% after 100 revolutions (4 minutes at 25 rpm)
Disintegration:	NMT 30 minutes (without disc)*
Description:	White, oval, biconvex, tablets, Engraved “GAB” over partial bisect “600” on one side, “APO” on the other side

* The total time for the six tablets in the disintegration apparatus to completely disintegrate and pass though the mesh screen must not exceed 30 minutes.

Fenofibrate/Croscarmellose Sodium – Batches 7 to 10

The ingredient used in the formulation of the fenofibrate EP/BP tablets is listed in table 3.7. Sources of both fenofibrate EP/BP and croscarmellose sodium NF/EP are provided in table 3.1; there are no additional excipients in the fenofibrate EP/BP tablet formulation. A flow diagram of the process used for the preparation of fenofibrate EP/BP tablets is provided as figure 3.3, below. The targets in process CQAs for the compression process are listed in table 3.8.

Table 3.7: Composition of the fenofibrate EP/BP tablets listing the API and excipient used in batches 7 – 10

Item #	**Material Name**
1	FENOFIBRATE EP/BP
2	CROSCARMELLOSE SODIUM NF/EP

Table 3.8: The target in process CQAs during the compression process for batches 7 – 10 (fenofibrate EP/BP tablets)

Dies:	0.2620" x 0.5020", modified oval
Upper punches:	Modified oval, concave, unscored, embossed "APO"
Lower punches:	Modified oval, concave, unscored, embossed "FEN160"
Individual core tablet weight:	Target: 291 mg, range 276 mg to 306 mg
Weight of 10 core tablets:	Target: 2.91 g (Range: 2.82 g to 3.00 g)
Hardness:	Target: 5.5 kp (Range: 3.5 kp to 7.5 kp)
Thickness:	Target: 0.171 inch (Range: 0.167 inch to 0.175 inch)
Friability:	NMT 0.8%, after 100 revolutions (4 minutes @ 25 rpm)
Disintegration:	NMT 15 minutes (without discs)*
Description:	White to off-white, oval, core tablet engraved APO on one side, and FEN160 on and "FEN160" on the other side.

* The total time for the six tablets in the disintegration apparatus to completely disintegrate and pass though the mesh screen must not exceed 30 minutes.

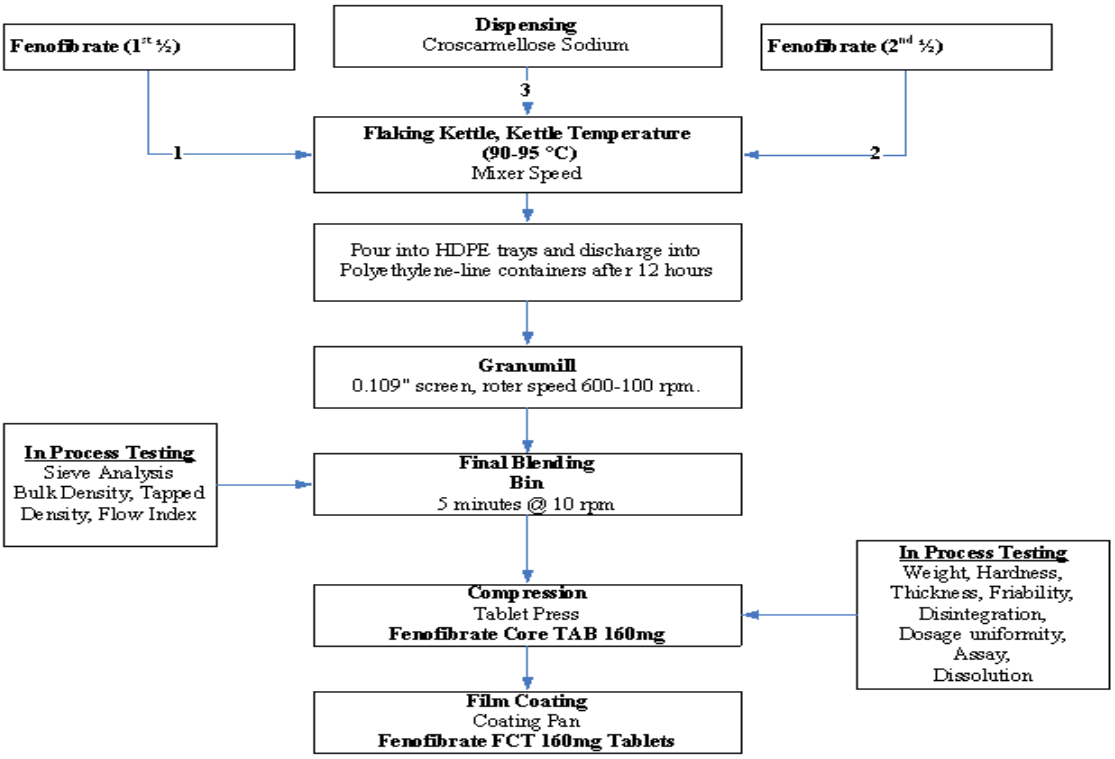


Figure 3.3: Process flow diagram describing the hot melt technology process used in the preparation of fenofibrate EP/BP tablets in batches 7 –10. Half of the fenofibrate EP/BP is charged to the kettle (1) and allow to melt at 90 -95°C before the second half is added (2). Once all of the fenofibrate EP/BP is melted the croscarmellose sodium NF/EP is then suspended (3) in the molten fenofibrate EP/BP.

3.4 - Material Characterization

The three APIs and two excipients were tested according to their respective C of As using the approved and validated method of analysis and C of A criteria for each material. These materials were tested by Apotex and the results were provided to me for use in this thesis. The C of A criteria for metformin HCl USP are compared in table 3.9, Gabapentin USP are compared in table 3.10, copovidone NF/EP are compared in table 3.11, Fenofibrate EP/BP are compared in table 3.12 and croscarmellose sodium NF/EP are compared in table 3.13 for the current and alternate sources of each material. The two materials can be described as being comparable if the requirements of the C of A met the predetermined specifications; however, it is worth noting that

the requirements of the C of A can and is often different for the two sources. If the C of A results were determined to be comparable for the two different sources of material, then there will be a need to test beyond the C of A to further determine if the materials are truly comparable. There were two requirements to determined additional testing requirements; the first is if the test is required in the current source C of A but not in the alternate source C of A or if the test is required in the alternate source C of A but not in the current source C of A, then the test will be performed. This was limited to particle size, bulk density, tapped density, specific surface area, surface weighted mean diameter and volume weighted mean diameter. The tests beyond the C of A included X-Ray Diffraction, Differential Scanning Calorimetric (DSC), Thermogravimetric Analysis (TGA), Image analysis, Fourier Transform Infra-Red (FTIR), Scanning Electron Microscope (SEM) and Brunauer, Emmett and Teller Surface Area (BET). With the exception of X-Ray Diffraction that was a requirement for the alternate source of metformin HCl, none of these tests were required on any of the other C of As.

There is no one tests beyond the C of A that can determine the equivalency of the two sources of material and as a result the tests listed above were performed. These test were selected based on the knowledge that they, either individually or in combination with others, can be used to differentiate between the same material from two different sources. The X-ray diffraction can be used to determine if there is any difference in the polymorphic form of the same APIs from different sources. The SEM can be used to determine if there are any morphological differences between the same excipients from different sources. The impact of these properties on the drug product and manufacturing process are discussed in chapter 1.

In addition to the C of A testing, the following additional analyses were performed for **each** source of **each** ingredient: image analysis, particle size by laser diffraction, specific surface

area, surface weighted mean diameter, volume weighted mean diameter and DSC. Powder X-Ray diffraction was performed on the three API's, and TGA and SEM analysis was performed on the two excipients. In addition, for metformin HCl USP *only*, FT-IR spectroscopic characterization, BET surface area and TGA were also performed.

A brief description of each test is described below[96]:

1. Powder X-Ray Diffraction (USP <776>) – approximately 1 gram of sample was weighted and grinded. The sample was then loaded into a standard sample holder and placed in PANalytical X-Ray diffraction system with a data collector.
2. Differential Scanning Calorimetric (USP <891>) – approximately 100mg of sample was weighed onto a tared zero aluminium pan and covered with the lid. The sample was loaded into a TA Instruments Q2000 differential scanning calorimetric unit and thermally equilibrated at 25°C. The sample was then heated to 180°C at a rate of 10°C/min; all activities were carried out under a nitrogen purge.
3. Thermogravimetric Analysis (USP <891>) – approximately 100mg of sample was weighed onto a platinum pan, with the precise weight recorded on the thermogram. The sample was loaded into a TA Instruments Q500 thermogravimetric analyzer and heated from room temperature to 200°C at a rate of 10°C/min, using the dynamic high resolution mode. All activities were carried out under a nitrogen purge.
4. Image analysis (USP <776>) – a small sample was spread onto a glass slide and mixed with a drop of 0.2% lecithin in mineral oil with a cover slip on top. The sample was then examined under polarized light using an Olympus BX61 microscope.
5. Scanning electron microscope (USP <776>) – a small sample was mounted onto and scanning electron microscope stub using carbon conductive tape. The sample was then

analyze using a Hitachi TM-3000 microscope under accelerating voltages of 15 Kilo Volts and charged up reduced mode.

6. Particle size by laser diffraction, specific surface area, surface weighted mean diameter and volume weighted mean diameter were all performed using the same method (USP <776>).

   The flow cell was installed and the dispersion unit connected onto the Malvern Mastersizer 2000 particle size analyser. A 0.04% lecithin in kerosene reagent was added to the dispersion unit until detected by the sensor. The system was set at 2500 rpm with no ultrasound and approximately 400mg of sample was added directly to the dispersion unit until the obscuration value reached between 5 - 20%. The sample was processed under "normal sensitivity" with the equivalent diameter distributions calculated on a volume percent and is reported as follows;

   D (v,0.1): - meaning that the volume at which 10% of the sample is under the target particle size equivalent diameter

   D (v,0.5): - meaning that the volume at which 50% of the sample is under the target particle size equivalent diameter

   D (v,0.9): - meaning that the volume at which 90% of the sample is under the target particle size equivalent diameter

   The target specification for each fraction, D (v,0.1), D (v,0.5) and D (v,0.9) is either NMT (not more than) or NLT (not less than) the target particle size equivalent diameter described in the individual specification for each material.

7. Fourier Transform Infra-Red (USP <851>) – a small sample was mixed and grounded with potassium bromide and made into a pellet by compressing the mixture under pressure. The

sample was loaded into a Perkin Elmer Spectrum 400 spectrometer and the spectrum was collected in transmittance mode.

8. Brunauer, Emmett and Teller Surface Area (USP <846>) – a sample of approximately 3 grams was weighed and loaded into a Micrometrics Gemini III 2375 surface area analyser. The sample was degassed under nitrogen at 40°C for 16 hours prior to testing using the multipoint measurement method.

Table 3.9: The C of A listing the test and specifications for each test for the current source, company A and alternate source, company B for metformin HCl USP

Test	Company A (Specifications)	Company B (Specifications)
Appearance	White, Crystalline powder	White, Crystalline powder
Identification	IR Spectrum: Corresponds to standard	IR Spectrum: Corresponds to standard
Identification	Positive for Chloride	Positive for Chloride
Loss on Drying	NMT 0.5%	NMT 0.5%
Sulphated Ash	NMT 0.1%	NMT 0.1%
Heavy Metals	NMT 10 ppm	NMT 10 ppm
Polymorphic Identity	N/A	X-ray diffraction: Corresponds to metformin HCl Form A standard
Appearance of solution	Clarity of Solution: Solution is clear Color of solution: Solution is Colorless	Clarity of Solution: Solution is clear Color of solution: Solution is Colorless
Organic Volatile Impurities	Methanol: NMT 1000 ppm Isopropanol: NMT 1000 ppm Methylene Chloride: NMT 600 ppm Chloroform: NMT 60 ppm Trichloroethylene: NMT 80 ppm N-Butanol – NMT 500 ppm 1,4-Dioxane: NMT 380 ppm	Methanol: NMT1000ppm
Residual Solvent	Trimethylamine: NMT 50 ppm	N/A
Related Compounds	MO RC1: NMT 0.02% MO RC2: NMT 0.05% MO RC3: NMT 0.1% Unidentified Impurity: NMT 0.10% each Total Impurity: NMT 0.6%	MT RC1: NMT 0.02% MT RC3: NMT 0.05% Unidentified Impurity: NMT 0.05% each Total Impurity (excluding MT RC3): NMT 0.2%
Assay	98.5 to 101.0% (dried basis)	98.5 to 101.0% (dried basis)
Bulk Density	0.6 to 0.9 g/cc	N/A
Particle Size (Sieve)	% Spl through #20 mesh: NLT 90% % Spl through #40 mesh: NLT 20% % Spl through #60 mesh: NLT 5%	N/A

N/A – Criteria not included in C of A and therefore not tested

Table 3.10: The C of A listing the test and specifications for each test for the current source, company X and alternate source, Company Y for gabapentin USP

Test	Company X (Specifications)	Company Y (Specifications)
Appearance	White to off-white powder	White to off-white powder
Identification	HPLC Retention Time: Corresponds to standard	HPLC Retention Time: Corresponds to standard
Identification	IR Spectrum: Corresponds to Standard	IR Spectrum: Corresponds to Standard
Identification	Polymorphic form III: NMT 5.0%	N/A
Assay	98.5 to 101.5% (Anhydrous basis)	98.0 to 102.0 % (Anhydrous basis)
Bulk Density	0.4 to 0.6 g/cc	0.40 to 0.66 g/cc
Tapped Density	0.6 to 1.0 g/cc	N/A
Heavy Metals	NMT 0.002%	NMT 0.002%
Limit of Chloride	NMT 0.01%	NMT 0.01%
Residual Solvent	Methanol: NMT 250 ppm Isopropanol: NMT 1000 ppm Toluene: NMT 100 ppm Acetone: NMT 100 ppm	Ethanol: NMT 0.2%
Particle Size	Percent smaller than 250 um: NLT 95% Percent smaller than 150 um: NLT 45%	N/A
pH	6.8 to 7.4	6.5 to 8.0
Related Compounds	GA RC2: NMT 0.05% Unidentified Impurity: NMT 0.05% each Total Impurities: NMT 0.30%	GA RC2: NMT 0.05% Unidentified Impurity: NMT 0.05% each
Related Compounds (Limit of late eluting impurities)	Any impurity: NMT 0.10% each	Any impurity: NMT 0.05% each
Total related Compounds	Total Impurities: NMT 0.5%	Total Impurities: NMT 0.5%
Residue on Ignition	NMT 0.1%	NMT 0.1%
Water	NMT 0.3%	NMT 0.5%

N/A – Criteria not included in C of A and therefore not tested

Table 3.11: The C of A listing the test and specifications for each test for the current process, copovidone NF/EP 35 and alternate process, copovidone NF/EP 20 for copovidone NF/EP

Test	Copovidone NF/EP 35 (Specifications)	Copovidone NF/EP 20 (Specifications)
Appearance	White or lightly yellowish powder	White or lightly yellowish powder
Identification	Corresponds to ID B (USP)	Corresponds to ID B (USP)
Identification	IR Spectrum: Corresponds to Standard	IR Spectrum: Corresponds to Standard
Appearance of Solution	Clarity: Sample solution is not more opalescent than reference suspension III Colour: Sample solution is not more intensely coloured than reference solution B5, R5, OR BY5	Clarity: Sample solution is not more opalescent than reference suspension III Colour: Sample solution is not more intensely coloured than reference solution B5, R5, OR BY5
Aldehydes	NMT 500 PPM(as acetaldehyde)	NMT 500 PPM(as acetaldehyde)
Ethenyl Acetate	35.3 to 41.4% (dried basis)	35.3 to 41.4% (dried basis)
Heavy Metals	NMT 20 ppm	NMT 20 ppm
Hydrazine	Any spot corresponding to salicylaldehydrazine in chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference standard (1 ppm)	Any spot corresponding to salicylaldehydrazine in chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference standard (1 ppm)
Impurity A	NMT 0.5%	NMT 0.5%
Loss on Drying	NMT 5.0%	NMT 5.0%
Monomers	NMT 0.1%	NMT 0.1%
Limit of Monomers	2-Pyrrolidone: NMT 0.5% Vinyl Acetate: NMT 0.001% 1-Vinyl-2-2Pyrrolidone: NMT 0.001%	2-Pyrrolidone: NMT 0.5% Vinyl Acetate: NMT 0.001% 1-Vinyl-2-2Pyrrolidone: NMT 0.001%
Nitrogen	7.0 to 8.0% (dried basis)	7.0 to 8.0% (dried basis)
Peroxides	NMT 0.35% (400PPM)	NMT 0.35% (400PPM)
Sulphated Ash	NMT 0.1%	NMT 0.1%
Viscosity (AS K-VALUE)	25.2 to 30.8% (dried basis)	25.2 to 30.8% (dried basis)
Particle Size	D (v,0.1): NLT 18um D (v,0.5): NMT 135um D (v,0.9): NMT 290um	D (v,0.1): NLT 18um D (v,0.5): NMT 135um D (v,0.9): NMT 290um

Table 3.12: The C of A listing the test and specifications for each test for the current source, Company J, and alternate source, Company K, for Fenofibrate EP/BP:

Test	Company J (Specifications)	Company K (Specifications)
Appearance	White to off white powder	White to off white powder
Identification	N/A	UV Spectrum: Corresponds to Standard
Identification	IR Spectrum: Corresponds to Standard	IR Spectrum: Corresponds to Standard
Melting Point	79 to 82 ^{o}C	79 to 82 ^{o}C
Halides (Expressed as Chloride)	NMT 100 ppm	NMT 100 ppm
Sulphates	NMT 100 ppm	NMT 100 ppm
Acidity	Volume of 0.1 M NaOH required NMT 0.2 mL	Volume of 0.1 M NaOH required NMT 0.2 mL
Loss on Drying	NMT 0.5%	NMT 0.5%
Sulphated Ash	NMT 0.1%	NMT 0.1%
Heavy Metals	0.002%	0.002%
Residual Solvents	Isopropanol: NMT 2000 ppm	Acetone: NMT 1000 ppm Isopropanol: NMT 2000 ppm Chloroform: NMT 60 ppm Toluene: NMT 890 ppm Butyl acetate: NMT 1000ppm
Related Compounds	FF RC1: NMT 0.1% FF RC2: NMT 0.1% FF RC4: NMT 0.2% FF RC5: NMT 0.10% FF RC6: NMT 0.10% FF RC7: NMT 0.10% FF RC8: NMT 0.10% Unidentified Impurity: NMT 0.10% each Total Impurities: NMT 0.5%	FF RC2: NMT 0.1% FF RC1: NMT 0.1% EP Imp. C: NMT 0.10% EP Imp. D: NMT 0.10% EP Imp. E: NMT 0.10% EP Imp. F: NMT 0.10% FF RC4: NMT 0.2% Unidentified Impurity: NMT 0.10% each Total Impurities: NMT 0.5%
Assay	98.0% to 102.0% (dried basis)	98.5% to 101.0% (dried basis)
Appearance of Solution	Solution is clear and not more intensely colored than reference solution BY6	Solution is clear and not more intensely colored than reference solution BY6
Bulk Density	0.50 to 0.70 g/cc	0.50 to 0.70 g/cc

N/A – Criteria not included in C of A and therefore not tested

Table 3.13: The C of A listing the test and specifications for each test for the current source, Company G, and alternate source, Company H, for croscarmellose sodium NF/EP:

Test	Company G (Specifications)	Company H (Specifications)
Appearance	White or greyish-white, free-flowing powder	White or greyish-white powder
Identification	Reaction with Methylene Blue: Sample absorbs methylene blue Appearance of solution after settling: A blue fibrous mass is formed	The sample absorbs the methylene blue and settles as a blue, fibrous mass
Identification	Corresponds to ID B. A reddish-violet Colour develops at the interface upon reaction with 1-Napthol TS	A reddish – violet Colour develops at the interface
Identification	Positive test for sodium	Positive to tests for sodium
Identification	Positive to flame test for sodium	N/A
Heavy Metals	NMT 20 ppm	NMT 10 ppm
Sulphated Ash	14.0 to 28.0% (dried basis)	14.0 to 28.0%
Microbial Limits	E.Coli: Absent in 1g Total Aerobic Microbial Count: NMT 1000 cfu/g Total Yeast and Mould Count: NMT 100 cfu/g	E.Coli: Absent in 1g Total Aerobic Microbial Count: NMT 1000 cfu/g Total Yeast and Mould Count: NMT 100 cfu/g
Particle Size	D (v,0.5): NM 60um D (v,0.9): NMT 155 UM	N/A
pH	N/A	5.0 to 7.0
Degree of Substitution	N/A	0.60 to 0.85 (dried basis)
Sodium Chloride & Sodium Glycolate	N/A	NMT 0.5% (dried basis)
Water Soluble substances	N/A	NMT 10.0%
Loss on Drying	N/A	NMT 10.0%
Settling Volume	10 – 30ml (From Manufacturer's C of A)	10.0 to 30.0 mL

N/A – Criteria not included in C of A and therefore not tested

3.5 - The Tablet Manufacturing Process

Metformin tablets (batches 1 and 2) were manufactured by direct compression manufacturing process. The process flow diagram is presented in figure 3.1. The tablets were stored in high density polyethylene bottles until testing. The required amount of metformin HCl USP, methylcellulose USP A15LV, microcrystalline cellulose NF M102, polyethylene glycol NF 8000, colloidal silicon dioxide NF and magnesium stearate NF were accurately weighed (Mettler Toledo, model XS204 and XS32001L). The metformin HCl USP, methylcellulose USP A15LV, microcrystalline cellulose NF M102 and colloidal silicon dioxide NF were screened using a Quadro Comil (Quadro Engineering, model 196) fitted with a 0.075" screen. The screened powders were then transferred to a 2.2 cu. ft. tumbler bin (Inox Industries, model IN-2.2) and mixed using a bin mixer (Servo – Lift, model PBL-600-H-FC-GP-575) for 24.5 minutes. The polyethylene glycol NF 8000 and magnesium stearate NF were hand screened through a 0.032" screen, added to the 2.2 cu. ft. tumbler bin and then mixed for an additional 1.5 minutes. The powder mix was then compressed into tablets using the instrumented tablet press (Korsch AG, model PH300 single sided). The tablet punch was 0.3125" x 0.6145" capsule shaped and standard cup in dimensions.

Gabapentin USP tablets (batches 3 –6) were manufactured by a compaction process. The process flow diagram is presented in figure 3.2. The tablets were stored in high density polyethylene bottles until testing. The required amount of gabapentin USP, copovidone NF/EP and magnesium stearate NF were accurately weighed. The gabapentin USP and copovidone NF/EP were screened using a Quadro comil fitted with a 0.045" screen. The screened powders were then transferred to a 2.2 cu. ft. tumbler bin and mixed for 10 minutes. The powder mix was then compacted into granules using the instrumented Gerteis compactor (Gerteis Maschinen +

Process Engineering AG, model Macro-Pactor 250/100/3) at targeted settings. The compacted granules were then transferred to a 2.2 cu. ft. tumbler bin. The magnesium stearate NF was hand screened through a 0.024" screen, added to the 2.2 cu. ft. Tumbler bin containing the compacted granules and then mixed for 3 minutes. The compacted granule mix was then compressed into tablets using the instrumented tablet press. The tablet punch was 0.3440" x 0.6875" modified concave, oval shape in dimensions.

Fenofibrate EP/BP tablets (batches 7 –10) were manufacture by a hot melt technology process. The process flow diagram is presented in figure 3.3. The tablets were stored in high density polyethylene bottles until testing. The required amount of Fenofibrate EP/BP and croscarmellose sodium NF/EP were accurately weighed. The Fenofibrate EP/BP was loaded into a 30 L stainless steel vessel and heated using a hot plate (Cimarec, model HP131535) to 100^{o}C until melted. The croscarmellose sodium NF/EP was then slowly added while mixing (Lightnin, model XIP25/XJ43) until a smooth, lump free suspension was formed. The suspension was poured into high density polyethylene containers to cool and solidify for at least 12 hours. The solid material was pulverized using a granumil (Fluid Air Inc., model GUM) fitted with a 0.625" screen. The material that went through the 0.625" screen was again pulverized using a granumil fitted with a 0.109" screen. The screened powders were then transferred to a 2.2 cu. ft. tumbler bin and mixed for 5 minutes. The milled granule mix was then compressed into tablets using the instrumented tablet press. The tablet punch was 0.2620" x 0.5020" modified oval, concave shape in dimensions.

3.6 - Processing tests

3.6.1 - Sieve Analysis

The sieve profile was obtained by weighting five grams of material and placing it on the top, #20 mesh screen, of a Gilsonic Autosiever (Gilson Company Inc., model GA-6). In addition to the #20 mesh screen the #40, #60, #80, #100, #200 and a fines screen collector were used. The autosiever tapped the material for 5 minutes. The material retained on each screen was weighed and reported as a percentage of the total initial weight (five grams) of the material. This was completed once for all batches at the final blend stage, while two additional samples were tested for batches 3 –10, during either the granulation stage (batches 3 –6) or the milling stage (batches 7 –10) at the beginning and end of their respective processes.

3.6.2 - Flow Index

In the pharmaceutical industry most powders are blended in bins and then flow through a discharge chute at the bottom of the bin to supply material to the tableting or capsule-filling machines. As a result, the ability of the material to flow through an orifice is of great value. This is also of value because of the need to deliver material to the die cavity of the tableting or capsule-filling machines to form a tablet or capsule, which is usually in the milligram range and rarely exceeds 1 gram. As a result a different approach is used to determine the flow of material to predict its ability to flow from the bin. This is done by using a Hanson Flodex Test Instrument, which utilizes a flow measurement disk at the bottom of a cylindrical container with an orifice at the centre of the disk ranging from 4 mm – 34 mm (figure 3.4)[97]. The materials ability to flow through a smaller orifices means that it has better flow properties.

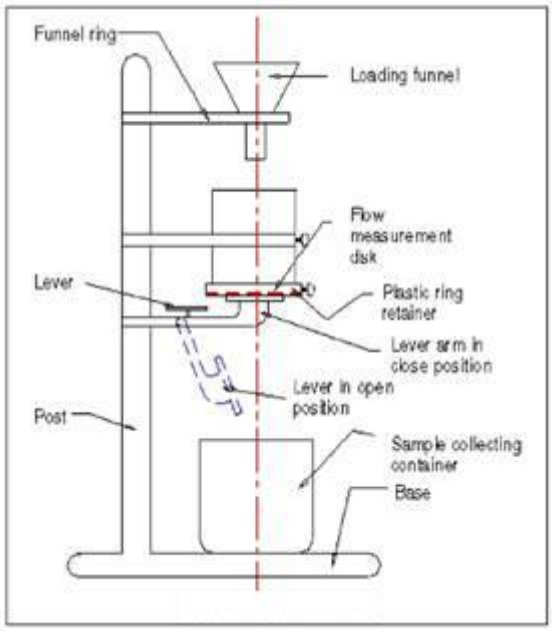


Figure 3.4: The Hanson Flodex Test Instrument used in the determination of blend powder flow properties for the three formulations[97].

The flow index was determined by weighing 100 grams of material and placing it in the flodex (Hansen Research, model 21-101-050) containing a disk with different orifices ranging from 4 mm to 34 mm. The orifice at which the material flows freely through was reported as the flow index. This was completed once for all batches at the final blend stage, while two additional samples were tested for batches 3 –10, during either the granulation stage (batches 3 –6) or the milling stage (batches 7 –10) at the beginning and end of their respective processes.

3.6.3 - Bulk Density

The bulk density is measured by pouring 100 mL of powder into a 100 mL graduated cylinder. The net weight is then recorded and the density was determined by dividing the weight by the volume (100 mL). This was completed once for all batches at the final blend stage, while two additional samples were tested for batches 3 –10, during either the granulation stage (batches 3 –6) or the milling stage (batches 7 –10) at the beginning and end of their respective processes.

3.6.4 - Tapped Density

The tapped density is measured by taking the graduated cylinder filled with powder from the bulk density testing and tapping it 100 times using a tap density tester (Vankel, model 50-12000). The final volume is recorded and the tapped density is determined by dividing the net weight from the bulk density testing by the final volume after the tapping. This was completed once for all batches at the final blend stage, while two additional samples were tested for batches 3 –10, during either the granulation stage (batches 3 –6) or the milling stage (batches 7 –10) at the beginning and end of their respective processes.

3.6.5 – Hausner ratio and Carr Index

The Hausner ratio is a measure of the ratio of the tapped bulk density over the poured bulk density calculated according to Equation 3.1. The Hausner Ratio can vary from approximately 1.2 to 1.6 with the powder becoming more cohesive and therefore less free flowing as the number increases. The Carr Index or compressibility index is the percentage of the tapped bulk density minus the poured bulk density divided by the poured bulk density and calculated according to Equation 3.2. The Carr Index Classification and Powder Flowability are described in table 3.14[53].

$$Hausner\ Ratio = \frac{tapped\ density}{poured\ density} \qquad \text{(Equation 3.1)}$$

$$Carr\ Index = \frac{tapped\ density - poured\ density}{poured\ density} \text{ X } 100 \qquad \text{(Equation 3.2)}$$

Table 3.14: Carr Index Classification and Powder Flowability used to theoretically characterize the APIs, Excipients and the blends of the 10 batches executed

Carr Index (%)	Powder Flowability
5 – 12	Free flowing
12 – 16	Good
18 - 21	Fair
23 - 35	Poor
33 - 38	Very poor
40	Extremely poor

3.7 - Critical Quality Attribute testing

3.7.1 - Tablet Weight

Ten (10) tablets from the start, 20%, 40%, 60%, 80% completion and end of each batch were individually weighed in milligrams (mg) on an analytical balance. The minimum weight, maximum weight, average weight, standard deviation (STDEV) and Coefficient of Variation (CV) was reported. Additional samples were tested for some of the batches at the start of the compression runs due to the fact that the CQAs were not met at the compression force that was initially targeted.

3.7.2 - Tablet Thickness

The thickness in inches (ins) were measured individually for 10 pre-weighed tablets from the start, 20%, 40%, 60%, 80% completion and end of each batches by using a hand held thickness gauge (Mitutoyo, model 547-300). The minimum thickness, maximum thickness, average thickness, STDEV and CV were reported.

3.7.3 - Tablet Hardness

The hardness in kilopound (kp) were measured individually for 10 pre-weighed tablets from the start, 20%, 40%, 60%, 80% completion and end of each batch by using a hardness tester

(Pharmatron, model 6D). The minimum hardness, maximum hardness, average hardness, STDEV and CV were reported.

3.7.4 - Tablet Friability

The friability was measured from the start, 20%, 40%, 60%, 80 % completion and end of each batch by weighing 10 tablets or approximately 6.5 grams and rotating the tablets in a friabilator (Vankel, model Friabilator and Sotax, model F1) at 25 Revolutions Per Minute for four minutes and twenty minutes respectively. The loss of weight was recorded as a percentage of the total initial weight at four minutes and then at twenty minutes.

3.7.5 - Tablet Disintegration

The disintegration was measured from the start, 20%, 40%, 60%, 80% completion and end of each batch by placing six tablets in the disintegration apparatus (Vankel, model Disintegration). The minimum time was recorded as the first tablet to completely disintegrate into granules and pass through a disk with an aperture of 1.8mm – 2.2mm and the maximum time was when the last tablet completely disintegrated and passed through a disk with an aperture of 1.8mm – 2.2mm.

3.8 – Drug product performance testing

3.8.1 - Uniformity of dosage unit

The dosage uniformity was assessed according to the USP requirements <USP 905> where the acceptable value for stage one testing is < 15.0%[96]. A composite sample was prepared by taking ten tablets from the start, 20%, 40%, 60%, 80% completion and end of each batch. The metformin HCl, gabapentin USP and fenofibrate EP/BP were tested by accurately weighing ten tablets randomly selected from the composite sample of each batch. The uniformity was then calculated using the following equation:

$$\%\ of\ claim = \frac{Weight\ of\ individual\ tablet\ x\ Assay\ results\ (\%)}{Average\ weight\ of\ 10\ tablets} \quad \text{(Equation 3.3)}$$

The Acceptable Value is calculated using the following equation:

$$Acceptable\ Value = \ |M - \bar{X}| + ks \quad \text{(Equation 3.4)}$$

Where;
M = Target value (100%)
$\bar{X}$ = Mean of individual content
k = Acceptable constant (2.4)
s = Sample STDEV

The Acceptable Value is based on the sum of two components, the first being how much difference there is between the target value (M) and the process mean ($\bar{X}$) which is $|M - \bar{X}|$.The second is the variability in the number of units tested which is calculated by multiplying the Acceptable constant k (2.4 for 10 tablets) with the STDEV of the 10 samples tested.

3.8.2 - Assay of API content in tablets

The assays of the API content in the tablets were assessed according to the USP requirements <USP 905> where the acceptance criterion for stage one testing is an average of 90% - 110% for the API present in 20 tablets[96]. The metformin HCl, gabapentin USP and fenofibrate EP/BP tablets were tested using their respective High Pressure Liquid Chromatography (HPLC) methods for assay. A composite sample was prepared by taking ten tablets from the start, 20%, 40%, 60%, 80% completion and end of each batch, twenty tablets from the composite sample was randomly selected and tested for assay of the API content.

Metformin Hydrochloride Tablets:

The mobile phase was 95% of phosphate buffer with a pH of 3.00 ± 0.05 and 5% of acetonitrile. The chromatographic conditions are listed in table 3.15. Twenty tablets were accurately weighed to determine the average weight. The tablets were grounded into a fine

powder and 200mg was weighed and transferred to a volumetric flask containing the mobile phase, used as the sample solvent. The solution was diluted to 0.1 mg/mL of metformin HCl. The standard was prepared by accurately weighing out 50mg of metformin HCl reference standard, transferred to a volumetric flask containing the sample solvent and diluted to 0.1 mg/mL. Sample solvent was injected to ensure the system is stable, follow by five calibrated standard injections, sample injections and one standard injection at the end.

Table 3.15: The chromatographic conditions for the HPLC equipment used to test for the assay of the API in the metformin HCl tablets

Parameter	**Specification**
Column type	Symmetry C 18
Dimensions	4.6 x 50 mm
Particle size	3.5 µm
Column temperature	25°C
Detector wavelength	218 nm
Needle wash	Acetonitrile/Water (1:1)
Column wash	Acetonitrile/Water (1:1)
Filter	Pall Acrodisc nylon 0.45 µm
Flow rate	1.0 mL/minute
Injection volume	10 µL
Total run time	5 minutes
Post run time	Off
Retention time	2.3 minutes
Trailing factor	NMT: 2.0
Column efficiency	NLT: 1000

Gabapentin USP Tablets:

The mobile phase was 94% of Phosphate buffer with pH of 6.90 ± 0.1 and 6% of Acetonitrile. The chromatographic conditions are listed in table 3.16.

Table 3.16: The chromatographic conditions for the HPLC equipment used to test for the assay of the API in the gabapentin USP tablets

Parameter	**Specification**
Column type	Waters Xbridge C 18
Dimensions	4.6mm x 25 cm
Particle size	5 µm
Column temperature	Ambient
Detector wavelength	210 nm
Needle wash	Acetonitrile/Water (3:47)
Column wash	Acetonitrile/Water (3:47)
Flow rate	1.2 mL/minute
Filter	Pall Acrodisc nylon 0.45 µm
Injection volume	10 µL
Total run time	10 minutes
Post run time	Off
Retention time	7.0 minutes
Trailing factor	NMT: 2.0
Column efficiency	NLT: 7000

Twenty tablets were accurately weighed to determine the average weight. The tablets were grounded into a fine powder and 100mg was weighed and transferred to a volumetric flask containing the mobile phase, used as the sample solvent. The solution was diluted to 4 mg/mL of gabapentin USP. The standard was prepared by accurately weighing out 100mg of gabapentin USP reference standard, transferred to a volumetric flask containing the sample solvent and diluted to 4 mg/mL. Sample solvent was injected to ensure the system is stable, follow by five calibrated standard injections, sample injections and one standard injection at the end.

Fenofibrate EP/BP Tablets:

The mobile phase was 20% of phosphate buffer with a pH of 3.0 ± 0.5 and 80% of acetonitrile. The chromatographic conditions are listed in table 3.17

Table 3.17: The chromatographic conditions for the HPLC equipment used to test for the assay of the API in the fenofibrate EP/BP tablets

Parameter	**Specification**
Column type	Waters Delta Pak C 18
Dimensions	3.9 x 150 mm
Particle size	5 µm
Column temperature	Ambient
Detector wavelength	290 nm
Needle wash	Acetonitrile/Water (80:20)
Column wash	Acetonitrile/Water (80:20)
Filter	Pall Acrodisc nylon 0.45 µm
Flow rate	1.0 mL/minute
Injection volume	10 µL
Total run time	8 minutes
Post run time	Off
Retention time	2.5 minutes
Trailing factor	NMT: 2
Column efficiency	NLT: 2000

Twenty tablets were accurately weighed to determine the average weight. The tablets were grounded into a fine powder and 50mg was weighed and transferred to a volumetric flask containing the mobile phase, used as the sample solvent. The solution was diluted to 0.05 mg/mL of fenofibrate EP/BP. The standard was prepared by accurately weighing out 50mg of fenofibrate EP/BP reference standard, transferred to a volumetric flask containing the sample solvent and diluted to 0.05 mg/mL. Sample solvent was injected to ensure the system is stable, follow by five calibrated standard injections, sample injections and one standard injection at the end.

3.8.3 - Dissolution

The in-vitro drug release was performed for the manufactured tablets as per the drug product dissolution procedure using an automated dissolution system (Distek, model 2100A/2100B/2100C). The metformin HCl tablets, gabapentin USP tablets and fenofibrate EP/BP tablets were analyzed using Ultraviolet spectrophotometer. A composite sample was

prepared by taking ten tablets from the start, 20%, 40%, 60%, 80% completion and end of each batch. Six tablets were randomly selected from the composite sample of each batch and tested for dissolution. Any failure in the dissolution test will lead to a failure in the qualification of the alternate source of the material as it is the most critical test to determining equivalency of not only two sources of material but between any two drug product batches.

Metformin Hydrochloride tablets:

The dissolution medium was 1000 mL of 0.68% phosphate buffer prepared using potassium phosphate monobasic, pH was maintained using 1 N sodium hydroxide. The standard solution was prepared by accurately weighing 20mg of metformin HCl USP reference standard and diluting to a concentration of 0.01 mg/mL using the dissolution medium as the solvent. Each of the dissolution vessels were filled with 1000 mL of dissolution medium and allow to stand until the temperature stabilized, the operational parameters are listed in table 3.18. One tablet each was placed in each of the six dissolution vessels, the apparatus was immediately started with a stirring speed of 100 rpm. 10 mL was withdrawn at the specified time points for analysis. The sample solution was prepared by transferring 4.0 mL of filtered sample into a 200 mL volumetric flask and dilute to volume using the dissolution medium. The UV spectrophotometer was zeroed with dissolution medium, the absorbance of standard solution was read; follow by sample solution and by standard solution at the end.

Table 3.18: The operational parameters for the dissolution apparatus used for the metformin HCl tablets dissolution test

Parameter	**Specification**
pH	6.8 ± 0.05
Apparatus	USP 1 with baskets
Stirring speed	100 rpm
Time points	10, 15, 20, 30, 45, 60 minutes
Detector wavelength	234 nm
Stationary Cell	1.0 cm
Temperature	37.0 ± 0.5°C
Filter	0.45 µm Nylon

Gabapentin USP tablets:

The dissolution medium was 900 mL of 0.06N Hydrochloric acid prepared by adding 30 mL of hydrochloric acid to 6000 mL of purified water. Each of the dissolution vessels were filled with 900 mL of dissolution medium and allow to stand until the temperature stabilized, the operational parameters are listed in table 3.19. One tablet each was placed in each of the six dissolution vessels, the apparatus was immediately started with a stirring speed of 50 rpm. 3 mL was withdrawn at the specified time points for analysis.

Table 3.19: The operational parameters for the dissolution apparatus used for the gabapentin USP tablets dissolution test

Parameter	**Specification**
Apparatus	USP II with paddles
Stirring speed	50 rpm
Time points	5, 10, 15, 30, 45, 60 minutes
Stationary Cell	1.0 cm
Temperature	37.0 ± 0.5°C
Filter	0.45 µm Nylon

The mobile phase was 94% of Phosphate buffer with pH of 6.90 ± 0.1 and 6% of Acetonitrile. The chromatographic conditions are listed in table 3.16.

The standard was prepared by accurately weighing out 110 mg of gabapentin USP reference standard, transferred to a volumetric flask containing the sample solvent and diluted to 660 mg/mL. Dissolution medium was injected to ensure the system is stable, follow by five calibrated standard injections, sample injections and five standard injections at the end.

Fenofibrate EP/BP tablets:

The dissolution medium was 900 of 0.1N sodium lauryl sulphate prepared by dissolving 173.0 grams of sodium lauryl sulphate in 6,000 mL of purified water. The standard solution was prepared by accurately weighing 55 mg of fenofibrate EP/BP reference standard and diluting to a concentration of 0.018 mg/mL using a dissolution medium as the solvent.

Table 3.20: The operational parameters for the dissolution apparatus used for the fenofibrate EP/BP tablets dissolution test

Parameter	**Specification**
Apparatus	USP II with paddles
Stirring speed	100 rpm
Time points	5, 10, 15, 30, 45, 60 minutes
Detector wavelength	290 nm
Stationary Cell	1.0 cm
Temperature	37.0 ± 0.5°C
Filter	0.45 µm Nylon

Each of the dissolution vessels were filled with 900 mL of dissolution medium and allow to stand until the temperature stabilized, the operational parameters are listed in table 3.20. One tablet each was placed in each of the six dissolution vessels, the apparatus was immediately started with a stirring speed of 100 rpm. 10 mL was withdrawn at the specified time points for analysis. The sample solution was prepared by transferring 2.0 mL of filtered sample into a 25 mL volumetric flask and dilute to volume using the dissolution medium. The UV

spectrophotometer was zeroed with dissolution medium, the absorbance of standard solution was read; follow by sample solution and by standard solution at the end.

3.9 – Statistical evaluation

A *two tailed t-test* with a critical *p* (probability) value of 0.05 will be performed to evaluate if there is any significant difference with two different set of test results from two different sources of the API and Excipient (specific objective 2, section 2.4). The evaluation will be completed on the 5 pairs of materials listed in table 3.1 by comparing current source of material with the alternate source of material. For the purpose of this evaluation a minimum of three batches will be tested for each source of material and therefore at least three data point will be available for each test. The *p* value represents the probability that the two sets of results are from the same population (i.e. there is no actual difference between the means of the two sets). The probability *p* is derived based on the *t* value under the *t* distribution with the specific degree of freedom. The *t value* is the ratio of the difference in the average of the two sets of data and the combination of the STDEV and the sample size of the same two data sets. The degree of freedom is the total number of samples from both sources minus two, which represents the two means from the two sets of test results.

The significance level was set at 0.05, meaning that any *p* value less than 0.05 is indicative that probability that the two sets are from the same population is less than 5%; that is, the chance that there is no difference on their test results is 5% or less. This means the difference observed is true with a 95% confidence level. The *two tailed t-test* will be used to evaluate differences between the two sources of materials in the unit operations, CQAs, and drug product performance, if required (specific objectives 4 and 5).

3.10 – List of equipment used during the manufacturing and testing of the tablets

A list of all equipment used in the execution and testing of these ten batches is listed in table 3.21 and 3.21a.

Table 3.21: List of the equipment used during the testing of the raw materials used, manufacture of the tablets and testing of the tablets; with the equipment manufacturer name and the equipment model number:

DESCRIPTION	MANUFACTURER	MODEL NUMBER
Quadro comil	Quadro Engineering	Model 196
Tablet press	Korsch AG	PH300 Single Sided
Compactor	Gerteis Maschinen + Process Engineering AG	MACRO-PACTOR 250/100/3
Granumil	Fluid Air INC.	GUM
Mixer	Lightnin	X1P25/XJ43
Balance - LAB 200g	Mettler Toledo	XS204
Balance - 32100 G.	Mettler Toledo	XS32001L
Gauge-Thickness-Mitutoyo	Mitutoyo	547-300
Tester-Hardness-6D	Pharmatron	6D
Tester-Friability-Vankel	Vankel	FRIABILATOR
Tester-Friability-Sotax	Sotax	F1
Tester-Flowability-Flodex	Hanson Research	21-101-050
Sieve-Shaker-Gilsonic	Gilson Company INC.	GA-6
Tester-Density-Tap-Vankel	Vankel	50-1200
Sieve-Shaker-Rotap	Tyler	RX-29
Mini Bin-2.2 Cu Ft	INOX Industries	IN-2.2
Tester-Disintegration-Vankel	Vankel	DISINTEGRATION
Disintegration Apparatus	Hanson Research	39-400-460
Hot Plate-Cimarec	Cimarec	HP131535
Blender-Mini Bin	Servo-Lift	PBL-600-H-FC-GP-575
Kit-Test Weight	Mettler Toledo	CLASS F
Particle Size Analyzer	Malvern	MASTERSIZER2000
Surface Area Analyzer	Micrometrics	GEMINI III 2375
Polarized Microscope	Olympus	BX60/BX61
Stereomicroscope	Olympus	SZX12
Scanning Electron Microscope	Hitachi	TM3000

Table 3.21a: List of the equipment used during the testing of the raw materials used, manufacture of the tablets and testing of the tablets; with the equipment manufacturer name and the equipment model number:

FT-IR Microscope	Perkin Elmer	PARAGON1000PC/ SPECTRUN 400
Differential Scanning Calorimetry	TA Instruments	Q2000
Thermo Gravimetric Analyzer	TA Instruments	Q500
X - Ray Diffraction System	PanAnalytical L INC.	PW3040/60
Balance – Lab	Mettler Toledo	AX205/AG285/ PB211D/XP603S/ MX5/XP2U/XP56
Balance – Lab	Sartorius	BP211D
HPLC system	Agilent	1200/1201/1202 INFINITY SERIES
Dissolution System	Distek	2100A/2100B/2100C
pH Meter – Lab	Fisher Scientific	AR20
Purified Water System	Millipore	ADVANTAGE A10
Purified Water System	Thermo Scientific	7148
Timer – Lab	VWR	62344-641
Rotameter – Lab	Praxair	MS4-LRB-1/4-D5
Thermocouple - Lab	VWR	61220-601
Oven – Lab	Sheldon Manufacturing Inc.	1410M
IR Spectrophotometer	Perkin Elmer	SPECTRUM TWO

Chapter – 4: Results and Discussion

All results for the API and Excipient in – process testing and analytical testing are summarized below, and tabulated (in detail) in the appendices of this thesis. Results will be discussed in the same pairings and batch numbers introduced in Chapter 3.

4.1 - Metformin HCl USP (batch 1, company A; and batch 2, company B)

4.1.1 - Metformin HCl C of A testing

The two APIs from the two sources were tested according to the requirements of the C of A for each source and the C of A requirements were met (see table 4.1 and 4.1a). As a result of meeting specifications, the materials from the two sources would be deemed equivalent. There were differences in the specifications for organic volatile impurities and related compounds. The C of As for four batches from each source of material was evaluated to determine if there were any differences within the sources of the material. There was no substantial variability in the results from the C of A within the four batches for each source of API (refer to table A1.1 in the appendices). A CV of 25% and 40% was seen with the loss on drying (LOD) results from company A and B respectively, however, with a limit of NMT 0.5% and results reported to one decimal figure this was predictable. A similarly high CV of 24% and 26% was seen with methanol from company A and B respectively.

A *two tailed t-tests* with a critical *p* (probability) value of 0.05 was performed to determine if there were any significant differences between the two sources of material. The LOD and methanol tests were shown to be significantly different between the two sources of material. The mean LOD for Company A was 0.375 % with a STDEV of 0.096 %, the mean LOD for Company B was 0.125 % with a STDEV of 0.050 % and t-test: t(6) = -4.63, p-value = 0.0036. The mean methanol for Company A was 48.500 ppm with a STDEV of 11.504 ppm, the

mean methanol for Company B was 276.000 ppm with a STDEV of 71.447 ppm and t-test: $t(6) = 6.287$, p-value = 0.0008.

Moisture is known to impact both the compaction and compression processes of powders and can also impact the flow properties and stability of the drug product[98, 99]. The significant difference observed in the moisture could be a contributing factor to the challenges observed with the compression of the blend using Company B material (as discussed in section 4.1.3 of this chapter).

Table 4.1: The C of A listing the tests, specifications and testing results for metformin HCl USP API from Company A and Company B used in batch 1 and batch 2 respectively.

Test	Specifications	Results (Company A)	Results (Company B)
Appearance	White, Crystalline powder	Conforms	Conforms
Identification	IR Spectrum: Corresponds to standard	Conforms	Conforms
Identification	Positive for Chloride	Conforms	Conforms
Loss on Drying	NMT 0.5%	0.3%	0.2%
Sulphated Ash	NMT 0.1%	0.0%	0.0%
Heavy Metals	NMT 10 ppm	Less than 10 ppm	Less than 10
Polymorphic Identity	X-ray diffraction: Corresponds to metformin Form A standard	N/A	Conforms
Appearance of solution	Clarity of Solution: Solution is clear Color of solution: Solution is Colorless	Conforms Conforms	Conforms Conforms
Organic Volatile Impurities	Methanol: NMT 1000 ppm Isopropanol: NMT 1000 ppm Methylene Chloride: NMT 600 ppm Chloroform: NMT 60 ppm Trichloroethylene: NMT 80 ppm N-Butanol – NMT 500 ppm 1,4-Dioxane: NMT 380 ppm	61 ppm ND ND ND ND ND ND	238 ppm N/A N/A N/A N/A N/A N/A
Residual Solvent	Trimethylamine: NMT 50 ppm	13 ppm	N/A
Related Compounds	MO RC1: NMT 0.02% MO RC2: NMT 0.05% Unidentified Impurity: NMT 0.10% each Total Impurity: NMT 0.5% MO RC3: NMT 0.1% Total Impurity: NMT 0.6%	BRT BRT BRT BRT BRT BRT	N/A N/A N/A N/A N/A N/A

N/A – Criteria not included in C of A and therefore not tested

Table 4.1a: The C of A listing the tests, specifications and testing results for metformin HCl USP API from Company A and Company B used in batch 1 and batch 2 respectively.

Test	Specifications	Results (Company A)	Results (Company B)
Related Compounds	MT RC1: NMT 0.02% Unidentified Impurity: NMT 0.05% each Total Impurity: NMT 0.2% MT RC3: NMT 0.05%	N/A N/A N/A N/A	BRT BRT BRT ND
Assay of API	98.5 to 101.0% (dried basis)	99.9%	100.3%
Bulk Density	0.6 to 0.9 g/cc	0.7 g/cc	N/A
Particle Size (Sieve)	% through #20 mesh: NLT 90% % through #40 mesh: NLT 20% % through #60 mesh: NLT 5%	100% 85% 54%	N/A

N/A – Criteria not included in C of A and therefore not tested

Acronyms used in table 4.1 and 4.1a:
BRT – Below reporting threshold
IR – Infrared
MO RC – Metformin HCl related compound
MT RC – Metformin HCl related compound
ND – None detected
NLT – Not less than
NMT – Not more than
ppm – Parts per million

4.1.2 – Additional testing for metformin HCl

The additional tests performed were particle size, specific surface area, surface weighted mean diameter, volume weighted mean, bulk density, tapped density, FT-IR (Microscope), DSC, TGA, image analysis and powder X-Ray diffraction.

The C of A for material supplied by Company A has a requirement for bulk density and particle size while the C of A for material supplied by Company B does not; however both were tested for, bulk density, tapped density and particle size as a means of comparison. There were measurable differences in the results obtained for the bulk density, tapped density and the particle

size, with all of these properties being larger for the metformin HCl supplied by Company A (see table A1.2 in the appendices). The metformin HCl supplied by Company A also had higher specific surface area and volume weighted mean diameter while surfaced weighted mean diameter was substantially lower. The material supplied by Company A not only had a larger particle size, but also had a higher variation in sizes, ranging from 2 μm to 1000 μm, while material from Company B ranged in size from 10 μm to 900 μm, (see table A1.2 in the appendices). Image analysis was one of the tests completed that was not part of the C of A for either source; the images in figure 4.1 A and 4.1 B clearly indicate differences in the crystal shape and particle size of the two materials. The material supplied by Company A was more prismatic or bipyramid while material supplied by Company B was more acicular or needle like. While there was a significant difference in shape observed from the image analysis, the X-Ray diffraction pattern of the metformin HCl from Company A and Company B in figure 4.2, compare excellently to the reference profile for metformin HCl (crystal form A) and indicates that there were no other polymorphs present. The DSC thermograms (see figures A1.2 and A1.3 in the appendices) indicate that the phase transition for metformin HCl occurred at approximately the same temperature (232.7^{o}C and 231.9^{o}C for material from Company A or Company B, respectively) and over a similar temperature range (2.25°C and 1.4°C for material from Company A and Company B, respectively) indicting the similarities in the two materials. The TGA (see figures A1.4 and A1.5 in the appendices) indicates no difference in the physical and chemical properties of the material while the FT-IR (see figure A1.1 in the appendices) showed similar infrared absorption patterns.

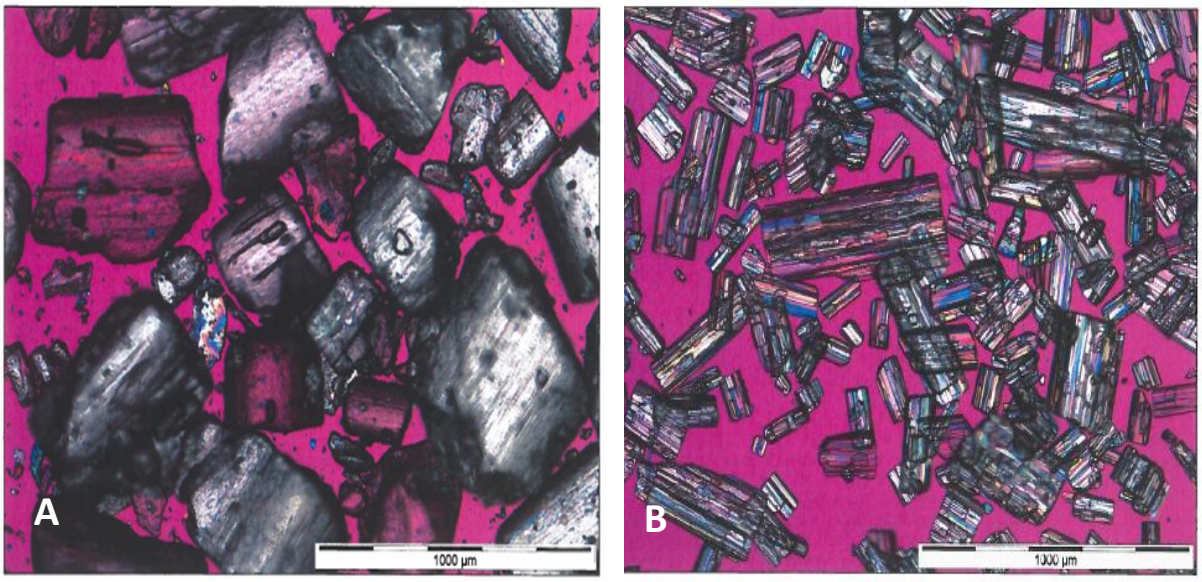


Figure 4.1: Image analysis for metformin HCl USP from Company A (A) and Company B (B). The differences in both particle size and shape are clearly evident.

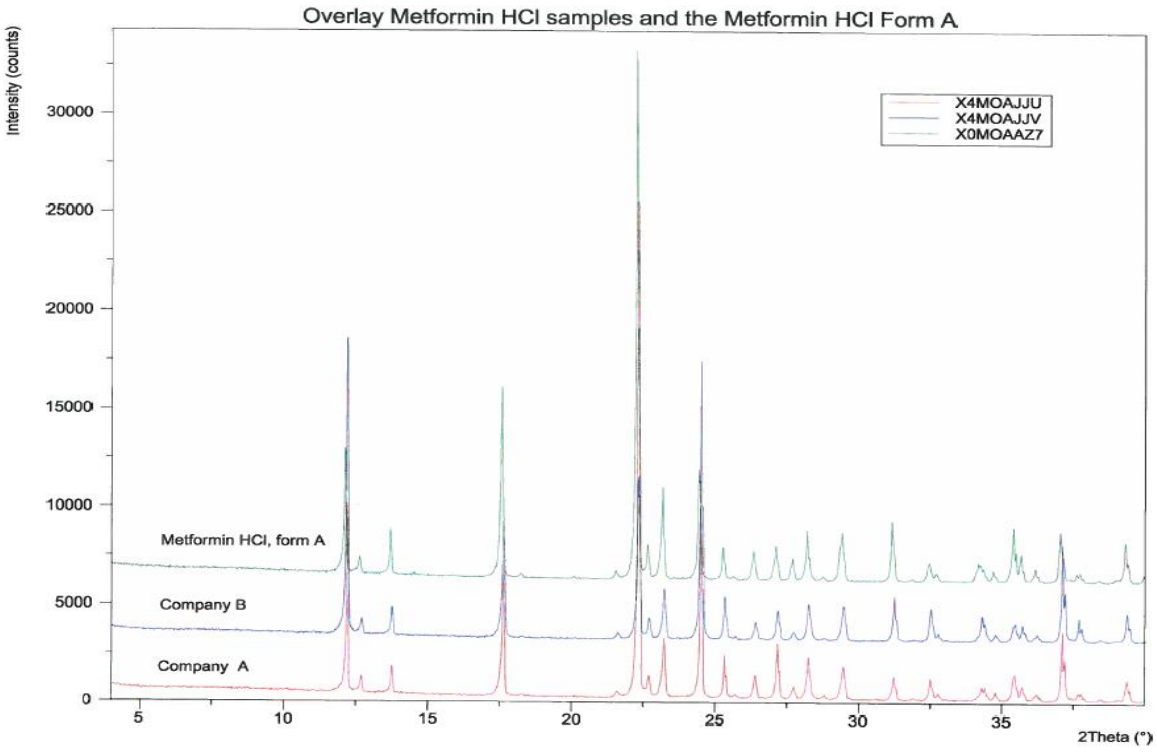


Figure 4.2: The powder X-Ray Diffraction spectrum for metformin HCl USP (Company A, Company B, and Standard Form A) indicating identical 2Theta values for major peaks. This clearly demonstrates that the material form both Company A and Company B are the same crystalline From A.

The relative rate at which molecules deposit on the crystal faces ultimately determines the final shape of a crystal[100]. It was already discussed in the introduction that many factors such as the degree of supersaturation, crystallizing solvent, temperature, rate of cooling and others can all affect the rate of deposition on the faces and therefore have an impact on the properties of the crystals[25, 26]. A review of the manufacturing process for metformin HCl reveals two differences that could potentially explain the difference in particle size and morphology of the two materials. The first was the use of different solvents, with Company A using xylene and purified water during the reaction step, and methanol and purified water during the purification step. Company B uses isopropyl alcohol during the reaction step and ethanol during the purification step. The second and perhaps more substantial difference in the synthesis of metformin HCl is the difference in process, with Company A using two solvents at each stage indicating a two phase system using water as the solvent for the highly soluble metformin HCl and methanol for the impurities. These differences in the synthetic procedure for metformin HCl (shown in figure 4.3A and 4.3B) [101, 102] were likely the source of the difference in the material properties observed. In particular, the final step in the synthetic procedure used by Company A could result in less impurities being present in the final API as the two phase system is more efficient at removing residual solvents and impurities. This being said, the residual solvent and impurity levels reported by each company were comparable, with the exception of methanol being higher in the metformin HCl supplied by Company B.

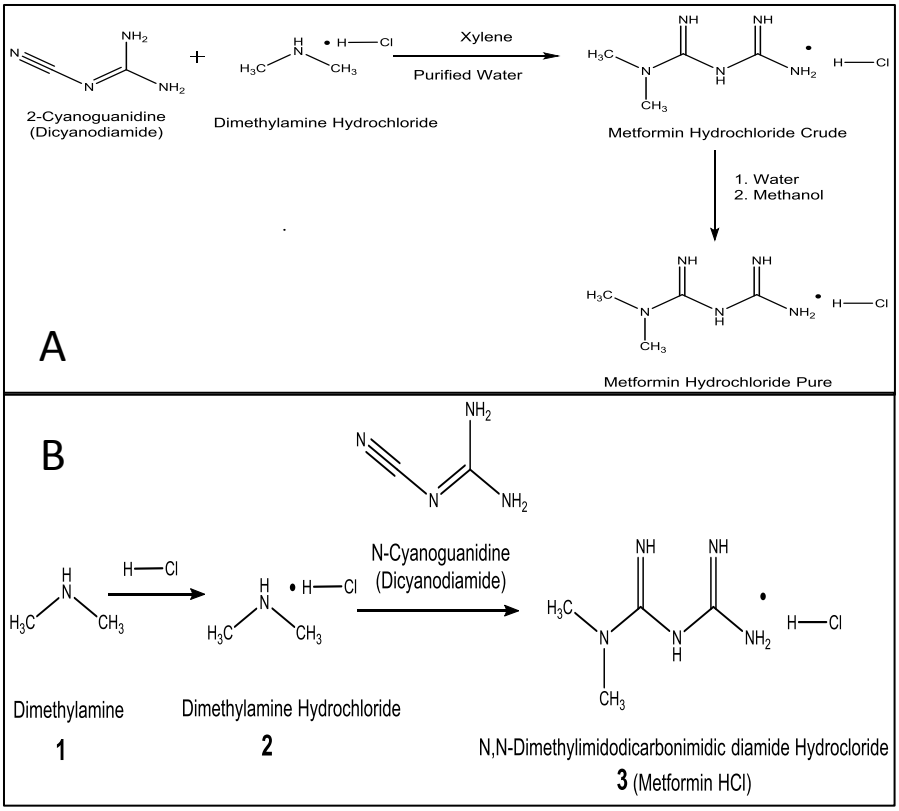


Figure 4.3: Synthetic schemes for metformin HCl manufactured by (A) Company A[101], and (B) Company B[102] showing differences in both the process and the solvents used in the manufacture of the APIs.

4.1.3 – Processing and critical quality attributes evaluation

The manufacturing process for the complete drug product was direct compression, with the final tablets containing 83.9% $^{w}/_{w}$ metformin HCl. The same lot of excipients was used in both batches (i.e. Batch 1 – Company A, and Batch 2 – Company B) and as a result, the physical properties of the blend were expected to be very similar to those for the respective API's. The resulting bulk density, tapped density and particle size of the blend prepared with metformin HCl from Company A was higher than the blend with API from Company B (see table A1.3 in the appendices).

It has been shown that there can be lot to lot variability on flow during processing of metformin HCl API depending on the age of the API[103]. It was therefore possible that the flow properties of

the two blends from different sources will be different. The Hausner ratio and Carr Index both provide an indication of the flowability of the blend [53], and as such both were calculated for the metformin HCl formulations and APIs from both sources.

The Hausner ratios were determined to be 1.24 and 1.31, respectively for the blends containing API from Company A and Company B respectively. These values indicate that the material flow was fair for both blends. The Carr Index was 24% and 31% respectively for the blends containing API from Company A and Company B indicating that the material flow was poor for both. Both of these measures indicated that the blend containing API from Company A had slightly better flow properties than the blend containing API from Company B. The Hausner ratio was 1.23 and 1.47 while the Carr Index was 23 % and 47 % (shown in table 4.2) respectively for the API from Company A and Company B indicating poor flow for material supplied by Company A and extremely poor flow for material supplied by Company B. These results can be directly correlated to the particle shapes observed from the image analysis in figure 4.1. The Hausner ratio and Carr Index for both the API and blends were similar for material supplied by Company A however a similar correlation did not exist for material supplied by Company B.

Table 4.2: Bulk densities, tapped densities and flow indices for the metformin HCl blends prepared using metformin HCl from Company A and Company B. Hausner ratios and Carr indices (calculated from the experimental density values) are also reported.

Property	**Metformin HCl (Company A)**	**Batch 1 (Company A)**	**Metformin HCl (Company B)**	**Batch 2 (Company B)**
Bulk density (g/mL)	0.69	0.66	0.45	0.55
Tapped density (g/mL)	0.85	0.82	0.66	0.72
Flow Index (mm)	N/A	5	N/A	5
Hausner Ratio	1.23	1.24	1.47	1.31
Carr Index (%)	23	24	47	31

N/A – Criteria not assessed

The above values for the Hausner ratios and Carr indices indicate that the flow and compressibility properties for material supplied by Company B were enhanced by the additional excipients added to the blend. The Hausner Ratio decreased by 11% and the Carr Index dropping from 47% to 31% indicating the blend has poor flow as compared to extremely poor flow for the API. The powder flow result obtained from both blends using a flodex test instrument was 5 mm, indicating comparable flow properties, and indicative of very good flow; this was also the observation during the actual execution of the tableting process.

The blend using metformin HCl obtained from the current source (Company A, batch 1) was compressed first on a Korsch PH300 press. The target in-process quality attributes during the compression are described in table 3.3. The press was set up as close as possible to the target quality attribute for the tablets and all were within the target range from the start to the end of the compression run (approximately one hour duration). The mean compression force at which all of the CQAs were met was 34 kN for the blend using metformin HCl from Company A. The tablet weight and friability remained fairly constant throughout the run; however, the mean hardness increased from 6.7 kp at the beginning of the tablet manufacturing process to 9.1 kp at the end, along with a corresponding drop in thickness and increase in disintegration time (see tables A1.4 and A1.5 in the appendices). There is no obvious cause for this change in the hardness (approximately 16%) over the course of the compression process as there was no change in the compression force used. It is known that the physical properties of metformin HCl can change over time[103]; although given the short compression run of one hour, it would be unlikely to be sufficient for such a change.

A mean compression force range of 17 kN – 57 kN was evaluated for the blend containing metformin HCl obtained from the alternative source (Company B); however, tablets

having comparable CQAs (specifically tablets made using API from Company B had a lower hardness and higher friability) as those prepared using metformin HCl from Company A, could not be manufactured. Target mean compression forces of 17 kN, 24.7 kN, 34 kN, 47.3 kN and 57 kN were evaluated, and a mean compression force of 34 kN was found to produce the best results, but again not with the same quality attributes as tablets prepared in batch 1. A similar trend was seen for tablet hardness with a mean value of 4.9 kp observed for tablets formed at the start of the run, increasing to 5.7 kp for tablets formed at the end of the run. Unlike for tablets formed in batch 1, no trend in tablet thickness or disintegration time was observed, as these attributes were more variable for batch 2.

The friability tests for tablets prepared with the alternate source metformin HCl (Company B) did not meet specifications (see table A1.5 in the appendices) with several tablets "capping" during testing. The occurrence of capping is where the top or cap of the tablet breaks off; usually during the ejection process however can also occur over a period of time (shown in figure 4.4).

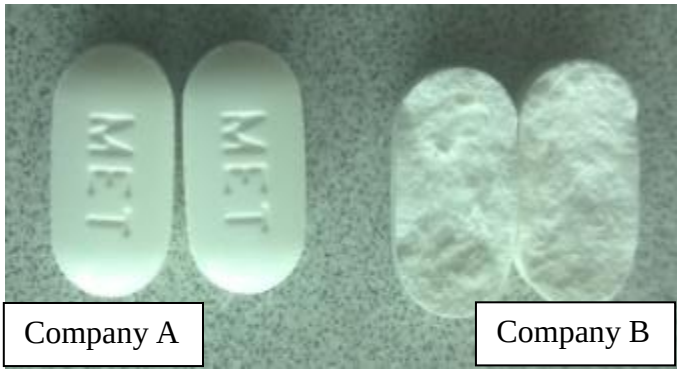


Figure 4.4: An example of capped metformin HCl tablets obtained from Company B's API compare to un-capped tablets obtains from Company A's API

There are several factors that can cause capping including entrapment of air, short dwell time or the time that the tablet is held in between the punches to form a tablet, insufficient pre-

compression, and the presence of too many fines (very small particles), which do not adhere as well as larger particles[80]. The blend containing Company B's metformin HCl contained 56.2% (see table A1.3 in the appendices) of material that was 200 mesh or finer, while the blend containing Company A's API contained 33.8% of material that was 200 mesh or finer; a difference of 22.4% that was likely one of the causes of the lower hardness and the capping observed for tablets prepared using metformin HCl from Company B. The compression behavior is governed by the viscoelastic properties of the blend, which can also be responsible for capping. The particles in the die cavity rearrange and then experience fragmentation or deformation (shown in figure 1.4 from Chapter 1) or both depending on the brittleness of the particles forming a tablet[53, 80]. The tablet will then go through a relaxation process that is directly related to the elastic properties of the material. The tablet must be strong enough to withstand this force or the tablet will fall apart or can cap if the rate and extent of this process is too great[80]. Particle shape can impact the flow and packing properties of the blend and therefore can impact the tablet properties. The particle shapes (figure 4.1), which were different for the two sources of metformin HCl, was likely a contributing factor to the differences observed in the in-process quality attributes; given that particle shape is not typically evaluated, there would be no way of determining from a review of the C of A that these materials would in fact behave differently.

4.1.4 – Drug product performance

The assay, dosage uniformity and dissolution (shown in table 4.3) of tablets manufactured using metformin HCl from Company A were consistently 2-3% higher than for those prepared using metformin HCl from Company B; however, the variability for both sets of tablets was less than 1% STDEV for the dissolution and dosage uniformity. The in – vitro performance was

similar regardless of the source of metformin HCl, with tablets fully dissolved within 10 minutes for both batches.

Table 4.3: Drug product performance test of assay, dosage uniformity and dissolution results for batch 1 (Company A) and batch 2 (Company B)

	Company A (%)		Company B (%)	
Assay	100.9		98.8	
Dosage Uniformity				
1	100.5		98.6	
2	101.5		99.0	
3	100.4		98.0	
4	101.9		99.4	
5	99.9		98.6	
6	101.1		98.3	
7	101.8		99.8	
8	101.0		99.7	
9	100.7		98.9	
10	100.3		97.8	
Min	99.9		97.8	
Max	101.9		99.8	
Mean	100.91		98.81	
SD	0.67		0.62	
AV	0.70		2.67	
Dissolution Time points	Dissolution	STDEV	Dissolution	STDEV
10mins	102	1	99	1
15mins	102	1	99	0
20mins	102	1	99	0
30mins	102	1	99	0
45mins	102	1	99	0
60mins	102	1	99	0

In summary, there were substantial differences observed for tablets manufactured using metformin HCl obtained from Company B, and these differences subsequently lead to challenges in the compression process and ultimately to CQA failures for tablets manufactured using metformin HCl from Company B. These differences were both in properties reported on the C of A such as LOD and methanol as well as properties not reported on the C of A such as particle

size and particle shape. The differences in the two materials did not have an impact on the in vitro performance of the tablets, and therefore one can propose that these would also not have an impact on the in-vivo performance; however, the decreased hardness and increased friability would result in a failure of the batch based on the CQAs, which would have represented a significant loss for the generic manufacturer.

4.2 - Gabapentin USP with copovidone NF/EP 35 (batch 3, Company X; and batch 4, Company Y)

4.2.1 – Gabapentin USP C of A testing

The gabapentin USP obtained from Company X and Company Y were each tested according to the requirements of the C of A for each source; all C of A requirements were met (see table 4.4). Contrary to the above case with metformin HCl, for the two sources of gabapentin USP there were differences in the specifications for assay, bulk density, residual solvents and related compounds. The C of A for material supplied by Company X has additional specification for tapped density, particle size and identification for Polymorphic form III, which the material from Company Y does not have. The only residual solvent present in material supplied by Company Y was ethanol, while material from Company X contains methanol, isopropanol, toluene and acetone. The C of As for four batches from each source of material was evaluated to determine if there were any differences within the sources of material. There was no substantial variability in the results from the C of A within the four batches for each source of API (refer to table A2.1 in the appendices).

A *two tailed t-tests* with a critical *p* (probability) value of 0.05 was performed to determine if there were any significant differences between the two sources of material. The bulk density test was shown to be significantly different between the two sources of material. The mean bulk density for Company X was 0.600 g/cc with a STDEV of 0.000 g/cc, the mean bulk

density for Company Y was 0.505 g/cc with a STDEV of 0.017 g/cc and t-test: t(6) = -10.97, p-value = 0.0001.

This difference can have an impact on the manufacturing process and drug product due to the high concentration of API in the formulation. This will impact the bin fill volume, and therefore the mixing properties of the materials which can lead to segregation and potential dosage uniformity challenges with the drug product. The manufacturing process includes compaction and from the data it was determined that the difference in bulk density between the two sources of material did not impact on the CQAs of the process or the drug product (refer to section 4.2.3).

Table 4.4: The C of A listing the tests, specifications and testing results for gabapentin USP API from Company X and Company Y used in batches 3 and 5, and batches 4 and 6 respectively

Test	Specifications	Results (Company X)	Results (Company Y)
Appearance	White to off-white powder	Conforms	Conforms
Identification	HPLC Retention Time: Corresponds to standard	Conforms	Conforms
Identification	IR Spectrum: Corresponds to Standard	conforms	Conforms
Identification	Polymorphic form III: NMT 5.0%	Conforms	N/A
Assay	98.5 to 101.5% (Anhydrous basis)	99.7%	N/A
Assay	98.0 to 102.0% (Anhydrous basis)	N/A	99.2
Bulk Density	0.4 to 0.6 g/cc	0.6 g/cc	N/A
Bulk Density	0.40 to 0.66 g/cc	N/A	0.51 g/cc
Tapped Density	0.6 to 1.0 g/cc	0.8 g/cc	N/A
Heavy Metals	NMT 0.002%	Less than 0.002%	Less than 0.002%
Limit of Chloride	NMT 0.01%	0.00%	0.01%
Residual Solvent	Methanol: NMT 250 ppm Isopropanol: NMT 1000 ppm Toluene: NMT 100 ppm Acetone: NMT 100 ppm	35 ppm 64 ppm 0 ppm 2 ppm	N/A
Residual Solvent	Ethanol: NMT 0.2%	N/A	0.0%
Particle Size	Percent smaller than 250 um: NLT 95% Percent smaller than 150 um: NLT 45%	99% 82%	N/A
pH	6.8 to 7.4	7.2	N/A
pH	6.5 to 8.0	N/A	7.2
Related Compounds	GA RC2: NMT 0.05% Unidentified Impurity: NMT 0.05% each Total Impurities: NMT 0.30%	BRT BRT BRT	BRT BRT N/A
Related Compounds (Limit of late eluting impurities)	Any Impurity: NMT 0.05% each	N/A	ND
Related Compounds (Limit of late eluting impurities)	Any impurity: NMT 0.10% each	ND	N/A
Total related Compounds	Total Impurities: NMT 0.5%	BRT	BRT
Residue on Ignition	NMT 0.1%	0.0%	0.0%
Water	NMT 0.3%	0.0%	N/A
Water	NMT 0.5%	N/A	0.0%

N/A – Criteria not included in C of A and therefore not tested

Acronyms used in table 4.4:
BRT – Below reporting threshold
HPLC – High pressure liquid chromatography
IR – Infrared
GA RC – Gabapentin USP related compound
ND – None detected
NLT – Not less than
NMT – Not more than
ppm – Parts per million

4.2.2 – Additional testing for gabapentin USP

The additional tests performed were particle size, specific surface area, surface weighted mean diameter, volume weighted mean, tapped density, DSC, image analysis and powder X-Ray diffraction.

From this work, the particle sizes obtained from laser diffraction for gabapentin USP supplied by Company Y were not only substantially larger than those obtained for gabapentin USP from Company X but also had a larger distribution, ranging from 12 μm to 900 μm for gabapentin USP from Company Y compared to a range of 1μm to 500 μm for that supplied by Company X. In addition material supplied by Company Y had higher surface weighted mean diameter and volume weighted mean diameter but a lower specific surface area (see table A2.2 in the appendices). Image analysis was one of the tests performed that were not part of the reported C of A. Images in figure 4.5 indicates a similar acicular or needle like structure for both materials. The images also reflect the difference in the particle size observed, with material supplied by Company X being finer/smaller.

There are four polymorphic forms for Gabapentin USP reported in the literature with polymorphic form II being supplied commercially[104, 105]. Company X includes a specification (on the C of A) for polymorphic form III of NMT (not more than) 5.0% and a claim to be supplying

the more stable polymorphic form II. Company Y does not have this limit for polymorphic form III, but similarly claims to be supplying polymorphic Form II.

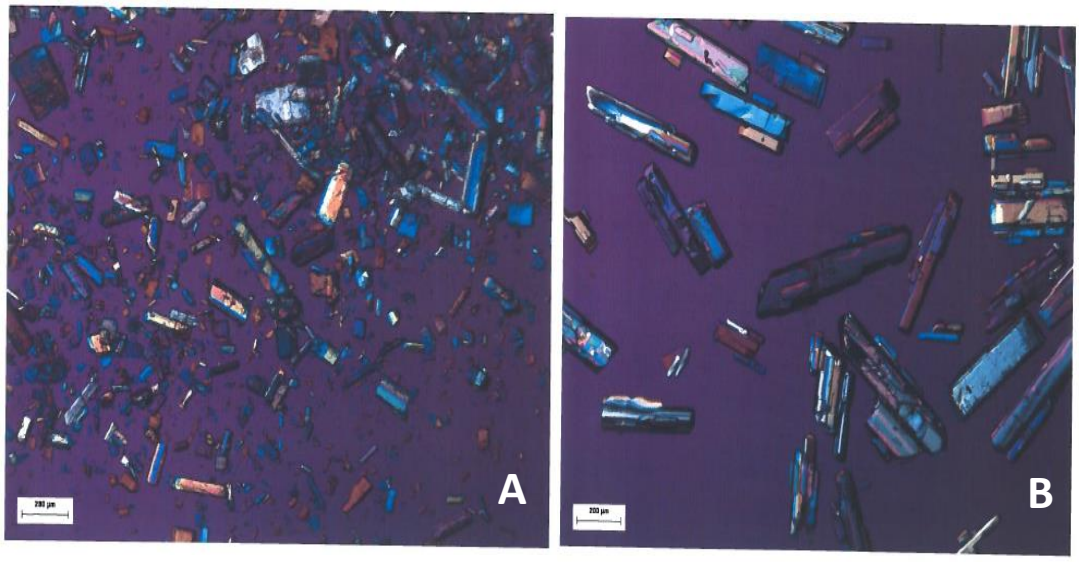


Figure 4.5: Image analysis for gabapentin USP samples from (A) Company X, and (B) Company Y. Both materials possess a needle-like or acicular crystal shape, also, the difference in particle size is clearly evident.

The X-Ray diffraction spectrum in figure 4.6 indicates that both sources were producing the same polymorphic form, which we can safely conclude to be polymorphic form II. The intensity of the peaks were slightly different for the two materials, and while several factors such as the orientation, position and shape of the crystals can contribute to this, the most likely cause was the difference in the particle size. The DSC thermograms, (see figure A2.1 and A2.2 in the appendices), show the start of the phase transition for gabapentin USP at the same temperature of 175.7°C for both sources of material, with temperature ranges for the transition of 1.72°C and 2.47°C for material obtained from Company X and Company Y, respectively. This provides additional confirmation of the similarities in the two structures.

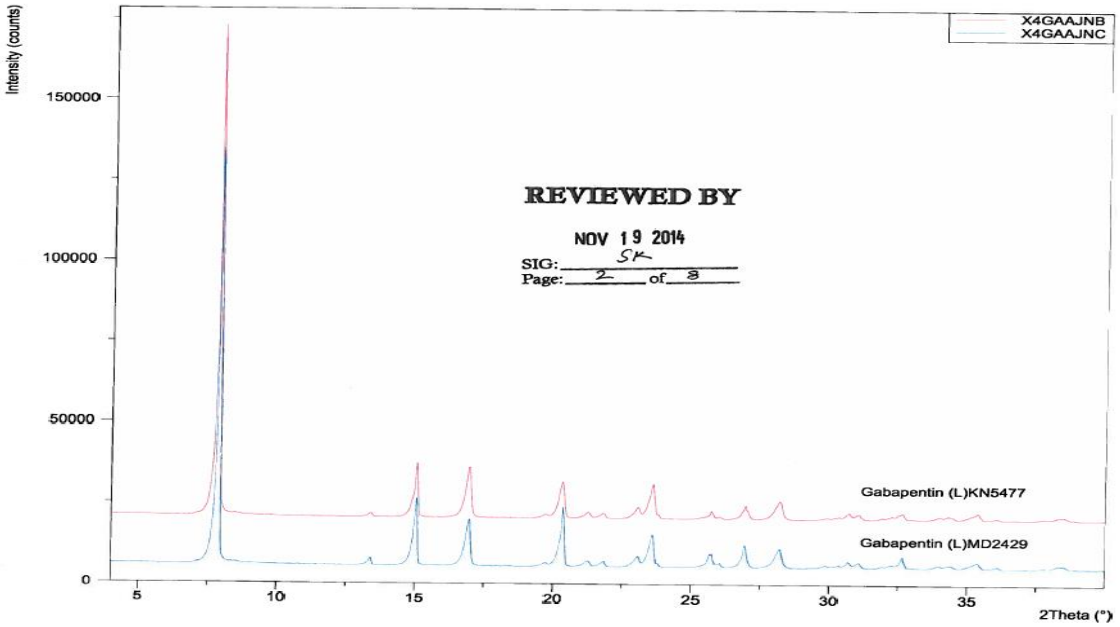


Figure 4.6: The powder X-Ray diffraction spectra for gabapentin USP obtained from Company X (blue) and Company Y (red) indicating identical 2Theta values for major peaks. This clearly demonstrates that the material from both Company X and Company Y is the same crystalline Form II.

A review of the manufacturing process for gabapentin USP from each source reveals many differences, with Company X first synthesizing gabapentin USP lactam from cyclohexane 1,1-diacetic acid as the starting material for the synthesis of gabapentin USP , figure 4.7[106]. Company Y synthesizes gabapentin USP from 1,1-cyclohexane-diacetic acid-monoamide through a two-step reaction process, figure 4.8[107]. The other noticeable difference was that Company Y uses only one solvent, ethanol, while Company X uses acetone, methanol and isopropyl alcohol in the final recrystallization process. These differences in the process likely resulted in the variation observed in particle size between the two materials; however, the difference in particle size could also be as a result of mechanical stress introduced during the latter stages of the process such as drying and milling. It is known that many factors, such as manufacturing process and solvent use, can impact the crystal form and crystal habit and

therefore it is notable that the shape of the crystal for both materials was very similar although the manufacturing process and solvents used were different for the two materials.

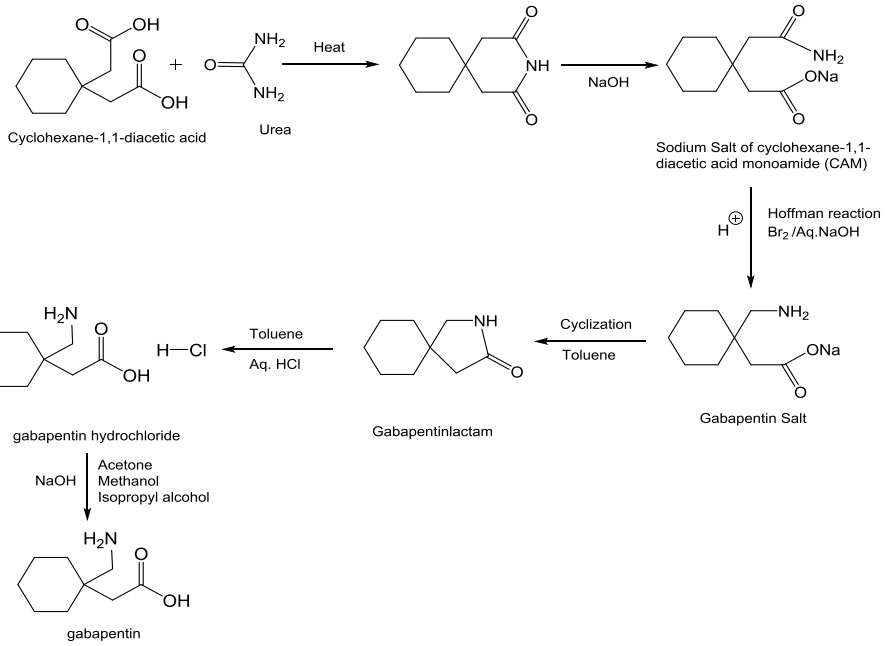


Figure 4.7: Synthetic route for gabapentin USP for material from Company X, showing a difference in both the process and the solvents used in the manufacture of the API compare to Company Y[106].

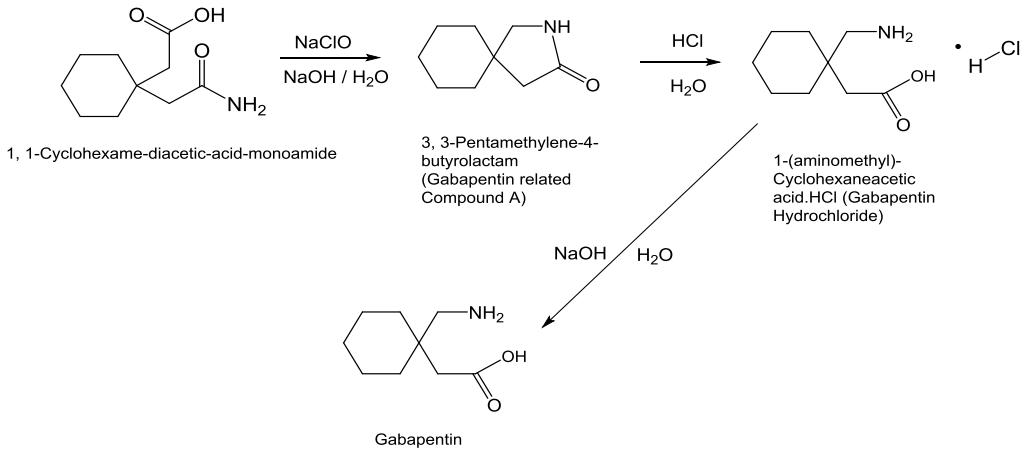


Figure 4.8: Synthetic route for gabapentin USP for material from Company Y, showing a difference in both the process and the solvents used in the manufacture of the API compare to Company X[107].

4.2.3 - Processing and critical quality attributes evaluation

The manufacturing process for the gabapentin USP tablets was via blending; compaction, followed by compression, with the formulation containing gabapentin USP, copovidone NF/EP and magnesium stearate NF (see table 3.4 in Chapter 3). As gabapentin USP is a crystalline material (as compared to an amorphous material), which typically does not compress well, a compaction followed by compression process was developed for the manufacturing of the drug product[108] instead of a direct compression process as was used for the metformin HCl tablets described above. The same lot of excipients was used in both blends (batch 3 and batch 4) and therefore the source of gabapentin USP was expected to have an impact, if any, on the physical properties of the blend, compaction process, compression process and the resulting tablets.

The Hausner ratios and Carr indices for both gabapentin USP from each source, along with those for the granulated blends prepared using gabapentin USP from each source are reported in table 4.5. The Hausner ratio for gabapentin USP supplied by Company X was 1.22 while the Hausner ratio for gabapentin USP from Company Y was 1.25 suggests free flowing properties for both material. Similar results were obtained for the Carr indices, which were 22% and 25% for gabapentin USP supplied by Company X and Company Y, respectively. The copovidone NF/EP 35 had a Hausner ration of 1.27 and a Carr Index of 27 %, suggesting poor to fair flow for the excipient (see table 4.8 for a comparison with copovidone NF/EP 20, in section 4.3.3 below). The materials were blended and the blend was then compacted using a Gerteis compactor with target process parameters listed in table 3.5 and the resulting granulation was over blended with magnesium stearate NF prior to compression. The granulation for batch 3 was coarser with 10% more retained on the 20 mesh and 9% less on the fines for Company X API (see table A2.3 in the appendices). The Hausner ratio for the granulation blends was 1.24 and

1.26, while the Carr Index was 24% and 26% respectively for material supplied by Company X and Company Y. The Hausner ratio and Carr Index for the granulation with material from Company X and Company Y were comparable to their respective APIs; also, both results were very close to the excipient, copovidone NF/EP 35. The flow index, which was 18mm for both granulation blends, also shows the similarity of the two granulation blends.

Table 4.5: Bulk densities, tapped densities and flow indices for the gabapentin USP blends prepared using gabapentin USP from Company X and Company Y and copovidone NF/EP 35. Hausner ratios and Carr indices (calculated from the experimental density values) are also reported.

Property	**Gabapentin USP (Company X)**	**Batch 3 (Company X)**		**Gabapentin USP (Company Y)**	**Batch 4 (Company y)**	
	Results	Results	STDEV	Results	Results	STDEV
Bulk density (g/mL)	0.60	0.54	0.00	0.51	0.57	0.04
Tapped density (g/mL)	0.73	0.67	0.00	0.64	0.72	0.04
Flow Index (mm)	N/A	18	3.1	N/A	18	1.2
Hausner Ratio	1.22	1.24	0.00	1.25	1.26	0.02
Carr Index (%)	22	24	0.00	25	26	1.50

N/A – Criteria not assessed

The granulation blends were compressed on a Korsch PH300 press with the target in process quality attributes listed in table 3.6.The press was set up as close as possible to the target quality attribute for the tablets and all were within the target range from the start to the end of the compression run; approximately one hour in duration. The mean compression force at which all of the CQAs were achieved was 47.0 kN with granulation blend using Company X API. The tablet weight, hardness, thickness, friability and disintegration all remain consistent throughout the run (see table A2.4 in the appendices).

A mean compression force of 47.0 kN was targeted to achieve the same CQAs with granulation blend using Company Y's API and all were within the range specified. The mean hardness, however, was 24 kp which was higher than the 22 kp achieved in batch 3; the disintegration time was also slightly higher. As a result the mean compression force was reduced

to 38.5 kN and all of the CQAs were achieved and were comparable to the Company X API at 47.0 kN. The tablet weight, hardness, thickness, friability and disintegration all remain consistent throughout the compression run which was approximately one hour duration at 38.5 kN (see table A2.5 in the appendices). The gabapentin USP obtained from Company Y was measurably coarser than that from Company X; however, the resulting granulation was 9% finer.

4.2.4 – Drug product performance

The assay and dosage uniformity of tablets using Company Y gabapentin USP was 2% higher than that for Company X; however, the in – vitro performance was similar for both formulations, with tablets fully dissolved at 100 % after 60 minutes (see table 4.6). With the exception of the compression force, the particle size and bulk density of the gabapentin USP API and the sieve results for the granulation, there was no other noticeable difference observed with the gabapentin USP itself, the manufacturing process, or the CQAs for both sources. The differences in the two sources of gabapentin USP did not have an impact on the in vitro performance and therefore one can propose that it will similarly not have an impact on the in-vivo performance of the tablets.

Table 4.6: Drug product performance test of assay, dosage uniformity and dissolution results for batch 3 (Company X (copovidone NF/EP 35)) and batch 4 (Company Y (copovidone NF/EP 35))

	Company X (copovidone NF/EP 35) (%)		Company Y (copovidone NF/EP 35) (%)	
Assay	98.1		99.8	
Dosage Uniformity				
1	97.9		101.1	
2	98.4		99.8	
3	98.9		98.8	
4	97.9		99.8	
5	98.1		99.9	
6	98.5		99.9	
7	96.7		100.2	
8	98.4		99.6	
9	98.4		99.5	
10	98.0		99.6	
Min	96.7		98.8	
Max	98.9		101.1	
Ave	98.12		99.82	
STDEV	0.62		0.61	
AV	3.37		1.65	
Dissolution Time points	Dissolution	STDEV	Dissolution	STDEV
5mins	21	1	22	1
10mins	35	1	37	2
15mins	52	1	54	2
30mins	84	1	84	2
45mins	99	1	98	1
60mins	100	1	100	1

4.3 - Gabapentin USP with copovidone NF/EP 20 (batch 5, Company X; and batch 6, Company Y)

4.3.1 – Copovidone NF/EP C of A testing

The supplier of copovidone EP/NF uses two different sizes of fluid bed processor to produce their commercial quantities of copovidone NF/EP. These two materials are supplied by Company D and were denoted as copovidone NF/EP 35 and copovidone NF/EP 20. The same sources of gabapentin USP from batch 3 (Company X) and batch 4 (Company Y) were used for

batches 5 and 6 respectively, using copovidone manufactured from the smaller fluid bed processor (copovidone NF/EP 20) in place of the copovidone NF/EP 35 used in batches 3 and 4. The copovidone from the two different fluid bed processors were tested according to the requirements of the C of A for each; the requirements were met for both samples (see table 4.7). The specifications were the same for both materials with the exception for Limit of Monomers which was required for copovidone NF/EP 35 and not for copovidone NF/EP 20. The ethenyl acetate and LOD was slightly higher for copovidone NF/EP 35 while the particle size was higher copovidone NF/EP 20. The C of As for four batches from each source of material was evaluated to determine if there were any differences within the two sources of material. There was no substantial variability in the results from the C of A within the four batches for each source of copovidone (refer to table A3.1in the appendices).

A *two tailed t-tests* with a critical *p* (probability) value of 0.05 was performed to determine if there were any significant differences between the two sources of material. The particle size (d(90)) test was shown to be significantly different between the two sources of material. The mean particle size (d(90)) for copovidone NF/EP 35 was 173.750 μm with a STDEV of 6.021 μm, the mean particle size (d(90)) for copovidone NF/EP 20 was 211.750 μm with a STDEV of 20.056 μm and t-test: t(6) = -3.63, p-value = 0.0110. The potential impact of particle size on the manufacturing process and drug product is discussed in detail in section 1.6.4.

Table 4.7: The C of A listing the tests, specifications and testing results for copovidone NF/EP 35 and copovidone NF/EP 20 excipient used in batches 3 and 4, and batches 5 and 6 respectively.

Test	Specifications	Results (Copovidone NF/EP 35)	Results (Copovidone NF/EP 20)
Appearance	White or lightly yellowish powder	Conforms	Conforms
Identification	Corresponds to ID B (USP)	Conforms	Conforms
Identification	IR Spectrum: Corresponds to Standard	Conforms	Conforms
Appearance of Solution	Clarity: Sample solution is not more opalescent than reference suspension III Colour: Sample solution is not more intensely coloured than reference solution B5, R5, OR BY5	Conforms Conforms	Conforms Conforms
Aldehydes	NMT 500 PPM(as acetaldehyde)	0 ppm	0 ppm
Ethenyl Acetate	35.3 to 41.4% (dried basis)	38.2%	36.8%
Heavy Metals	NMT 20 ppm	Less than 20 ppm	Less than 20 ppm
Hydrazine	Any spot corresponding to salicylaldehydrazine in chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with the reference standard (1 ppm)	ND	ND
Impurity A	NMT 0.5%	BRT	0.1%
Loss on Drying	NMT 5.0%	3.2%	2.3%
Monomers	NMT 0.1%	0.0%	0.0%
Limit of Monomers	2-Pyrrolidone: NMT 0.5% Vinyl Acetate: NMT 0.001% 1-Vinyl-2-2Pyrrolidone: NMT 0.001%	0.07% ND BQL	N/A
Nitrogen	7.0 to 8.0% (dried basis)	7.0%	7.2%
Peroxides	NMT 0.35% (400PPM)	Less than 400 ppm	Less than 400 ppm
Sulphated Ash	NMT 0.1%	0.0%	0.0%
Viscosity (AS K-VALUE)	25.2 to 30.8% (dried basis)	26.0	25.4
Particle Size	D (v,0.1): NLT 18um D (v,0.5): NMT 135um D (v,0.9): NMT 290um	34 85 179	59 128 239

N/A – Criteria not included in C of A and therefore not tested

Acronyms used in table 4.7:
BQL – Below quantification limit
ID – Identification
IR – Infrared
ND – None detected
NLT – Not less than
NMT – Not more than
ppm – Parts per million

4.3.2 – Additional testing for Copovidone NF/EP

The additional tests performed were specific surface area, surface weighted mean diameter, volume weighted mean, bulk density, tapped density, DSC, TGA, image analysis and SEM.

The surface weighted mean diameter and volume weighted mean diameter was higher for copovidone NF/EP 20 while the specific surface area was higher for copovidone NF/EP 35 (see table A3.2 in the appendices).

Image analysis of the copovidone NF/EP samples presented in figure 4.9, along with scanning electron micrographs for each sample in figure 4.10, did not reveal any noticeable differences between the two materials (other than the difference in the particle size and specific surface area already noted). The DSC thermograms (figure 4.11 A and B) confirm that the material was amorphous in nature, while the TGA (see figure A3.1and A3.2 in the appendices) indicates no difference in the physical and chemical properties between the two materials. The loss of weight observed during the TGA correlates with the difference in the LOD results observed during the C of A testing with copovidone NF/EP 35 having a slightly larger LOD compared to copovidone NF/EP 20.

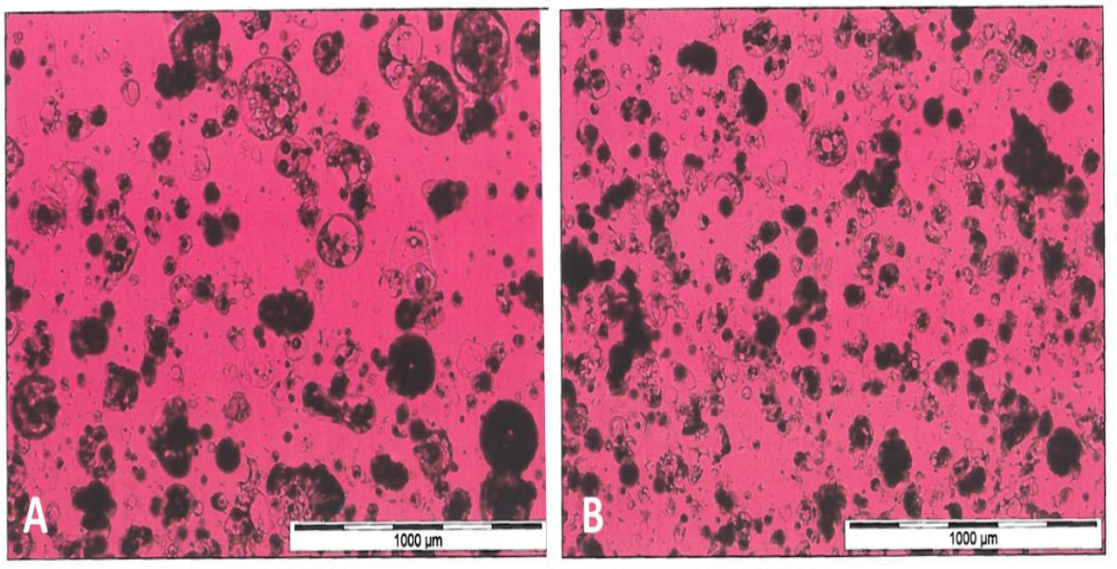


Figure 4.9: Image Analysis for (A) copovidone NF/EP 20; and (B) copovidone NF/EP 35, clearly indicating the similarity in the morphology of the two materials but no clear indication of the difference in particle size

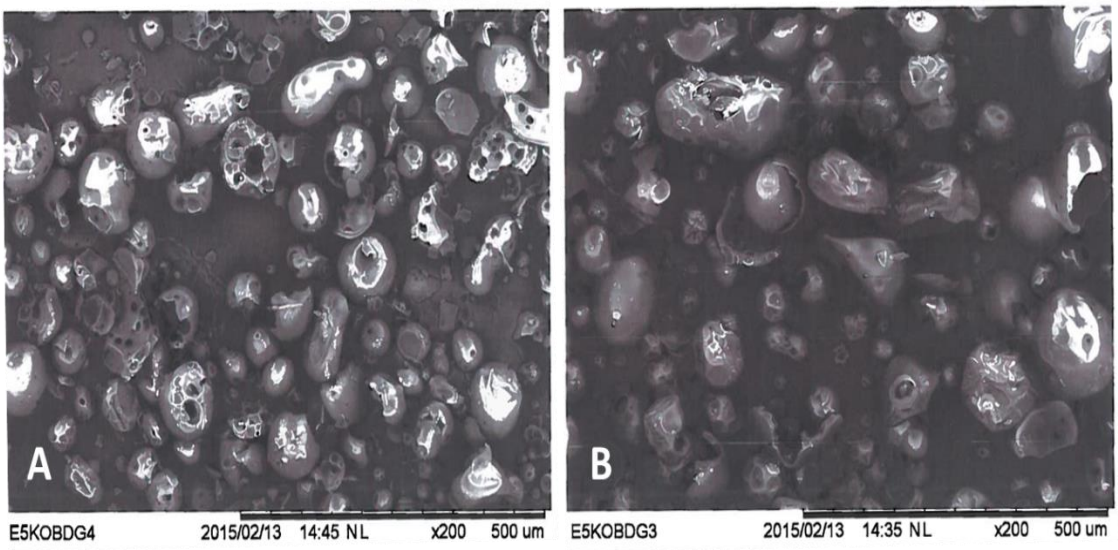


Figure 4.10: Scanning electron micrographs for (A) copovidone NF/EP 35; and (B) copovidone NF/EP 20; with fractures clearly visible and supporting the 78% higher specific surface area obtained for material (A) copovidone NF/EP 35

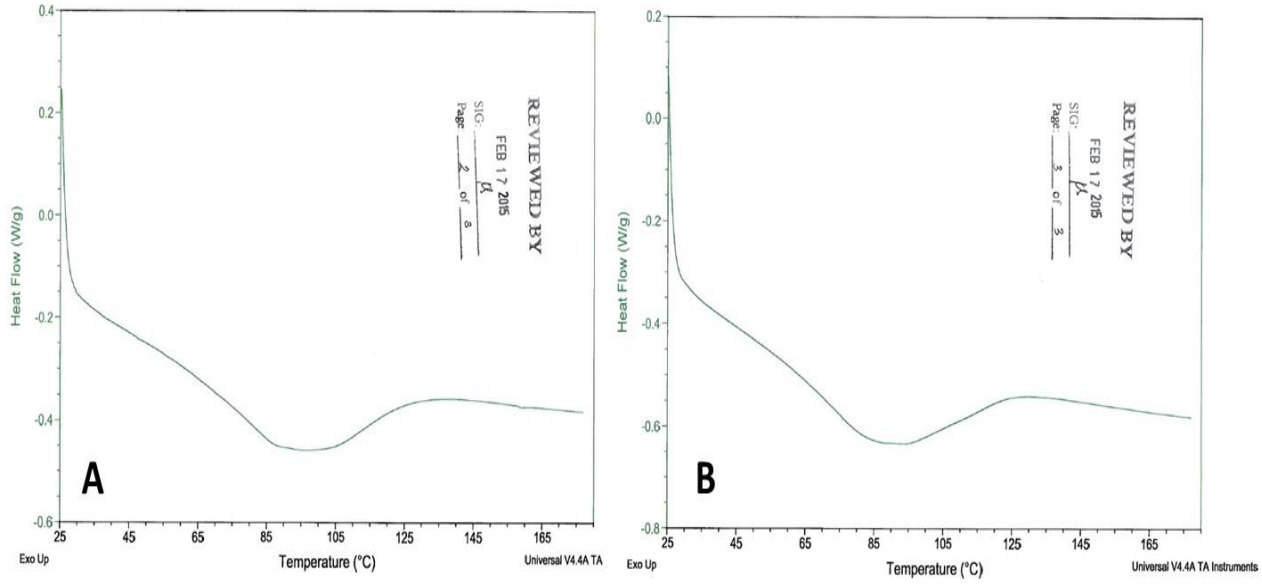


Figure 4.11: The DSC thermograms for (A) copovidone NF/EP 20; and (B) copovidone NF/EP 35 indicating comparable spectrums and confirming the amorphous nature of both materials.

4.3.3 - Processing and critical quality attributes evaluation

The manufacturing process for the granulation of batches 5 and 6 was the same as with batches 3 and 4, using the same process parameters as in table 3.5 Also, the same lots of gabapentin USP and magnesium stearate NF used in batches 3 and 4 were used for batches 5 and 6. The Hausner ratio and Carr Index for copovidone NF/EP 20 were 1.19 and 19% respectively (shown in table 4.8), indicating fair to good flow for this material; recall from section 4.2 that the Hausner ratio and Carr Index for copovidone NF/EP 35 were 1.27 and 27%, respectively, indicating poor to fair flow properties. The resulting granulation blend was slightly finer (44% vs 38%) for batch 5 using gabapentin USP from company X (see table A3.3 in the appendices).

The Hausner ratios and Carr indices for the granulation blends prepared using copovidone NF/EP 20 are found in table 4.8. Generally the flow properties of the granulation blends prepared using copovidone NF/EP 20 are very similar to the properties for granulation blends using copovidone NF/EP 35 (see table 4.5 above vs table 4.8 below). The Hausner ration

and Carr Index for the granulation blend containing copovidone NF/EP 20 and gabapentin USP from company X was similar to the granulation blend containing copovidone NF/EP 20 and gabapentin USP from company Y (see table 4.5 vs table 4.8). The Hausner ratio and Carr Index was better for copovidone NF/EP 20; however, this did not translate into similar flow properties for the granulation blends. The flow index was 18mm for both granulation blends, which demonstrates the similarity of these two granulation blends and the two granulation blends from batches 3 and 4 (which also both had a flow index of 18 mm).

Table 4.8: Bulk densities, tapped densities and flow indices for the gabapentin USP blends prepared using gabapentin USP from Company X and Company Y and copovidone NF/EP 20. Hausner ratios and Carr indices (calculated from the experimental density values) are also reported.

Property	**Copovidone NF/EP 20**	**Batch 5 (Company X)**		**Copovidone NF/EP 35**	**Batch 6 (Company Y)**	
	Results	Results	STDEV	Results	Results	STDEV
Bulk density (g/mL)	0.36	0.57	0.02	0.30	0.56	0.02
Tapped density (g/mL)	0.43	0.72	0.02	0.38	0.71	0.02
Flow Index	N/A	18	2.0	N/A	18	1.2
Hausner Ratio	1.19	1.26	0.01	1.27	1.27	0.00
Carr Index (%)	19	26	1.03	27	27	0.43

N/A – Criteria not assessed

The granulation blends were compressed on a Korsch PH300 press, with the blend containing gabapentin USP from company X and copovidone NF/EP 20 being compressed first, also targeting the same in process quality attributes used for batches 3 and 4, listed in table 3.6. The press was set up as close as possible to the target quality attribute using the same mean compression force of 47 kN used in batch 3 (which is the base line for the gabapentin USP batches), however, the mean hardness obtained (18 kp) was below the 22 kp obtained in batches 3 and 4. A mean compression force of 37 kN, which was close to the force of 38.5 kN used in batch 4, was also evaluated, with the obtained hardness being 16 kp. The compression force was increased to 64 kN, at which point a hardness of 20 kp was achieved for batch 5 which was

below the 22 kp consistently achieved for batches 3 and 4. The compression force of 64 kN was used to run batch 5 which was approximately 1 hour in duration. A compression force above 64 kN was not attempted to achieve 22 kp hardness due to the physical limitation of the compression tooling and compression machine.

A compression force of 60 kN was targeted to achieve the CQAs for the granulation blend in batch 6; all attributes were found to be within the ranges specified. Compression forces of 38.5 kN and 47 kN were also evaluated, and the hardness achieved at 38.5 kN was 17 kp (again below target) while the hardness achieved 47 kN was 19 kp. While comparable hardness of 22 kp was achieved at 60 kN for batch 6, it was ran at 47 kN and 19kp hardness (see table 4.9). This was done to prevent the possibility of any damage to the compression tooling and compression machine.

Table 4.9: Mean compression forces, mean hardness and hardness STDEV for the gabapentin USP tablets prepared using gabapentin USP from Company X and Company Y and copovidone NF/EP 35 and copovidone NF/EP 20, showing the higher compression force require for tablets using copovidone NF/EP 20 and gabapentin USP from Company X

	Compression Force (kN)	Hardness (kp)	
	Results	Results	STDEV
Batch 3 Company X and Copovidone NF/EP 35	47	22	1.6
Batch 4 Company Y and Copovidone NF/EP 35	47	24	1.3
	38.5	22	0.9
Batch 5 Company X and Copovidone NF/EP 20	64	20	1.3
	47	18	1.8
	37	16	1.2
Batch 6 Company Y and Copovidone NF/EP 20	47	19	1.1
	38.5	17	1.2
	60	22	0.8

In comparing batches 3 and 4 with batches 5 and 6, it can be seen that a lower compression force was required to achieve comparable CQAs for tablets prepared using gabapentin USP from company Y, regardless of which source of copovidone (i.e. copovidone

NF/EP 20 or copovidone NF/EP 35). This clearly indicates that while the copovidone NF/EP is the binder in the gabapentin USP tablet formulation, the compression properties were also impacted by the source and physical properties of the gabapentin USP itself.

4.3.4 – Drug product performance evaluation

The assay and dosage uniformity of tablets prepared with copovidone NF/EP 20 were comparable, regardless of the source of gabapentin USP (batches 5 and 6). The in – vitro performance was also comparable for both batches 5 and 6, with tablets fully dissolved within 45 minutes (see table 4.10). With the exception of the compression force, the particle size for copovidone NF/EP, and the sieve results for the granulation blends, there were no other noticeable differences for batches 5 and 6, regardless of the source of gabapentin USP. As was the case for batches 3 and 4, the minor differences observed for the two sources of gabapentin USP did not have an impact on the in vitro performance of the resulting tablets, and again one can propose that there would be no impact on the in-vivo performance.

Table 4.10: Drug product performance test of assay, dosage uniformity and dissolution results for batch 5 (Company X (copovidone NF/EP 20)) and batch 6 (Company Y (copovidone NF/EP 20))

	Company X (copovidone NF/EP 20) (%)		Company Y (copovidone NF/EP 20) (%)	
Assay	98.6		99.3	
Dosage Uniformity				
1	98.4		100.3	
2	98.1		98.3	
3	97.9		99.1	
4	99.0		99.3	
5	98.8		100.2	
6	98.7		100.4	
7	97.7		98.5	
8	99.4		99.0	
9	98.7		98.6	
10	99.2		99.0	
Min	97.7		98.3	
Max	99.4		100.4	
Ave	98.59		99.27	
STDEV	0.55		0.81	
AV	2.72		2.68	
Dissolution Time points	Dissolution	STDEV	Dissolution	STDEV
5mins	21	2	23	2
10mins	36	2	38	1
15mins	51	2	54	2
30mins	85	1	86	1
45mins	99	1	100	1
60mins	100	1	101	1

4.4 - Comparison of gabapentin USP formulations having the same source of gabapentin USP and different sources of copovidone NF/EP (batch 3 vs. batch 5 and batch 4 vs. batch 6)

Gabapentin USP tablets manufactured using gabapentin USP obtained from Company X, and copovidone NF/EP 35 (batch 3) was used as the reference tablets for all the gabapentin USP formulations. In this section, we will examine a pair wise comparison of batches 3 and 5, and

batches 4 and 6, in order to evaluate the impact of the two different sources of copovidone NF/EP for tablets formulated with gabapentin USP obtained from company X and company Y, respectively. For the reference tablets (batch 3) the granulation blend was coarser with 16% more material being retained on the 20 mesh screen and 23% less material retained on the 200 mesh plus fines screen for the blend using copovidone NF/EP 35, as compared to the results obtained for the blend using copovidone NF/EP 20 (batch 5). The compression force at which all CQAs were achieved was 47 kN using copovidone NF/EP 35 (batch 3) while the compression force at which all physical properties was achieved using copovidone NF/EP 20 (batch 5) was much higher at 64 kN (see table 4.9). Compression forces of 37 kN and 47 kN were also evaluated for the blend using copovidone NF/EP 20; however, higher friability and lower hardness were achieved (see tables A2.4 and A3.4 in the appendices). Interestingly, the Hausner ratios of 1.24 and 1.26, and Carr indices of 24% and 26% (shown in table 4.11), respectively for granulation blends using copovidone NF/EP 35 and copovidone NF/EP 20; however, the Hausner ratio and Carr Index for the two source copovidone NF/EP samples (see table 4.8) were quite different. Even with the higher compression forces used for copovidone NF/EP 20 the hardness was slightly lower, while the 4 and 20 minutes friability and the thickness were higher (batch 5). The weight, disintegration, flow, assay and CU results were comparable regardless of the source of copovidone, and the in – vitro performance was similar for both batches (3 and 5).

Table 4.11: Comparison of in process test results for gabapentin USP formulations with gabapentin USP tablets made with gabapentin USP API from Company X and the two different sources of copovidone (batch 3 vs. batch 5), showing the higher compression force require for tablets using copovidone NF/EP 20 (batch 5)

	Batch 3	Batch 5		
20 mesh (12+20 mesh) (%)	36.04	20.32		
80 mesh (40+60+80 mesh) (%)	36.64	35.55		
Fines (100+200+ Fines mesh) (%)	27.12	43.75		
Bulk density (g/mL)	0.54	0.57		
Tapped density (g/mL)	0.67	0.72		
Hausner Ratio	1.24	1.26		
Carr Index (%)	24	26		
Compression Force (kN)	47	64	47	37
Hardness (kp)	22	20	18	16

The comparison with the two different copovidone NF/EP materials was also made for tablets prepared using gabapentin USP obtained from Company Y (batches 4 and 6). The granulation blends had comparable sieve fractions and flow indices. The compression force at which all of the CQAs were achieved was 38.5 kN for tablets prepared in batch 4 (Company Y gabapentin USP with Copovidone NF/EP 35) while the compression force at which all physical properties were achieved for batch 6 (Company Y gabapentin USP with Copovidone NF/EP 20) was 56% higher at 60 kN. An attempted was made to use this same compression force (47 kN) for batch 4 (company Y gabapentin USP and copovidone NF/EP 35); however the hardness and disintegration time were higher, and the tablet thickness was lower. Similarly, compression forces of 38.5 kN and 47 kN were evaluated for batch 6 (company Y gabapentin USP with copovidone NF/EP 20), with a lower than target hardness achieved at 38.5 kn and a slightly higher hardness of 19 kp at 47 kN (shown in table 4.12). The Hausner ratio and Carr Indices were similar for the two granulation blends, and were also comparable to the granulation blends using Company X gabapentin USP; even with the differences in the Hausner ratios and Carr Indices for the two copovidone materials (see table 4.8). Despite the higher compression forces

used for Copovidone NF/EP 20 the hardness was slightly lower. The weight, thickness, friability, disintegration, flow, assay and CU results were comparable between the two copovidone, and the in – vitro performance was also similar (see tables 4.6 and 4.10). The above results clearly indicate that the copovidone materials produced using the two different fluid bed processors had different physical characteristics, not captured in the C of As; and the minor differences observed between the two materials were not sufficient to explain the difference in the performance.

Table 4.12: Comparison of in process test results for gabapentin USP formulations with gabapentin USP tablets made with gabapentin USP API from Company Y and the two different sources of copovidone (batch 4 vs. batch 6), showing the higher compression force require for tablets using copovidone NF/EP 20 (batch 6)

	Batch 4		Batch 6		
20 mesh (12+20 mesh) (%)	26.4		23.87		
80 mesh (40+60+80 mesh) (%)	37.2		36.68		
Fines (100+200+ Fines mesh) (%)	35.6		38.46		
Bulk density (g/mL)	0.57		0.56		
Tapped density (g/mL)	0.72		0.71		
Hausner Ratio	1.26		1.27		
Carr Index (%)	26		27		
Compression Force (kN)	38.5	47	47	38.5	60
Hardness (kp)	22	24	19	17	22

These results also support the need to perform additional characterizations prior to the introduction of a new source of excipients as this work clearly demonstrates that equivalency **cannot** be determined by a simple comparison of C of As. In these batches several tests beyond the C of A were completed; one of which was specific surface area. There was a clear difference in the specific surface area, 0.124 square meters per gram for copovidone NF/EP 35 compare to 0.0697 square meters per gram for copovidone NF/EP 20, between the two materials and the difference in particle size observed does not compensate for the greater than 75% difference in specific surface area. Copovidone NF/EP generally is spherical in shape and the difference in surface area was more likely due to fractures in the spheres. This will also lead to more effective

bonding when the materials are compressed resulting in lower compression force require to produce the same physical properties of the tablet.

4.5 - Comparison of gabapentin USP formulations having different sources of gabapentin USP and different sources of copovidone (batch 3 vs. batch 6 and batch 4 vs. batch 5)

This pair wise comparison evaluates the two different copovidone NF/EP with the two different gabapentin USP sources.

Table 4.13: Comparison of in process test results for gabapentin USP formulations with gabapentin USP tablets made with gabapentin USP API from Company X and copovidone NF/EP 35 and gabapentin USP API from Company Y and copovidone NF/EP 20 (batch 3 vs. batch 6), showing the higher compression force require for tablets using copovidone NF/EP 20 (batch 6)

	Batch 3	Batch 6		
20 mesh (12+20 mesh) (%)	36.04	23.87		
80 mesh (40+60+80 mesh) (%)	36.64	36.68		
Fines (100+200+ Fines mesh) (%)	27.12	38.46		
Bulk density (g/mL)	0.54	0.56		
Tapped density (g/mL)	0.67	0.71		
Hausner Ratio	1.24	1.27		
Carr Index (%)	24	27		
Compression Force (kN)	47	47	38.5	60
Hardness (kp)	22	19	17	22

The compression force at which all of the CQAs were achieved was 47 kN for Company X gabapentin USP with copovidone NF/EP 35, which was the baseline batch in batch 3. The compression force at which all physical properties was achieved for Company Y gabapentin USP with copovidone NF/EP 20 was 60 kN. Compression forces of 38.5 kN and 47 kN were also evaluated for Company Y gabapentin USP with copovidone NF/EP 20 with lower than target hardness achieved at 38.5 kN and slightly higher hardness of 19kp at 47 kN. The Hausner ratio and Carr Index were similar for the two granulation blends with the Hausner ratio of 1.24 and

1.27 and Carr Index of 24% and 27% respectively was obtained for granulation blends from Company X gabapentin USP with copovidone NF/EP 35 and Company Y gabapentin USP with copovidone NF/EP 20. It was concluded earlier that the copovidone NF/EP 35 had better compressibility properties and as a result produce comparable CQAs at a lower compression force when compare to ccopovidone NF/EP 20, the same was also true for the gabapentin USP where Company Y require a lower compression force to achieve comparable CQAs when compare to Company X gabapentin USP. A change in the source of the API and the excipient yielded equivalent results; however, when tested individually there was variability in the results. This equivalent result was achieved despite the fact that the granulation was coarser with 12% more on 20 mesh and 10% less on 100 mesh plus 200 mesh plus fines for Company X gabapentin USP with copovidone NF/EP 35 (see table 4.13). The weight, thickness, friability, disintegration, flow, assay and CU results were comparable between the two batches also, the in – vitro performance was similar (see tables 4.6 and 4.10).

Table 4.14: Comparison of in test process results for gabapentin USP formulations with gabapentin USP tablets made with gabapentin USP API from Company Y and copovidone NF/EP 35 and gabapentin USP API from Company X and copovidone NF/EP 20 (batch 4 vs. batch 5), showing the higher compression force require for tablets using copovidone NF/EP 20 and gabapentin USP from Company X (batch 5)

	Batch 4		Batch 5		
20 mesh (12+20 mesh) (%)	26.4		20.32		
80 mesh (40+60+80 mesh) (%)	37.2		35.55		
Fines (100+200+ Fines mesh) (%)	35.6		43.75		
Bulk density (g/mL)	0.57		0.57		
Tapped density (g/mL)	0.72		0.72		
Hausner Ratio	1.26		1.26		
Carr Index (%)	26		26		
Compression Force (kN)	38.5	47	64	47	37
Hardness (kp)	22	24	20	18	16

This pair wise comparison also evaluates the different copovidone NF/EP with the different API sources. This pair wise comparison evaluate the two batches at the extreme end of their physical characteristics with the compression force at which all CQAs were achieved was 38.5 kN for Company Y gabapentin USP with copovidone NF/EP 35 while 66% more compression force, 64 kN, was require by Company X gabapentin USP with copovidone NF/EP 20 to achieve comparable CQAs (see table 4.14). A compression force of 47 kN was also evaluated for Company Y gabapentin USP with copovidone NF/EP 35 and both the hardness and disintegration time were higher when compared to the results at 38.5 Kn (see table A2.5). The friability at both 4 minutes and 20 minutes were approximately 10% higher for Company Y gabapentin USP with copovidone NF/EP 35. While the granulation was slightly finer (36% vs 44%) for 100 mesh plus 200 mesh plus fines for Company X gabapentin USP with copovidone NF/EP 20, it was unlikely the root cause for the much higher force require to create tablets of comparable physical properties. A change in the gabapentin USP source produced the best results, batch 4, a change in excipient source produce the worse result, batch 5. Even with the extended testing it was difficult to predict the performance of the change in source of gabapentin USP and copovidone NF/EP, and after the experiments it was difficult to pin point the exact properties that resulted in the difference in performance. What was clear is that any change to the source of any material can impact the manufacturing process and CQAs, however, the in-vitro performance of the drug product was not impacted and therefore one can conclude that the in vivo performance will also not be impacted.

4.6 - Pair wise evaluation of granulation, weight, hardness and thickness for batches 3, 4, 5, and 6 (gabapentin USP tablets)

In addition to the pair wise comparisons described above, an evaluation was carried using the six distinct pairings of data to determine if there was any difference between the change in a particular material and the in process critical quality attributes measured during the manufacturing of the drug product (weight, hardness and thickness). The six pairings are (X ($35m^3$) - Y ($35m^3$)), batches 3 and 4, (X ($20m^3$) - Y ($20m^3$)) batches 5 and 6, (Y ($35m^3$) – Y ($20m^3$)) batches 4 and 6, (X ($35m^3$) - Y ($20m^3$)) batches 3 and 6, (Y ($35m^3$) – X ($20m^3$)) batches 4 and 5 and (X ($35m^3$) - X ($20m^3$)) batches 3 and 5. The granulation blends were also examined in order to determine any trend between the materials and the percentage difference of each pair retained on each sieve fraction.

The beginnings, figure 4.12, of the granulation process were analyzed and all showed the same trends, with noticeable differences within each pair was observed as the particle size gets smaller/finer specifically at the 100 mesh fraction. Company X gabapentin USP with copovidone NF/EP 35 (batch 3) produced the largest particle size granulation while the Company X gabapentin USP with copovidone NF/EP 20 (batch 5) produced the finest particle size granulation; however, the granulations for Company Y gabapentin USP and the two sources of copovidone NF/EP did not show the same correlation and were similar (see table 4.12).

The same evaluation was also completed for the compression process, where the weight, hardness, and thickness of the tablets were evaluated for the 6 comparison pairs described above. The percentage differences for each of the 6 pairs are presented in figure 4.13 for differences in the weight (figure 4.13A), hardness (figure 4.13B), and thickness (figure 4.13C), are presented as a function of time during the manufacture process with samples taken at the start and at 20% intervals during the compression run and at the end (total time for the manufacture of each batch was approximately one hour).

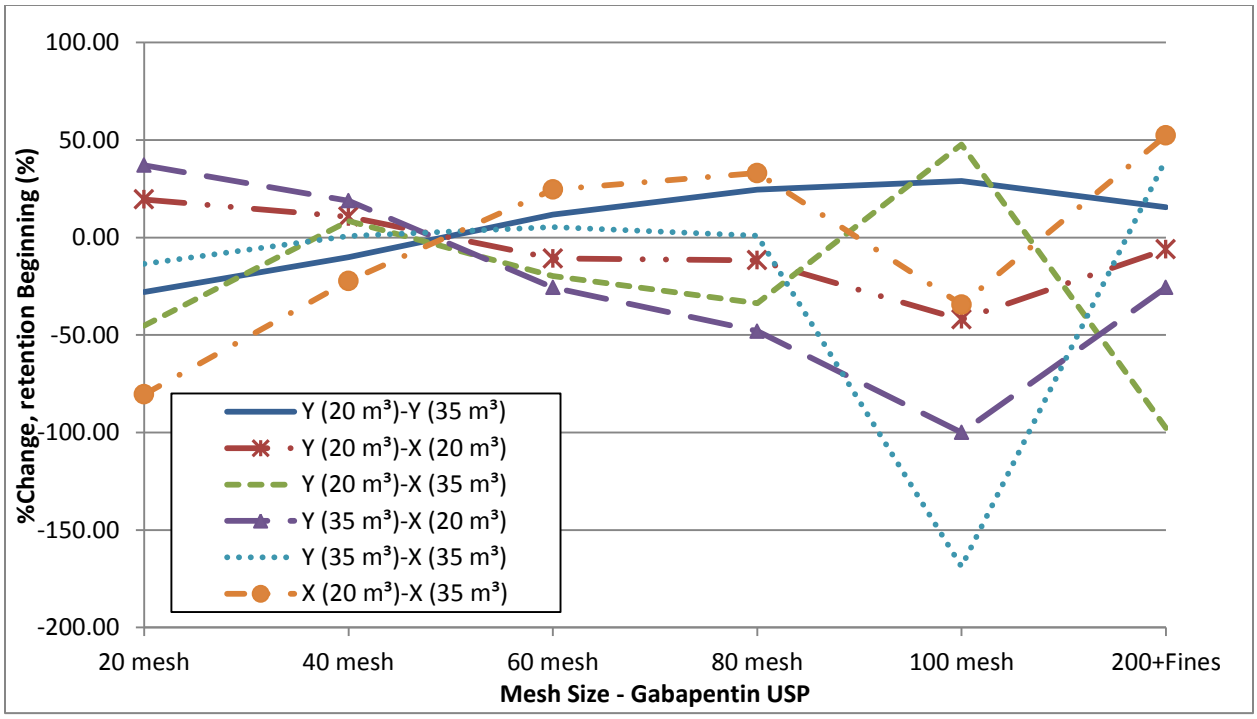
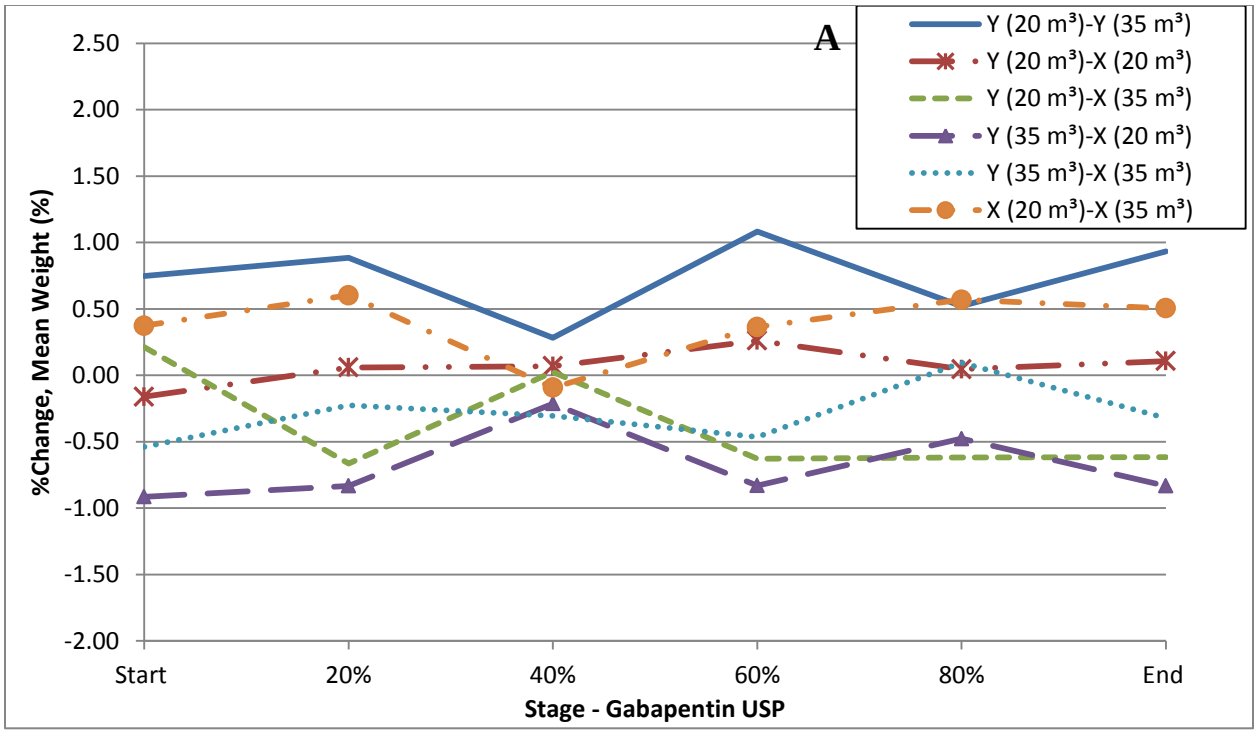
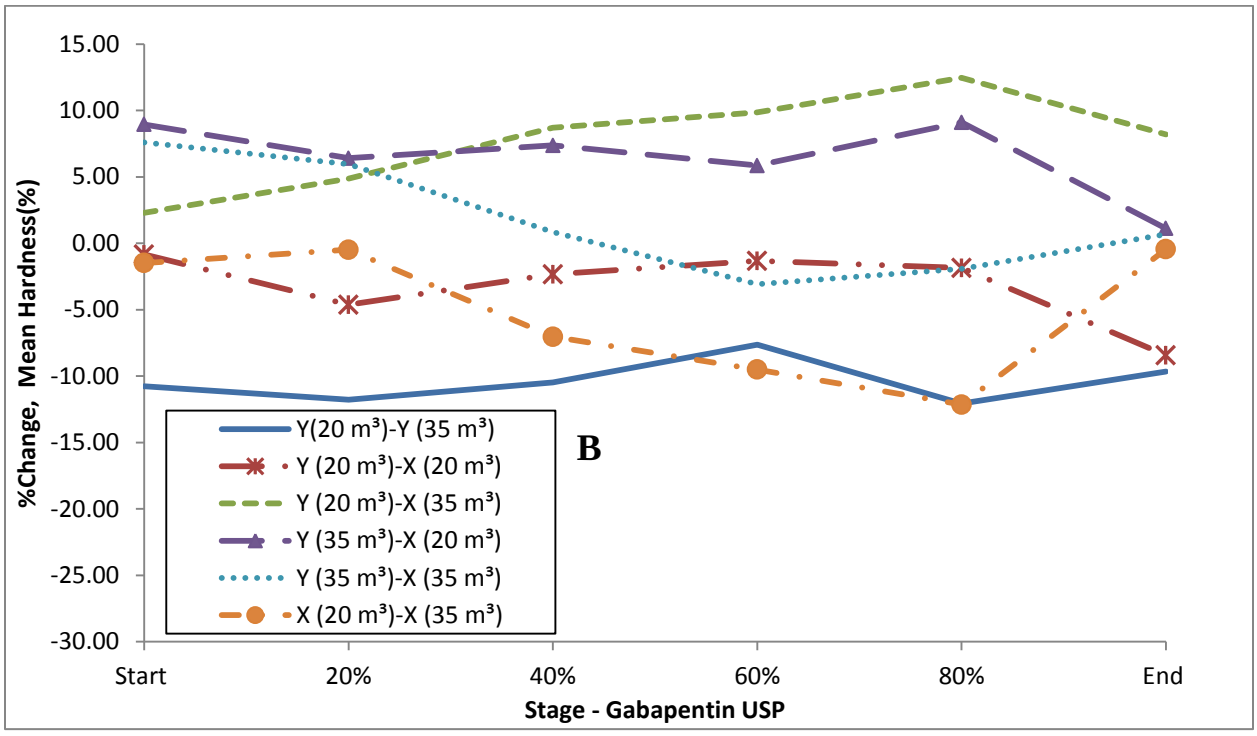


Figure 4.12: The pairwise percentage differences in the amount of each granulation blend retained on each sieve fraction for gabapentin USP batches with the largest difference observed at the 100 mesh fraction.





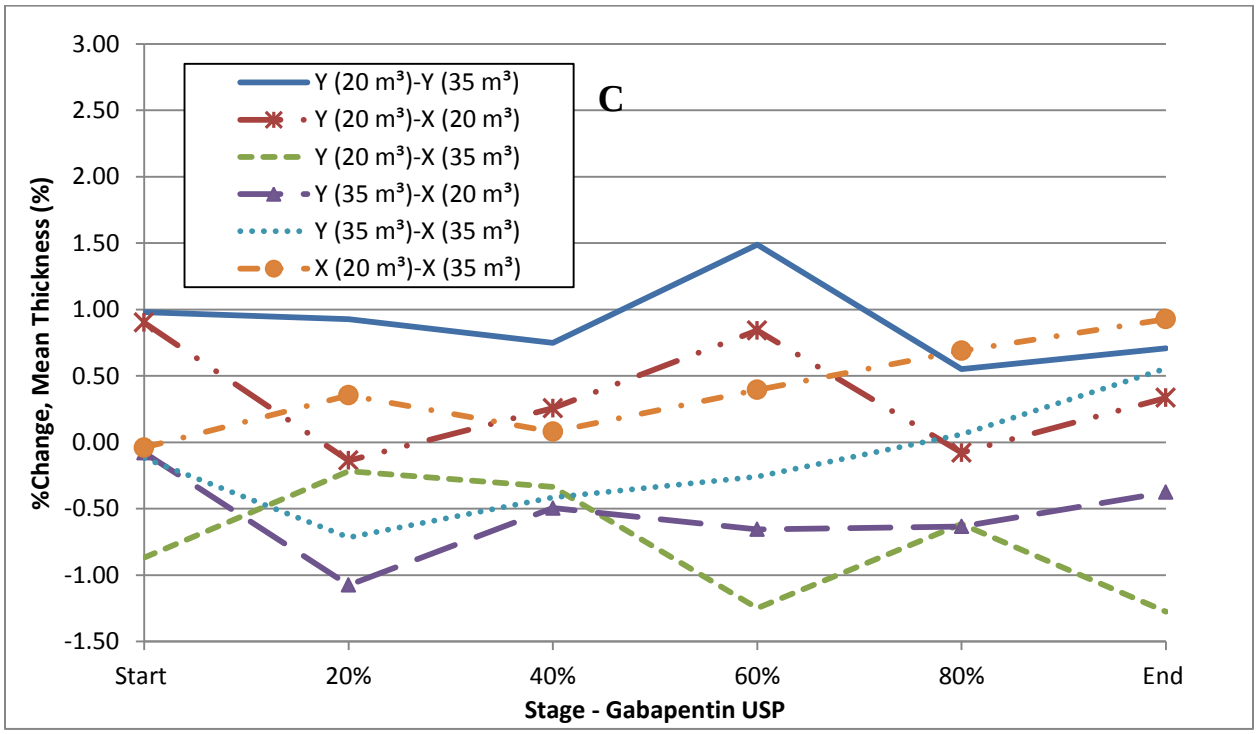


Figure 4.13: The percentage difference for each comparison pair of gabapentin USP tablets for the differences in the: A) weight; B) hardness; and C) thickness with less than ± 2 % difference observed with weight and thickness and a ± 10 % difference with hardness.

There was no trend observed over time for weight, hardness, or thickness, and generally if the difference was positive at the start of the compression process it remained positive, and if it was negative it remained negative throughout the compression run. This observation was more likely a function of the setup of the critical quality attributes at the beginning of the compression run, as the start closely compares to the end of the compression run.

4.7 – Fenofibrate EP/BP tablets (Batch 7 Company J, Batch 8 Company K; croscarmellose sodium NF/EP supplied by Company G)

4.7.1 – Fenofibrate EP/BP C of A testing

Fenofibrate EP/BP samples from each source were tested according to the requirements of the C of A for each source, and in both cases the C of A requirements were met (see tables 4.15 and 4.15a). There was a minor difference in the specification for assay with fenofibrate EP/BP supplied by Company J having a limit of 98.0% to 102.0% and fenofibrate EP/BP supplied by Company K having a limit of 98.5% to 101.0%. The fenofibrate EP/BP supplied by Company J contains one residual solvent, isopropanol, while fenofibrate EP/BP supplied by Company K also contains isopropanol in addition to four additional solvents: acetone; chloroform; toluene; and butyl acetate. The bulk density specification was the same for both sources; however, material supplied by Company K was 30% denser at 0.61 g/cc compare to 0.47 g/cc for Company J. The tapped density was almost the same at 0.72 g/cc and 0.71 g/cc respectively (see table A4.2 in the appendices). The C of As for four batches from Company J and three batches from Company K was evaluated to determine if there were any differences within the two sources of material. There was no substantial variability in the results from the C of A within the batches for each source of API (refer to table A4.1).

A *two tailed t-tests* with a critical *p* (probability) value of 0.05 was performed to determine if there were any significant differences between the two sources of material. The Isopropanol, total impurities and bulk density tests were shown to be significantly different between the two sources of material. The mean Isopropanol for Company J was 331.750 ppm with a STDEV of 15.629 ppm, the mean Isopropanol for Company K was 1075.000 ppm with a STDEV of 24.245 ppm and t-test: $t(5) = 49.81$, p-value = < 0.0001. The mean total impurities for Company J was 0.128 % with a STDEV of 0.013 %, the mean total impurities for Company K was 0.000 % with a STDEV of 0.000 % and t-test: $t(5) = -17.13$, p-value = < 0.0001. The mean bulk density for Company J was 0.530 g/cc with a STDEV of 0.012 g/cc, the mean bulk density for Company K was 0.647 g/cc with a STDEV of 0.012 g/cc and t-test: $t(5) = 13.23$, p-value = < 0.0001. These differences, specifically the bulk density, can have an impact on the manufacturing process and drug product, however, this was not observed (refer to section 4.7.3)

Table 4.15: The C of A listing the tests, specifications and testing results for fenofibrate EP/BP API from Company J and Company K used in batches 7 and 9, and batches 8 and 10 respectively

Test	Specifications	Results (Company J)	Results (Company K)
Appearance	White to off white powder	Conforms	Conforms
Identification	UV Spectrum: Corresponds to Standard	N/A	Conforms
Identification	IR Spectrum: Corresponds to Standard	Conforms	Conforms
Melting Point	79 to 82 ^{o}C	82 $^{\circ}$C	82 °C
Halides (Expressed as Chloride)	NMT 100 ppm	Less than 100 ppm	Less than 100 ppm
Sulphates	NMT 100 ppm	Less than 10 ppm	Less than 100 ppm
Acidity	Volume of 0.1 M NaOH required: NMT 0.2 mL	0.1 mL	0.1 mL
Loss on Drying	NMT 0.5%	0.1%	0.4%
Sulphated Ash	NMT 0.1%	0.1%	0.0%
Heavy Metals	0.002%	Less than 0.002%	Less than 0.002%
Residual Solvent	Acetone: NMT 1000 ppm Isopropanol: NMT 2000 ppm Chloroform: NMT 60 ppm Toluene: NMT 890 ppm Butyl acetate: NMT 1000ppm	N/A 342 ppm N/A N/A N/A	7 ppm 1103 ppm 7 ppm 71 ppm ND

N/A – Criteria not included in C of A and therefore not tested

Table 4.15a: : The C of A listing the tests, specifications and testing results for fenofibrate EP/BP API from Company J and Company K used in batches 7 and 9, and batches 8 and 10 respectively

Test	Specifications	Results (Company J)	Results (Company K)
Related Compounds	FF RC1: NMT 0.1% FF RC2: NMT 0.1% FF RC4: NMT 0.2% FF RC5: NMT 0.10% FF RC6: NMT 0.10% FF RC7: NMT 0.10% FF RC8: NMT 0.10% Unidentified Impurity: NMT 0.10% each Total Impurities: NMT 0.5%	BRT ND 0.13% BRT ND BRT BRT BRT 0.13%	N/A
Related Compounds	FF RC2: NMT 0.1% FF RC1: NMT 0.1% EP Imp. C: NMT 0.10% EP Imp. D: NMT 0.10% EP Imp. E: NMT 0.10% EP Imp. F: NMT 0.10% FF RC4: NMT 0.2% Unidentified Impurity: NMT 0.10% each Total Impurities: NMT 0.5%	N/A	N/D BRT ND BRT BRT BRT BRT BRT BRT
Assay	98.0% to 102.0% (dried basis)	99.6%	N/A
Assay	98.5% to 101.0% (dried basis)	N/A	100.1%
Appearance of Solution	Solution is clear and not more intensely coloured than reference solution BY6	Conforms	Conforms
Bulk Density	0.50 to 0.70 g/cc	0.54 g/cc	0.66 g/cc

N/A – Criteria not included in C of A and therefore not tested

Acronyms used in table 4.15 and 4.15a:
BRT – Below reporting threshold
EP Imp. – European Pharmacopeia impurity standard
FF RC – Fenofibrate EP/BP related compound
IR – Infrared
M – Molar
ND – None detected
NMT – Not more than
ppm – Parts per million
UV – Ultraviolet

4.7.2 - Additional testing for fenofibrate EP/BP

The additional tests performed were particle size, specific surface area, surface weighted mean diameter, volume weighted mean, tapped density, DSC, image analysis and powder X-Ray diffraction.

There was no specification for particle size but the test results indicates that fenofibrate EP/BP supplied by Company K was much coarser with a D(v,0.1) of 97µm, D(v,0.5) of 229µm and D(v,0.9) of 509µm; compared to values of D(v,0.1) of 22µm, D(v,0.5) of 78µm and D(v,0.9) of 250µm for fenofibrate EP/BP supplied by Company J. In addition fenofibrate EP/BP supplied by Company J had a lower surface weighted mean diameter and volume weighted mean diameter but a considerable higher (3.3x) surface area. The image analysis (see figure 4.14) indicates different crystal structures for the two materials with fenofibrate EP/BP supplied by Company J being platy (figure 4.14A), while fenofibrate EP/BP supplied by Company K was more prismatic in shape (figure 4.14B). The image analysis also reflects the noticeable differences in the particle size observed, with fenofibrate EP/BP supplied by Company K been coarser.

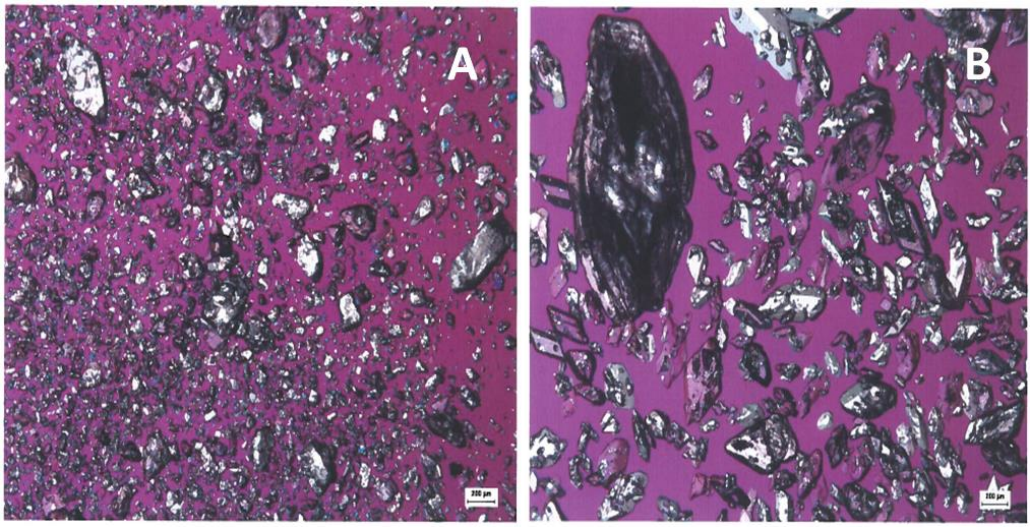


Figure 4.14: Image Analysis for fenofibrate EP/BP from: (A) Company J; (B) Company K. The differences in both particle size and particle shape are clearly evident.

There are two polymorphic forms and an amorphous solid of fenofibrate reported by the literature with polymorphic form I being supplied commercially[109]. There is a metastable Form II, which is formed by crystallizing amorphous fenofibrate, grinding, or exposure to high humidity; Form II converts back to Form I within a few days. Company J claims to be supplying Form I, and while Company K does not make this claim, their materials have a specification for melting point, 79°c to 82°c, which is characteristic of Form I. This was confirmed by DSC (thermograms are provided as figures A4.1 and A4.2 in the appendices), which indicates the start of the phase transition at a temperature of 79.6 °C for both materials; the temperature range over which the transition occurred was 0.6 °C and 0.9 °C, respectively, for fenofibrate EP/BP supplied by Company J and fenofibrate EP/BP supplied by Company K, again indicating the similarities in the two materials. The X-Ray diffraction spectrum (see figure 4.15) clearly indicates that both sources were producing polymorphic form I when compare to the reference standard (Exhibit A in figure 4.15).

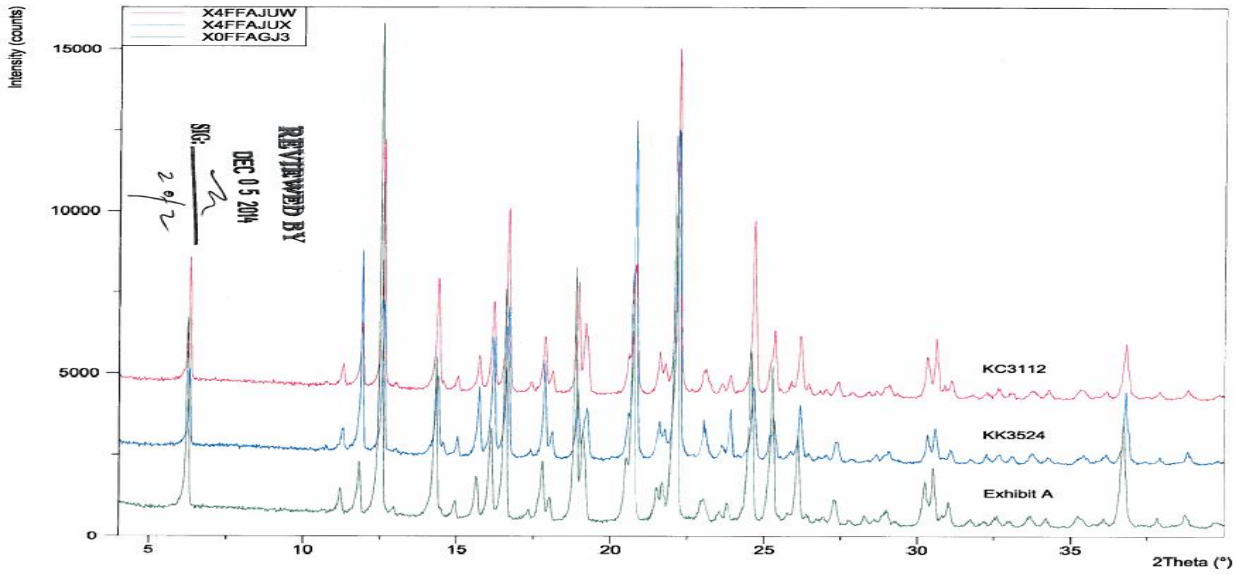


Figure 4.15: The powder X-Ray Diffraction for fenofibrate EP/BP; Company J (purple, KC3112), Company K (light blue, KK3524), and reference material (dark blue, Exhibit A) indicating identical 2Theta values for major peaks. This clearly demonstrates that the material from both Company J and Company K are the same crystalline Form I.

A review of the manufacturing process reveals many differences between fenofibrate EP/BP manufactured by each company; however, both use 4-chloro-4-hydroxybenzophenone as a starting material. Company J describes 4-chloro-4-hydroxybenzophenone as a starting material (see figure 4.16)[110] using a condensation process to produce crude fenofibrate I which then goes through a two - step purification process. Company K describes the formation of pure fenofibrate in four steps (see figure 4.17)[111]; step one was formation of 4-chloro-4-hydroxybenzophenone, step two was formation of fenofibrate acid, step three was formation of crude fenofibrate and step four was purification. Each of the four steps require an additional *nine* processes to complete, for a total of *thirty six* steps from start to end, that includes agitation, reflux, cooling, distillation, centrifuge, filtration, extraction, washing, separation, crystallization, drying, milling and blending. While it was not described in detail, it is expected that each of these nine processes at each step will have defined critical processing parameters and CQAs, highlighting the difficulty and complexity of making APIs. These differences in the process can result in the variation observed in particle size between the two materials; however, the differences could also be as a result of mechanical stress introduced during the latter stages of the process such as drying and milling. It is know that many factors such as the manufacturing process and solvent use can impact the crystal form and crystal habit and can therefore the differences in shape and particle size of the crystal for both materials can be supported.

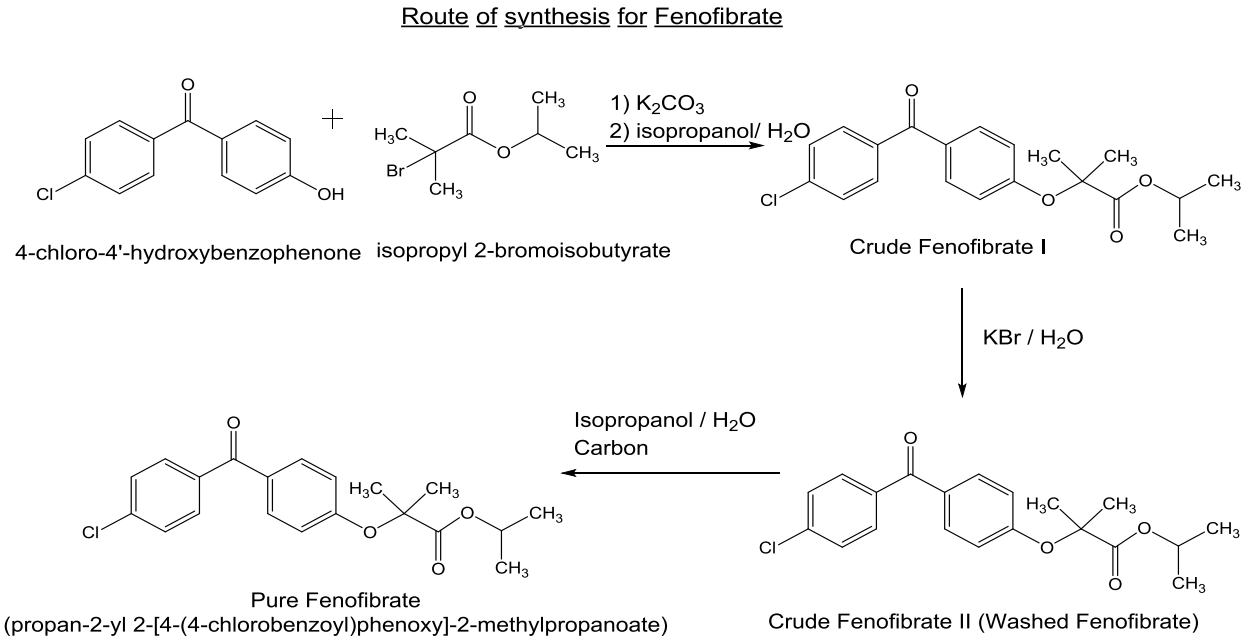


Figure 4.16: Synthetic route for fenofibrate EP/BP for material from by Company J, showing the similarity in both the process and the solvents used in the manufacture of the API compare to Company K[110]

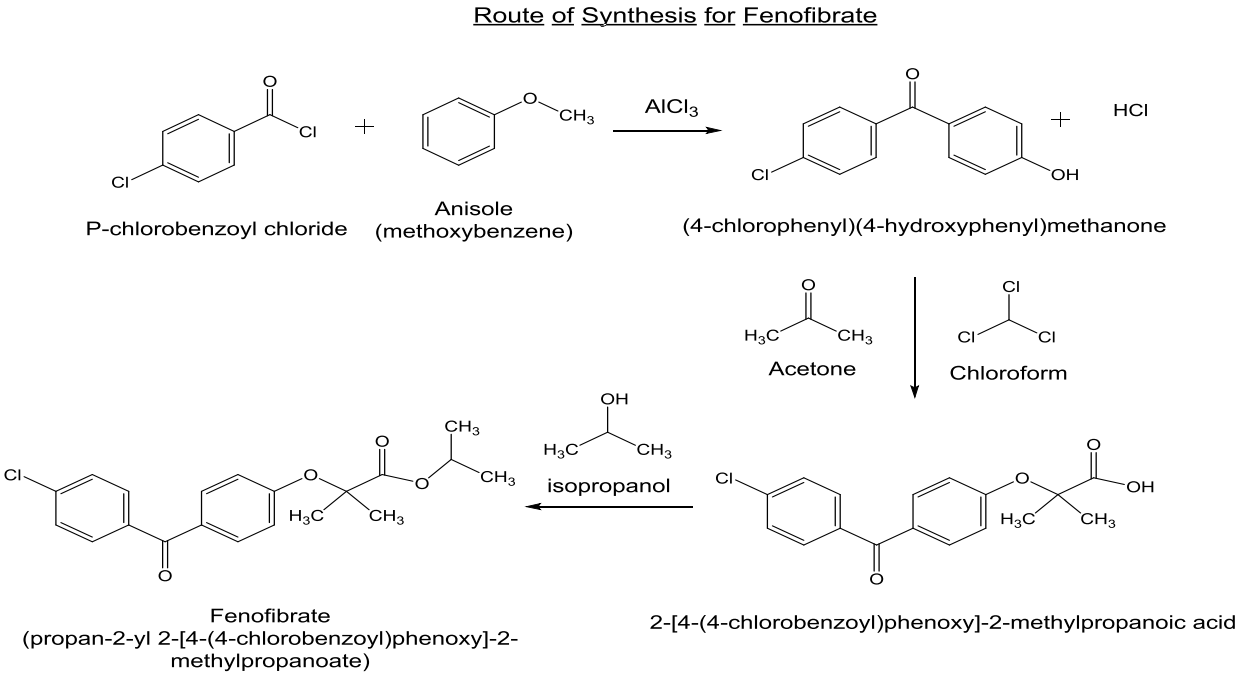


Figure 4.17: Synthetic route for fenofibrate EP/BP for material from Company K showing the similarity in both the process and the solvents used in the manufacture of the API compare to Company J[111]

4.7.3 – Processing and critical quality attributes evaluation

The manufacturing process for the fenofibrate EP/BP was a hot melt extrusion, followed by pulverization of the cooled solids, and then compression of the pulverized blend. The formulation contained fenofibrate BP/EP and croscarmellose sodium NF/EP. Fenofibrate EP/BP is a BCS class II drug, with low solubility and high permeability; the hot melt technology was used to enhance the solubility and dissolution rate of the drug product[112]. The process involves crystallization of the drug substance in an excipient matrix to enhance its physiochemical properties and any change to material or processing conditions can impact the resulting mixture[113]. The Hausner ratio and Carr Index for the pure fenofibrate EP/BP supplied by Company K were 1.18 and 18% respectively, indicating that the material had much better flow and compressibility properties compared to fenofibrate EP/BP supplied by Company J which Hausner ratio and Carr Index of 1.51 and 51% respectively (see table 4.16 below).

Table 4.16: Bulk densities, tapped densities and flow indices for pulverized fenofibrate EP/BP blends prepared using fenofibrate EP/BP from Company J and Company K, and croscarmellose sodium NF/EP from Company G. Hausner ratios and Carr indices (calculated from the experimental density values) are also reported.

Property	**Fenofibrate EP/BP (Company J)**	**Batch 7 (Company J)**		**Fenofibrate EP/BP (Company K)**	**Batch 8 (Company K)**	
	Results	Results	STDEV		Results	STDEV
Bulk density (g/mL)	0.47	0.59	0.03	0.61	0.57	0.05
Tapped density (g/mL)	0.71	0.81	0.03	0.72	0.81	0.05
Flow Index	N/A	30	1.15	N/A	32	1.15
Hausner Ratio	1.51	1.37	0.04	1.18	1.42	0.05
Carr Index (%)	51	37	3.88	18	42	5.33

N/A – Criteria not assessed

Due to the hot melt process, this property was not expected to influence the physical properties of the final blend. The API and excipient were heated to approximately 100°C until a uniform, molten mass was achieved. The material was then poured into high density

polyethylene container to solidify for at least twelve hours, after which it was pulverized twice using a Granumil fitted with 0.625" screen follow by a 0.109" screen. The resulting material was blended with itself prior to compression. The resulting in process granulation blend sieve range targets and results are indicated in table 4.17 and shows that they are very similar for both blends. The results for the sieve analysis, bulk density, tapped density, flow index as well as the resulting Hausner ratio, Carr index were all very similar. The Hausner ratios of 1.37 and 1.42, Carr indices of 37% and 42%, and flow indices of 30 and 32, respectively for fenofibrate EP/BP from Company J and Company K, were obtain for the granulation blends (see table 4.16). All three measures are indicative of a poor flowing and poorly compressible material, which was the observation during the compression process.

Table 4.17: The target sieve analysis range and results for the granulation blend for batches 7 and 8, showing the similarity of the sieve analysis, but with higher variability for batch 8 using fenofibrate EP/BP form Company K.

Sieve Analysis	Limits (%)	Batch 7		Batch 8	
		Results (%)	STDEV	Results (%)	STDEV
20 + 40 mesh	18 - 53	42.8	4.41	45.9	9.18
60 + 80 mesh	0 - 34	12.2	0.90	10.9	0.70
100 + 200 + Fines	22 - 74	45.0	3.23	43.5	8.69

The granulation blends were compressed on a Korsch PH300 press with the target in process quality attributes listed in table 3.8. The press was set up as close as possible to the target quality attribute for the tablets and all attributes were within the target range from the start to the end of the compression run which was approximately one hour in duration (see tables A4.4 and A4.5 in the appendices). The mean compression force at which all of the CQAs were achieved was 5.3 kN for the granulation blend using fenofibrate EP/BP from Company J. The tablet hardness, thickness, friability and disintegration values all remained consistent throughout the

run. The weight was variable throughout the compression run with a STDEV range of 3.3 mg to 11.2 mg. A mean compression force of 5.3 kN was also targeted to achieve the same CQAs for the granulation blend using fenofibrate EP/BP from Company K, and all attributes were found to be well within the range specified. The weight was slightly more consistent than for the run using fenofibrate EP/BP from Company J; however it was still variable with a STDEV range of 6.7 mg to 9.4 mg. The tablet hardness, thickness, friability and disintegration again all remained consistent throughout the run.

The mean compression force at which all physical properties was achieved was the same for both sources of API at 5.3 kN. This was achieved despite the differences observed in the fenofibrate EP/BP obtained from Company K, having a bulk density approximately 30% higher than that for Company J, a particle size that was much higher with a visibly shape difference . In addition the Company K fenofibrate EP/BP had a higher volume weighted mean diameter, surface weighted mean diameter, and 300% less specific surface area. The resulting physical characteristics of the granulation blend and finished tablets were independent of the physical properties of the fenofibrate EP/BP API, and suggests that the hot melt process may be particularly useful in the formulation of tablets using materials from alternate sources as this method nullifies any difference observed in the physical properties of the API.

4.7.4 – Drug product performance evaluation

The assay, dosage uniformity and dissolution of tablets manufactured using fenofibrate EP/BP supplied by Company J were consistently higher than those for tablets manufactured using fenofibrate EP/BP supplied by Company K; however, the variability for both was less than 4% STDEV (for the dissolution and dosage uniformity). The in – vitro performance was similar

regardless of fenofibrate EP/BP source with > 85% dissolved within 15 minutes for both (see table 4.18).

In summary, there were measurable differences observed in the material from the two fenofibrate EP/BP sources; however, these differences did not carry over to the manufacturing process or the drug product. The differences in the two materials ultimately did not have an impact on the in vitro performance and therefore one can propose that there would similarly be no impact on the in-vivo performance.

Table 4.18: Drug product performance test of assay, dosage uniformity and dissolution results for batch 7 (Company J (croscarmellose sodium NF/EP G)) and batch 8 (Company K (croscarmellose sodium NF/EP G))

	Company J (croscarmellose sodium NF/EP G) (%)		Company K (croscarmellose sodium NF/EP G) (%)	
Assay	97.7		96.0	
Dosage Uniformity				
1	97.1		97.7	
2	93.1		94.9	
3	96.7		93.2	
4	102.5		97.2	
5	102.2		96.9	
6	98.3		94.1	
7	100.0		97.5	
8	91.9		100.0	
9	96.0		91.2	
10	99.0		96.9	
Min	91.9		91.2	
Max	102.5		100.0	
Ave	97.68		95.96	
SD	3.49		2.58	
AV	10.70		10.23	
Dissolution Time points	Dissolution	STDEV	Dissolution	STDEV
5mins	76	5	67	4
10mins	97	4	87	2
15mins	103	4	93	2
30mins	104	4	96	2
45mins	105	3	96	2
60mins	105	4	96	2

4.8 - Fenofibrate EP/BP tablets (Batch 9 Company J, Batch 10 Company K; croscarmellose sodium NF/EP supplied by Company H)

4.8.1 – Croscarmellose sodium NF/EP C of A testing

The same two sources and lots of fenofibrate EP/BP used in the manufacture of batches 7 and 8 were also used in the manufacture of batches 9 and 10, which differed in the source of croscarmellose sodium NF/EP, now supplied by Company H. The croscarmellose sodium NF/EP from the two different sources was tested according to the requirements of the C of A for each and these requirements were met (see table 4.19). The specifications were similar for croscarmellose sodium NF/EP supplied from both sources with one clear exception; material supplied by Company G has a specification for particle size while material supplied by Company H does not. The results obtained on the C of A were also comparable with two exceptions, settling volume and sulphated ash. The specification for settling volume was 10 – 30 milliliters for both sources, with a settling volume of 15 milliliters determined in this work for croscarmellose sodium NF/EP supplied by Company G (batch 7 and 8), and 25 milliliters obtained for croscarmellose sodium NF/EP supplied by Company H (batch 9 and 10). Croscarmellose sodium NF/EP is a super disintegrant and the ability of the disintegrant to absorb water and break the tablet apart is measured by the settling volume. The higher the milliliter of water absorb the faster the disintegration time is expected to be. However, despite the 10 milliliter difference in the settling volume the disintegration times were comparable for the two sets of tablets. The disintegration time for batch for batches 7 and 8 range from 3 minutes 35 seconds to 7 minutes 18 seconds, while the disintegration time for batches 9 and 10 range from 4 minutes 48 seconds to 8 minutes 42 seconds. The results obtained are likely due to the higher compression force of 7.4 kN and 7.5 kN used in batch 9 and 10 compare to the 5.3 kN used in batch 7 and 8.

Table 4.19: : The C of A listing the tests, specifications and testing results for croscarmellose sodium NF/EP excipient from Company G and Company H used in batches 7 and 8, and batches 9 and 10 respectively

Test	Specifications	Results (Croscarmellose Sodium NF/EP G)	Results (Croscarmellose Sodium NF/EP H)
Appearance	White or greyish-white, free-flowing powder	Conforms	N/A
Appearance	White or greyish-white powder	N/A	Conforms
Identification	Reaction with Methylene Blue: Sample absorbs methylene blue Appearance of solution after settling: A blue fibrous mass is formed	Conforms Conforms	Conforms Conforms
Identification	Corresponds to ID B. A reddish-violet colour develops at the interface upon reaction with 1-Napthol TS	Conforms	Conforms
Identification	Positive to test for Sodium	Conforms	Conforms
Identification	Positive to flame test for sodium	Conforms	N/A
Heavy Metals	NMT 20 ppm	Less than 20 ppm	N/A
Heavy Metals	NMT 10ppm	N/A	Less than 10 ppm
Sulphated Ash	14.0 to 28.0% (dried basis)	16.5%	19.9%
Microbial Limits	E.Coli: Absent in 1g Total Aerobic Microbial Count: NMT 1000 cfu/g Total Yeast and Mould Count: NMT 100 cfu/g	Absent Less than 100 cfu/g Less than 100 cfu/g	Absent Less than 100 cfu/g Less than 100 cfu/g
Particle Size	D (v,0.5): NM 60um D (v,0.9): NMT 155 um	37 um 85 um	N/A
pH	5.0 to 7.0 (From Manufacturer's C of A)	6.7	6.7
Degree of Substitution	0.60 to 0.85 (dried basis) (From Manufacturer's C of A)	0.77	0.73
Sodium Chloride & Sodium Glycolate	NMT 0.5% (dried basis) (From Manufacturer's C of A)	0.15%	0.4%
Water Soluble substances	NMT 10.0% (From Manufacturer's C of A)	4.2	4.6%
Loss on Drying	NMT 10.0% (From Manufacturer's C of A)	2.4	1.9%
Settling Volume	10 – 30ml (From Manufacturer's C of A)	15 mL	25.0 mL

N/A – Criteria not included in C of A and therefore not tested

Acronyms used in table 4.19:
Cfu/g – Colony forming unit in 1 gram
ID – Identification
NMT – Not more than
ppm – Parts per million

The specification for sulphated ash was 14.0% to 28.0% (dried basis) and the result obtained was 16.5% for croscarmellose sodium NF/EP supplied by Company G and 19.9% obtain for croscarmellose sodium NF/EP supplied by Company H. The C of As for three batches from Company G and four batches from Company H were evaluated to determine if there were any differences within the two sources of material. There was no substantial variability, other than that mentioned above, in the results from the C of A within the batches for each source of API (refer to table A5.1).

A *two tailed t-tests* with a critical *p* (probability) value of 0.05 was performed to determine if there were any significant differences between the two sources of material. The settling volume test was shown to be significantly different between the two sources of material. The mean settling volume for Company G was 15.333 mL with a STDEV of 0.577 mL, the mean settling volume for Company H was 23.000 mL with a STDEV of 1.414 mL and t-test: t(5) = 8.69, p-value = 0.0003.

4.8.2 - Additional testing for croscarmellose sodium NF/EP

The additional tests performed were particle size, specific surface area, surface weighted mean diameter, volume weighted mean, bulk density, tapped density, DSC, TGA, image analysis and SEM.

The particle size was also tested for croscarmellose sodium NF/EP supplied by Company H and the results were comparable to the results obtained for material supplied by Company G. The surface weighted mean diameter, volume weighted mean diameter, and specific surface area

were similar for both sources of material, with the surface weighted mean diameter and volume weighted mean diameter being slightly higher and the specific surface area was slightly lower for material supplied by Company H (see table A5.2 in the appendices) . The image analysis of the two different sources of material (see figure 4.18) shows that the particles were similar in shape and size, while SEM (see figure 4.19) of the two sources of material shows that the morphology was slightly different, with material supplied by Company G been more globular while material supplied by Company H was more fibrous. The DSC thermograms (figures A5.1 and A5.2 in the appendices) confirm that the materials were amorphous in nature, while the thermogravimetric analysis (figures A5.3 and A5.4 in the appendices) correlates to the difference observed in the LOD results between the two materials during the C of A testing.

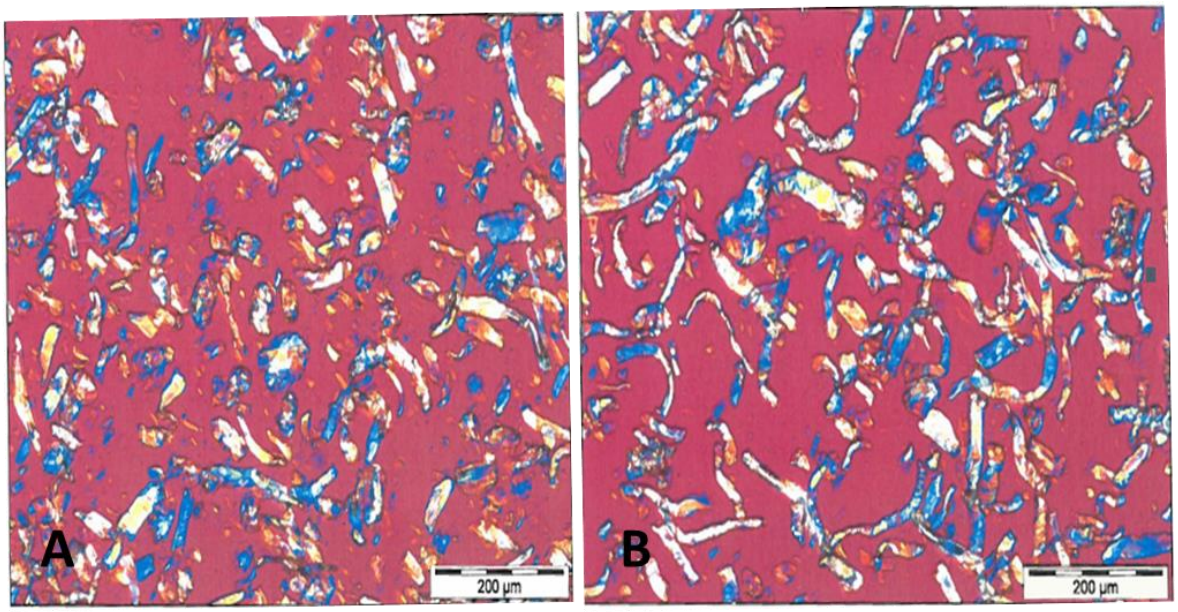


Figure 4.18: Image Analysis for croscarmellose sodium NF/EP supplied by: (A) Company G; (B) Company H, clearly indicating the similarity in the morphology of the two materials but no clear indication of the difference in specific surface area

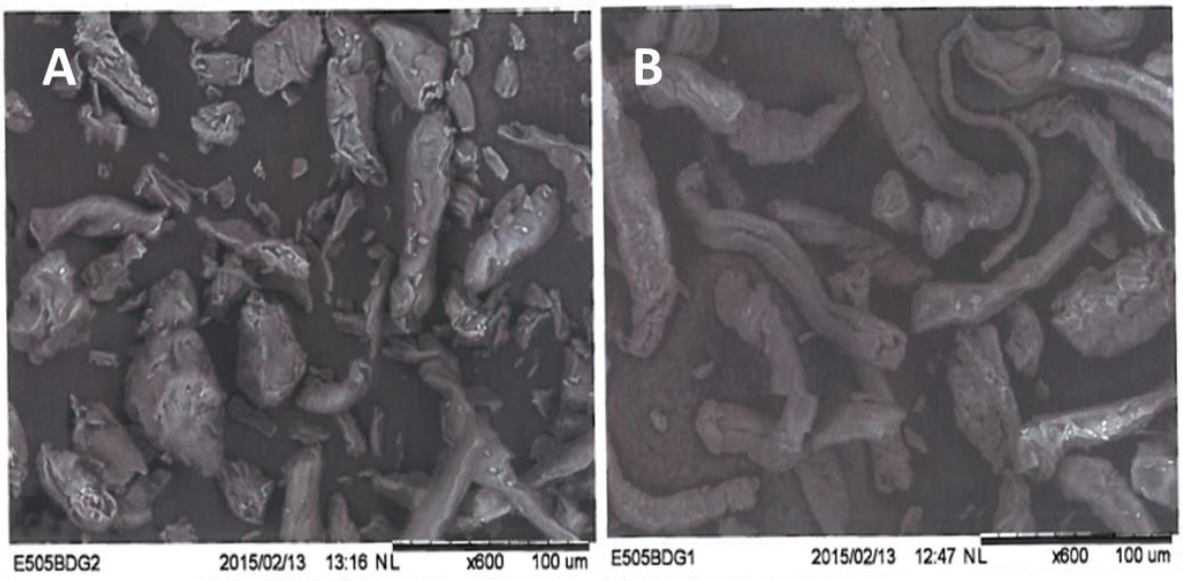


Figure 4.19: Scanning Electron Micrographs for croscarmellose sodium NF/EP supplied by: (A) Company G; (B) Company H, with fractures clearly visible and supporting the 76% higher specific surface area obtained for Company G croscarmellose sodium NF/EP(A).

4.8.3 - Processing and critical quality attributes evaluation

The hot melt manufacturing process used for batches 9 and 10 were the same as for batches 7 and 8 and targets the same in process granulation blend sieve range (as indicated in table 4.17). The Hausner ratios and Carr Indices for croscarmellose sodium NF/EP from both sources are reported in table 4.21, and the values both indicate poor to fair flow for this excipient. The sieve analysis results (table 4.20) for the two granulation blends were almost identical, with less than one percentage difference in the sieve fractions between batches 9 and 10, which was similar to the difference observed in batches 7 and 8. The two granulations blends were, however, slightly finer than that of the previous two batches. The particle size for material from Company H was coarser and the other material properties of the croscarmellose sodium NF/EP could not explain the difference in granulation. The result is likely a function of the manufacturing process that includes a very aggressive milling step using a hammer mill. The bulk density and the tapped density were the same for both batches 9 and 10, and as a result the Hausner ratio and Carr index

were the same at 1.46 and 46% respectively. The flow index of 32mm was the same for both granulation blends confirming the similarity and poor flow characteristics of the two granulation blends.

Table 4.20: The target sieve analysis range and results for the granulation blends for batches 9 and 10, showing the similarity in both the sieve analysis and variability using croscarmellose sodium NF/EP from Company H.

Sieve Analysis	Limits (%)	Batch 9		Batch 10	
		Results (%)	STDEV	Results (%)	STDEV
20 + 40 mesh	18 - 53	40.0	6.91	39.8	6.86
60 + 80 mesh	0 - 34	8.9	1.68	8.6	1.40
100 + 200 + Fines	22 - 74	50.9	5.86	51.3	5.52

Table 4.21: Bulk densities, tapped densities and flow indices for pulverized fenofibrate EP/BP blends prepared using fenofibrate EP/BP from Company J and Company K, and croscarmellose sodium NF/EP from Company H. Hausner ratios and Carr indices (calculated from the experimental density values) are also reported.

Property	Croscarmellose sodium NF/EP (Company G)	Batch 9 (Company J)		Croscarmellose sodium NF/EP (Company H)	Batch 10 (Company K)	
	Results	Results	STDEV		Results	STDEV
Bulk density (g/mL)	0.54	0.52	0.03	0.51	0.52	0.05
Tapped density (g/mL)	0.68	0.76	0.07	0.65	0.76	0.06
Flow Index	N/A	32	0.00	N/A	32	1.41
Hausner Ratio	1.26	1.46	0.07	1.27	1.46	0.04
Carr Index (%)	26	46	7.12	27	46	4.39

N/A - Criteria not assessed

As for batches 7 and 8, granulation blends for batches 9 and 10 were compressed on a Korsch PH300 press with the target in process quality attributes listed in table 3.8. The press was again set up as close as possible to the target quality attribute for the tablets and all attributes were within the target range from the start to the end of the compression run, which was approximately one hour duration. The mean compression force at which all of the CQAs were

achieved was 7.4 kN for batch 9 (fenofibrate EP/BP) from Company J and croscarmellose sodium NF/EP from Company H). The tablet hardness, thickness, friability and disintegration all remain consistent throughout the run, the weight, however, was variable throughout with a STDEV range of 6.0 mg to 10.3 mg. A mean compression force of 7.4 kN was also targeted to achieve the same CQAs for batch 10 (fenofibrate EP/BP) from Company K and croscarmellose sodium NF/EP from Company H) and all were well within the range specified at a slightly higher mean compression force of 7.5 kN (see tables A5.4 and A5.5 in the appendices). This difference of 0.1 kN was not significant and was a function of the variability in the compression machine. The weight was as variable in batch 10 as that observed in batch 9 with a STDEV range of 6.8 mg to 10.1 mg while the tablet hardness, thickness, friability and disintegration all remain consistent throughout the run. The compression force at which all physical properties were achieved was approximately 40 % higher in batches 9 and 10 using croscarmellose sodium NF/EP from Company H; as compared to the 5.3 kN use in batches 7 and 8 using croscarmellose sodium NF/EP from Company G. These results further supports the conclusion that the resulting physical characteristics of the granulation blends and tablets were independent of the physical properties of the fenofibrate EP/BP API from the two different sources and that the manufacturing process was more strongly influenced by the croscarmellose sodium NF/EP excipient source. The slightly higher disintegration time observed for batches manufactured using croscarmellose sodium NF/EP supplied by Company H was likely due to the relatively higher compression force used during the compression. The higher compression force used during tablet manufacture also impacted the 20 minutes friability testing, with broken tablets obtained using croscarmellose sodium NF/EP supplied by Company G but not when croscarmellose sodium NF/EP supplied by Company H was used. While the 20 minutes friability

is not an official specification or in process control, it is usually carried out in the drug product development process during the compression run to evaluate the potential for issues during the coating process.

4.8.4 – Drug product performance evaluation

The assay, dosage uniformity and dissolution of tablets manufactured using fenofibrate EP/BP from either source were similar, with the variability for dosage uniformity less than 1.5% and dissolution less than 6%. The in – vitro performance was similar for both sources of fenofibrate EP/BP with a different source of croscarmellose sodium NF/EP and was > 85% dissolved within 15 minutes for both (see table 4.22). While there were measureable differences observed between the two fenofibrate EP/BP sources, with the exception of the compression force, the manufacturing process and drug product performance was similar to that observed in batches 7 and 8. The different source of croscarmellose sodium NF/EP did not have an impact on the in vitro performance and therefore one can propose that it will also not have an impact on the in-vivo performance of the drug product.

Table 4.22: Drug product performance test of assay, dosage uniformity and dissolution results for batch 9 (Company J (croscarmellose sodium NF/EP H)) and batch 10 (Company K (croscarmellose sodium NF/EP H))

	Company J (croscarmellose sodium NF/EP H) (%)		Company K (croscarmellose sodium NF/EP H) (%)	
Assay	99.9		99.2	
Dosage Uniformity				
1	100.5		101.5	
2	99.7		99.1	
3	99.9		98.3	
4	100.0		98.8	
5	98.3		99.3	
6	102.4		96.5	
7	98.8		98.6	
8	101.3		99.2	
9	99.6		99.5	
10	99.0		101.7	
Min	98.3		96.5	
Max	102.4		101.7	
Ave	99.95		99.25	
SD	1.24		1.30	
AV	3.02		3.88	
Dissolution Time points	Dissolution	STDEV	Dissolution	STDEV
5mins	52	5	54	2
10mins	83	2	87	2
15mins	97	4	97	1
30mins	101	5	102	3
45mins	102	5	103	2
60mins	101	5	103	2

4.9 - Comparison of fenofibrate EP/BP formulations having the same source of fenofibrate EP/BP and different sources of croscarmellose sodium NF/EP (batch 7 vs. batch 9 and batch 8 vs. batch 10)

Fenofibrate EP/BP tablets manufactured using fenofibrate EP/BP obtained from Company J, and croscarmellose sodium NF/EP from Company G (batch 7) were used as the

reference tablets for all the fenofibrate EP/BP formulations. In this section, we will examine a pair wise comparison of batches 7 and 9, and batches 8 and 10, in order to evaluate the impact of the two different sources of croscarmellose sodium NF/EP for tablets formulated with fenofibrate EP/BP obtained from company J and company K, respectively. For the reference tablets (batch 7) the granulation blend was slightly coarser as compared to the results obtained for the blend using croscarmellose sodium NF/EP from company G (batch 9). The compression force at which all CQAs was achieved was 5.3 kN using croscarmellose sodium NF/EP from company G (batch 7) while the compression force at which all physical properties was achieved using croscarmellose sodium NF/EP from company H (batch 9) was higher at 7.4 kN. Interestingly, the Hausner ratios of 1.37 and 1.46, and Carr indices of 37% and 46% (shown in table 4.23), respectively for granulation blends using croscarmellose sodium NF/EP from company G and company H were similar; while, the Hausner ratio and Carr Index for the two sources of croscarmellose sodium NF/EP samples were almost identical (see table 4.21). Even with the much higher compression forces used for croscarmellose sodium NF/EP from company H the weight, hardness, thickness, 4 minutes friability, disintegration, flow, assay and CU results were comparable regardless of the source of croscarmellose sodium NF/EP, and the in – vitro performance was similar for both batches (7 and 9). The only exception is that the 20 minute friability for batch 7 (croscarmellose sodium NF/EP from company G) had broken tablets while batch 9 (croscarmellose sodium NF/EP from company H) did not.

The comparison with the two different croscarmellose sodium NF/EP materials was also made for tablets prepared using fenofibrate EP/BP obtained from Company K (batches 8 and 10). The same observation made for the comparison between batches 7 and 9 can be made for the comparison between batches 8 and 10 with one exception, and that is the hardness is slightly

lower for batch 8 using croscarmellose sodium NF/EP supplied by company G (see table 4.24). There are two other pair wise comparisons, batches 7 and 10 and batches 8 and 9; however, the conclusion is the same as above.

Table 4.23: Comparison of the in process test results for fenofibrate EP/BP formulations with fenofibrate EP/BP tablets made with fenofibrate EP/BP API from Company J and the two different sources of croscarmellose sodium NF/EP (batch 7 vs. batch 9), with the main difference of the compression force with the use of croscarmellose sodium NF/EP from Company H (batch 9)

	Batch 7	Batch 9
12+20 mesh (%)	42.8	40.0
60+80 mesh (%)	12.2	8.9
100+200+ Fines mesh (%)	45.0	50.9
Bulk density (g/mL)	0.59	0.52
Tapped density (g/mL)	0.81	0.76
Hausner Ratio	1.37	1.46
Carr Index (%)	37	46
Compression Force (kN)	5.3	7.4
Hardness (kp)	6	6

Table 4.24: Comparison of the in process test results fenofibrate EP/BP formulations with fenofibrate EP/BP tablets with fenofibrate EP/BP API from Company K and the two different sources of croscarmellose sodium NF/EP (batch 8 vs. batch 10), with the main difference of the compression force with the use of croscarmellose sodium NF/EP from Company H (batch 10)

	Batch 8	Batch 10
12+20 mesh (%)	45.9	39.8
60+80 mesh (%)	10.9	8.6
100+200+ Fines mesh (%)	43.5	51.3
Bulk density (g/mL)	0.57	0.52
Tapped density (g/mL)	0.81	0.76
Hausner Ratio	1.42	1.46
Carr Index (%)	42	46
Compression Force (kN)	5.3	7.5
Hardness (kp)	5	6

Chapter – 5: Summary and Future direction

The materials from the current and alternate sources used for the execution of the ten batches of tablets manufactured in this thesis demonstrate significant differences in the performance of materials, depending upon the source of the materials. These differences in materials supplied from alternate sources generally arise from differences in the synthetic procedures used to manufacture the various APIs and/or excipients, and can include different manufacturing processes, equipment, solvent and batch sizes, etc. These differences in processes then translate into differences in the physicochemical properties for each material. Physicochemical properties, identified in this thesis, that appear to be sensitive to differences in process include particle size, particle shape, densities, residual solvents; in most instances these differences were observed to impact the manufacturing process and the CQAs of the resulting drug product. It is clear that the evaluation of the C of A **must** be more in depth, and go beyond the alternate source material simply meeting the C of A specifications for the reference material.

Specifically relating to the comparisons in this thesis, the two sources of metformin HCl each met the specifications as outlined in the C of A; however, there were substantial differences in the particle size and bulk density of the two materials. The differences in the metformin HCl material were not overcome by the direct compression process resulting in processing challenges and CQA failures.

The two sources of gabapentin USP and copovidone also met specifications; however, measureable differences were observed in bulk density results between the two sources of gabapentin USP, and in particle size results between the two sources of copovidone. The gabapentin USP material from company X had smaller particle size but the resulting granulation was coarser and required much higher compression force to produce equivalent tablets when

compared to the alternate source from company Y. The copovidone NF/EP 35 was finer and had a different morphology than the copovidone NF/EP 20 and the resulting granulation was finer but required 36 % less compression force to produce equivalent tablets with gabapentin USP from company X.

The two sources of fenofibrate EP/BP and croscarmellose sodium NF/EP again met specification, but measureable differences were observed in bulk density results for fenofibrate EP/BP and settling volume and sulphated ash results for croscarmellose sodium NF/EP. The fenofibrate EP/BP from company J was finer but the resulting granulation, compression process and drug product were almost identical. The croscarmellose sodium NF/EP from company G was finer and had a different morphology and required relatively less compression force to produce equivalent tablets. Also, there was an obvious difference in the settling volume that did not impact the disintegration time.

As can be seen from the combined results in this study, the impact on the manufacturing unit operation varies from no impact for the fenofibrate EP/BP materials, to not meeting the CQAs for metformin HCl tablets with the new source of the active pharmaceutical ingredients. The impact of the material attributes such as particle size on the finished drug product can vary, depending on the drug product formulation and the manufacturing process. It is important to identify these differences earlier in the evaluation stage and to assess the impact, if any, on the manufacturing process and the drug product. The tests performed beyond the C of A for the various materials indicates that there were measureable differences in the particle shape, specific surface area, particle size, and densities while comparable results were obtained for the other tests. Importantly, these differences are not captured in the current C of A, and in most cases *could not* be captured using the existing C of A methods.

The ultimate test of any difference in the performance the drug product will be the performance of the drug product *in-vivo*; however, this is generally quite expensive to evaluate and therefore a surrogate test (i.e. the *in – vitro* performance), was evaluated in this work. There was very little, if any, difference between the two sets of active pharmaceutical ingredients and excipients used during this study. While this is most likely to be the case with respect to *in – vivo* performance, the failure of certain tablet CQAs introduces a level of uncertainty with respect to product performance. The requirement to deliver a robust drug product meeting all of the CQAs is as important as the *in vitro* performance, and is a prerequisite by the regulatory bodies to having a consistently performing drug product. The additional testing requirement, as discussed previously, will be dependent on the formulation and process, however, as a minimum test such as particle size, particle shape, bulk density and tapped density should be performed during the evaluation.

Countries around the world, especially the developed ones, are looking at ways to reduce their overall health care costs. With an aging population there will be continued and even increasing pressure to reduce these costs; however, there needs to be a balance between the cost and the quality of the drug product. The need to reduce the cost of prescription medication is currently driven by reducing the cost of the active pharmaceutical ingredients and the excipients use in the formulation of the drug product. Generic companies will launch the equivalent of a brand product at patent expiry and will pay a premium so that they can either be the first on the market or to get a significant market share. As part of the lifecycle management of the product, additional reduction in costs will be required to remain competitive in the market place. The process to qualify an alternate source is a long and costly one and it is an integral part of the strategy to reducing the overall cost of the drug product. If the assessment on the alternate source

material is not comprehensive and effective with respect to the identification of any potential impact on the process and/or quality attribute of the drug product, then the potential cost benefits of making the change may be lost or worse could result in a lost market opportunity. This can be due to several factors such as challenges in the manufacturing process, meeting CQAs and even potential failures of the manufacturing process and drug product. The cost difference between current an alternate source is mainly driven by the use of more efficient manufacturing processes and different raw (starting) material likely from a different sources. "Variability of Product Quality and manufacturability generally arise from two sources: raw material and processes"[95]. There is inherent variability in the manufacturing process and resulting material from batch to batch, and the quality of the final drug product is dependent on the understanding of the complexity of the interactions between the variables and the manufacturing process. This complexity increases significantly if a source of material is changed, and either the change or the material itself is not fully characterized; however, it is unrealistic to run every test on the new source of material to look for differences. The understanding of the material and impact on the manufacturing process and drug product should be known before the change is proposed. As a result, the critical material attributes should be identified during the development of the specific drug product. Monographs are set up to ensure safety and efficacy of the material; but these monographs cannot cover the individual requirement of every manufacturing process, formulation and corresponding drug product. The FDA guidance on Quality by Design, ICH Q7, good manufacturing practise guide for Active Pharmaceutical Ingredients, ICH Q8, pharmaceutical development and ICH Q11, development and manufacture of drug substance guidelines provide the framework under which products should now be developed, and thereby identifying the design space at the time of launching the product. This approach should

ultimately lead to drug product manufacturers defining the requirement of an alternate source upfront rather than looking for differences after, and trying to understand the impact, or worse, introduces the new source which results in a failure in the drug product. Understanding the impact of changes to the API and excipient, and having the ability to correlate these to potential issues with the manufacturing process and drug product CQAs prior to introducing an alternate source of material is critical. This will ensure that there is no disruption to the supply of the drug product and realisation of the cost benefits. This will lead to the ultimate goal of having the best quality product at the best possible price to the patient.

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Appendix A

Metformin Hydrochloride testing

Table A1.1: Additional C of A testing results for metformin HCl USP API from Company A and Company B used to evaluate variability within each source and between the two sources of material in chapter 4.

		Company A				Company B			
Test	Specifications	Batch 1	Batch 2	Batch 3	Batch 4	Batch 1	Batch 2	Batch 3	Batch 4
Appearance	White, crystalline powder	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	IR Spectrum: Corresponds to standard	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Positive for Chloride	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Loss on drying	NMT 0.5 %	0.4	0.3	0.5	0.3	0.2	0.1	0.1	0.1
Sulphated Ash	NMT 0.1%	0	0	0.1	0	0	0	0.1	0
Heavy Metals	NMT 10 ppm	LT 10	LT 10	LT 10	LT 10	LT 10	LT 10	LT 10	LT 10
Organic Volatile Impurities	Methanol: NMT 1000ppm	42	55	36	61	238	311	198	357
Organic Volatile Impurities	Isopropanol: NMT 1000ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Organic Volatile Impurities	Methylene Chloride: NMT 600ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Organic Volatile Impurities	Chloroform: NMT 60ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Organic Volatile Impurities	Trichloroethylene: NMT 80ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Organic Volatile Impurities	N-Butanol: NMT 500ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Organic Volatile Impurities	1,4-Dioxane: NMT 380ppm	ND	ND	ND	ND	N/A	N/A	N/A	N/A
Residual Solvents	Trimethylamine: NMT 50 ppm	16	12	12	13	N/A	N/A	N/A	N/A
Related Compounds	MO RC1: NMT 0.02%	BRT	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds	MO RC2: NMT 0.05%	BRT	BRT	BRT	BRT	N/A	N/A	N/A	N/A
Related Compounds	Unidentified Impurity: NMT 0.10% Each (A) NMT 0.05 % Each (B)	0.03	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds	Total Impurity: NMT 0.5% Each (A) NMT 0.2 % Each (B)	0.03	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds	MO RC3: NMT 0.1% (A) EP Impurity F (MT RC 3): NMT 0.05 % (B)	BRT	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds-	Total Impurities: NMT0.6%	0	BRT	BRT	BRT	N/A	N/A	N/A	N/A
Assay	98.5 - 101.0% (dried basis)	99.7	100.4	100.3	99.9	100.0	100.0	100.0	100.1
Bulk Density	0.6 - 0.9 g/cc	0.7	0.7	0.7	0.7	N/A	N/A	N/A	N/A
Particle Size	% through # 20 mesh: NLT 90 %	100	100	100	100	N/A	N/A	N/A	N/A
Particle Size	% through # 40 mesh: NLT 20 %	86	85	84	85	N/A	N/A	N/A	N/A
Particle Size	% through # 60 mesh: NLT 5 %	52	52	51	54	N/A	N/A	N/A	N/A

N/A – Criteria not included in C of A and therefore not tested

Table A1.2: Results of physical properties test beyond the C of A for metformin HCl USP (Company A and Company B)

	Company A	Company B
Specific Surface Area	0.06 Square Meter per Gram	0.0382 Square Meter per Gram
Surface Weighted Mean Diameter	99.981 um	157.187 um
Volume Weighted Mean Diameter	292.294 um	248.519 um
Particle Size laser Diffraction (um) D 10 D 50 D 90 Minimum Maximum	 62 243 600 2 1000	 91 209 470 10 900
Bulk Density (g/cc)	0.69	0.45
Tapped Density (g/cc)	0.85	0.66

<u>In process test results:</u>

Table A1.3: In – Process Blend results for batches 1 and 2 (Company A and Company B)

	Company A	Company B
Flow Index (mm)	5	5
Bulk Density (g/cc)	0.66	0.55
Tapped Density (g/cc)	0.82	0.72
Sieve Analysis (%) 40 mesh 60 mesh 80 mesh 100 mesh 200 mesh Fines	 14.4 28.0 14.6 8.6 19.4 14.4	 0.6 4.2 20.6 17.4 39.6 16.6

Table A1.4: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 1 (Company A)

	Start	20%	40%	60%	80%	End
Compression Force (kN)	34	34	34	34	34	34
Weight (mg)						
1	607.4	599.3	609.8	600.2	601	604.0
2	602.6	603.7	603.5	607.7	604	607.9
3	603.3	600.6	602.6	597.8	600	596.1
4	596.0	604.5	602.1	602.3	604	598.6
5	601.2	598.8	599.9	600.8	599	598.2
6	614.9	601.3	601.7	598.7	597	601.4
7	601.6	598.6	600.4	599.1	601	602.5
8	604.4	607.9	609.7	603.9	601	609.4
9	600.5	601.8	607.9	598.0	600	601.6
10	602.3	601.9	600.3	595.3	601	602.2
AVE	603.4	601.8	603.8	600.4	600.8	602.2
MIN	596.0	598.6	599.9	595.3	597	596.1
MAX	614.9	607.9	609.8	607.7	604	609.4
SD	5.0	2.9	3.9	3.5	2.1	4.1
CV (%)	0.8	0.5	0.6	0.6	0.3	0.7
Hardness (kp)						
1	6.1	6.1	8.3	8.2	8.9	9.9
2	6.2	7.7	9.8	7.8	10.2	9.8
3	6.6	8.0	6.7	8.7	10.5	8.7
4	5.7	6.9	7.8	8.4	8.1	9.5
5	7.4	8.7	9.4	7.6	8.7	8.3
6	7.0	7.4	8.4	9.1	7.8	7.9
7	7.3	8.4	8.6	9.0	10.2	8.3
8	7.0	8.3	7.5	8.9	9.7	9.5
9	6.3	9.1	10.3	9.8	8.3	8.7
10	7.5	7.9	8.8	8.5	7.7	10.2
AVE	6.7	7.9	8.6	8.6	9.0	9.1
MIN	5.7	6.1	6.7	7.6	7.7	7.9
MAX	7.5	9.1	10.3	9.8	10.5	10.2
SD	0.6	0.9	1.1	0.6	1.1	0.8
CV (%)	9.2	11.2	12.7	7.6	11.8	8.8
Thickness (ins)						
1	0.2165	0.2155	0.2150	0.2140	0.2150	0.2145
2	0.2160	0.2165	0.2160	0.2150	0.2165	0.2140
3	0.2165	0.2165	0.2150	0.2145	0.2155	0.2140
4	0.2170	0.2155	0.2150	0.2135	0.2150	0.2150
5	0.2195	0.2165	0.2155	0.2145	0.2140	0.2140
6	0.2195	0.2165	0.2150	0.2150	0.2130	0.2145
7	0.2165	0.2180	0.2155	0.2145	0.2130	0.2165
8	0.2190	0.2155	0.2150	0.2155	0.2175	0.2150
9	0.2170	0.2175	0.2155	0.2130	0.2145	0.2155
10	0.2160	0.2150	0.2150	0.2150	0.2135	0.2150
AVE	0.2174	0.2163	0.2153	0.2145	0.2148	0.2148
MIN	0.2160	0.2150	0.2150	0.2130	0.2130	0.2140
MAX	0.2195	0.2180	0.2160	0.2155	0.2175	0.2165
SD	0.0014	0.0009	0.0004	0.0008	0.0015	0.0008
CV (%)	0.7	0.4	0.2	0.4	0.7	0.4
Friability (%)						
4 mins	0.3	0.3	0.2	0.3	0.3	0.2
20 mins	3.0	2.1	2.2	1.4	1.5	1.4
Disintegration (Mins:Secs)						
Minimum	3:03	3:30	5:00	4:30	5:09	4:39
Maximum	3:45	6:00	6:00	5:45	6:15	6:05

Table A1.5: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 2 (Company B)

	Start	20%	40%	60%	80%	End	Start	Start	Start	Start
Compression Force (kN)	34	34	34	34	34	34	47.3	57	24.7	17
Weight (mg)										
1	592.1	607.5	592.5	597.5	597.4	596.5	610.2	596.3	601.0	595.3
2	592.4	593.8	596.5	593.5	592.0	602.1	599.9	589.2	594.8	597.6
3	594.0	595.7	606.0	604.4	596.5	604.0	608.8	598.2	593.8	587.1
4	592.0	594.3	592.2	594.1	604.2	596.7	611.2	592.1	605.0	601.1
5	591.8	594.6	593.7	594.6	591.4	597.2	601.1	592.3	593.7	595.3
6	603.8	594.5	593.3	595.1	592.9	594.4	598.8	589.9	595.6	595.0
7	596.6	594.5	598.2	599.6	591.4	604.0	599.7	602.7	589.9	599.5
8	606.0	593.0	606.1	606.1	596.5	593.8	608.2	598.3	598.2	598.5
9	607.6	602.2	600.1	601.2	592.5	593.5	602.7	591.5	593.6	597.0
10	598.1	600.4	602.3	593.7	600.6	599.0	616.7	598.4	587.4	593.7
AVE	597.4	597.1	598.1	598.0	595.5	598.1	605.7	594.9	595.3	596.0
MIN	591.8	593.0	592.2	593.5	591.4	593.5	598.8	589.2	587.4	587.1
MAX	607.6	607.5	606.1	606.1	604.2	604	616.7	602.7	605.0	601.1
SD	6.2	4.7	5.4	4.6	4.3	4.0	6.1	4.5	5.1	3.9
CV (%)	1.0	0.8	0.9	0.8	0.7	0.7	1.0	0.8	0.9	0.6
Hardness (kp)										
1	5.3	5.0	5.1	6.3	5.9	6.1	2.4	2.4	5.6	5.5
2	4.4	4.6	7.6	5.0	5.8	3.7	4.8	4.2	5.6	5.1
3	5.3	5.3	5.3	5.1	5.8	5.7	3.5	2.2	5.0	5.3
4	5.0	1.7	5	5.0	5.1	5.9	2.3	3.6	5.8	5.6
5	5.4	6.1	5.6	5.6	5.7	6.5	2.2	3.1	5.3	5.4
6	3.2	5.8	5.2	6.0	3.8	6.2	3.9	4.3	4.4	5.7
7	5.5	5.6	5.6	5.4	6.4	6.1	3.8	3.6	5.0	5.3
8	5.4	6.5	4.7	5.0	5.7	5.3	4.2	0.8	5.3	5.3
9	5.0	5.2	5.9	5.3	6.5	5.7	1.6	2.7	4.8	4.5
10	4.6	5.6	5.1	6.1	2.2	5.6	4.3	0.9	5.7	4.9
AVE	4.9	5.1	5.5	5.5	5.3	5.7	3.3	2.8	5.3	5.3
MIN	3.2	1.7	4.7	5.0	2.2	3.7	1.6	0.8	4.4	4.5
MAX	5.5	6.5	7.6	6.3	6.5	6.5	4.8	4.3	5.8	5.7
SD	0.7	1.3	0.8	0.5	1.3	0.8	1.1	1.2	0.4	0.4
CV (%)	14.3	25.8	14.7	9.1	25.0	13.7	32.9	44.4	8.5	6.7
Thickness (ins)										
1	0.2165	0.2155	0.2165	0.2180	0.2175	0.2150	0.2190	0.2165	0.2170	0.2210
2	0.2175	0.2180	0.2175	0.2185	0.2150	0.2155	0.2180	0.2165	0.2200	0.2230
3	0.2170	0.2180	0.2170	0.2150	0.2155	0.2150	0.2170	0.2165	0.2175	0.2235
4	0.2160	0.2160	0.2185	0.2155	0.2185	0.2170	0.2205	0.2170	0.2170	0.2225
5	0.2170	0.2165	0.2170	0.2165	0.2155	0.2185	0.2155	0.2165	0.2170	0.2220
6	0.2200	0.2155	0.2175	0.2150	0.2165	0.2170	0.2230	0.2155	0.2175	0.2220
7	0.2165	0.2195	0.2180	0.2155	0.2155	0.2155	0.2185	0.2165	0.2165	0.2230
8	0.2155	0.2170	0.2175	0.2155	0.2155	0.2145	0.2205	0.2215	0.2200	0.2220
9	0.2155	0.2165	0.2180	0.2160	0.2165	0.2150	0.2170	0.2165	0.2195	0.2235
10	0.2185	0.2165	0.2170	0.2190	0.2175	0.2165	0.2170	0.2155	0.2165	0.2215
AVE	0.2170	0.2169	0.2175	0.2165	0.2164	0.2160	0.2186	0.2169	0.2179	0.2224
MIN	0.2155	0.2155	0.2165	0.2150	0.2150	0.2145	0.2155	0.2155	0.2165	0.2210
MAX	0.2200	0.2195	0.2185	0.2190	0.2185	0.2185	0.2230	0.2215	0.2200	0.2235
SD	0.0014	0.0013	0.0006	0.0015	0.0012	0.0013	0.0022	0.0017	0.0014	0.0008
CV (%)	0.6	0.6	0.3	0.7	0.5	0.6	1.0	0.8	0.6	0.4
Friability (%)										
4 mins	Capped	0.3	0.4	0.4	0.3	0.3	Capped	Capped	0.4	0.5
20 mins	Capped	Capped	Capped	Capped	Capped	2.0	Capped	Capped	Capped	Capped
Disintegration (Mins:Secs)										
Minimum	3:26	3:55	4:05	3:39	3:56	3:25	3:56	5:05	1:54	0:17
Maximum	4:26	4:20	4:24	3:51	4:43	3:40	4:55	5:55	2:29	0:20

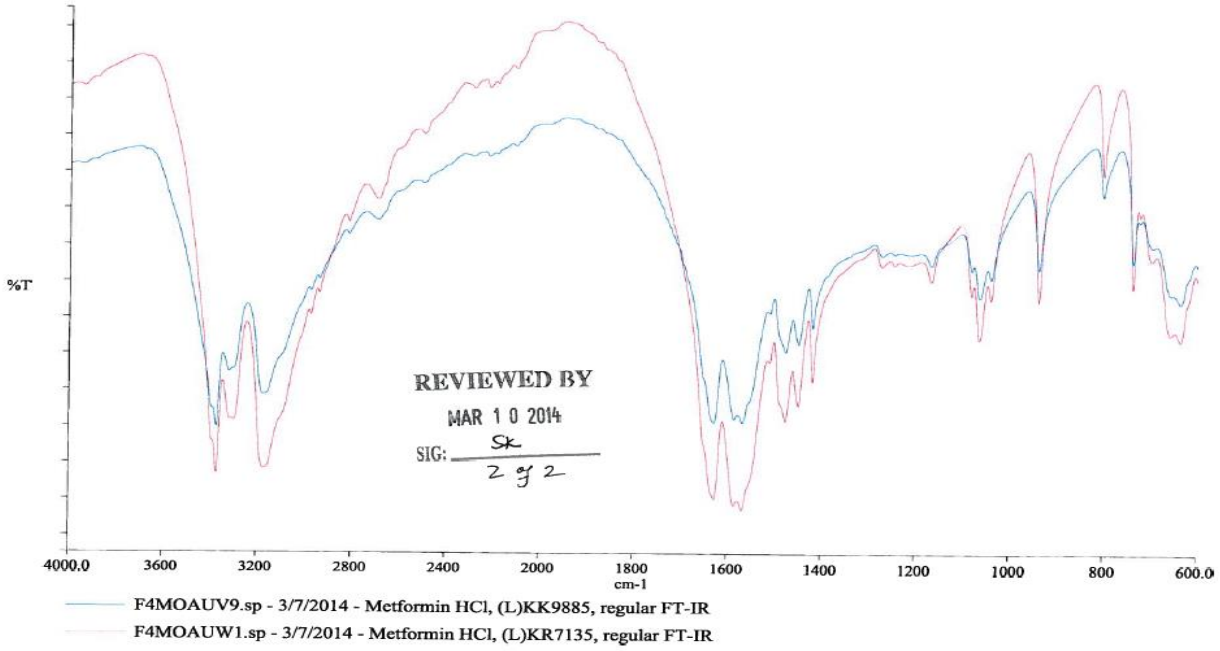

Figure A1.1: FT-IR (Microscope) Spectroscopic characterization for metformin HCl USP (Company A and Company B) clearly indicating similar profile for both sources of material

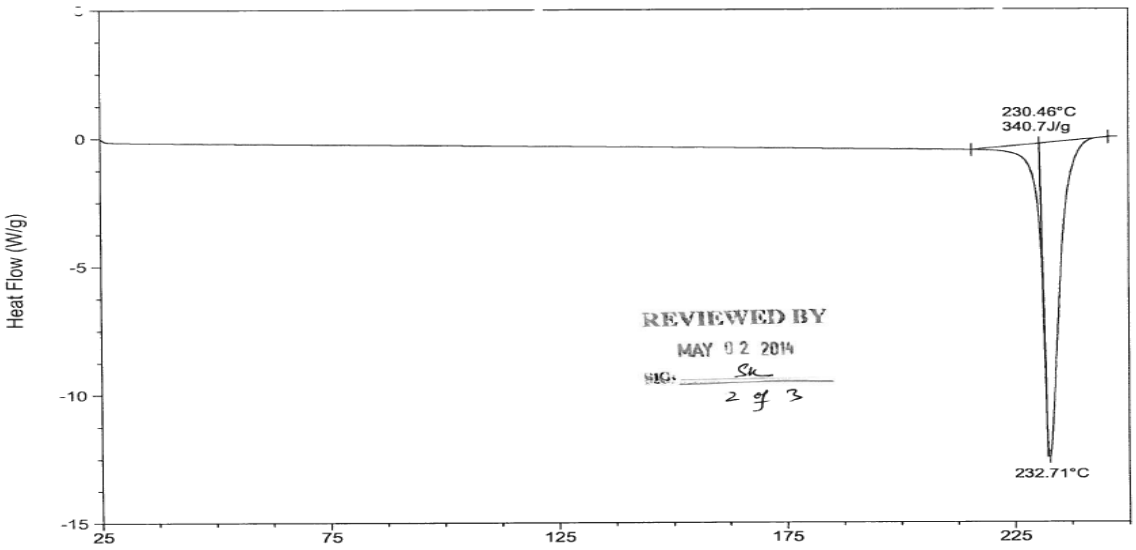

Figure A1.2: Differential Scanning Calorimetric Analysis for metformin HCl USP (Company A) showing the initiation of the phase transition at approximately the same temperature as material from Company B and confirming the crystalline nature of the material with a defined melting point

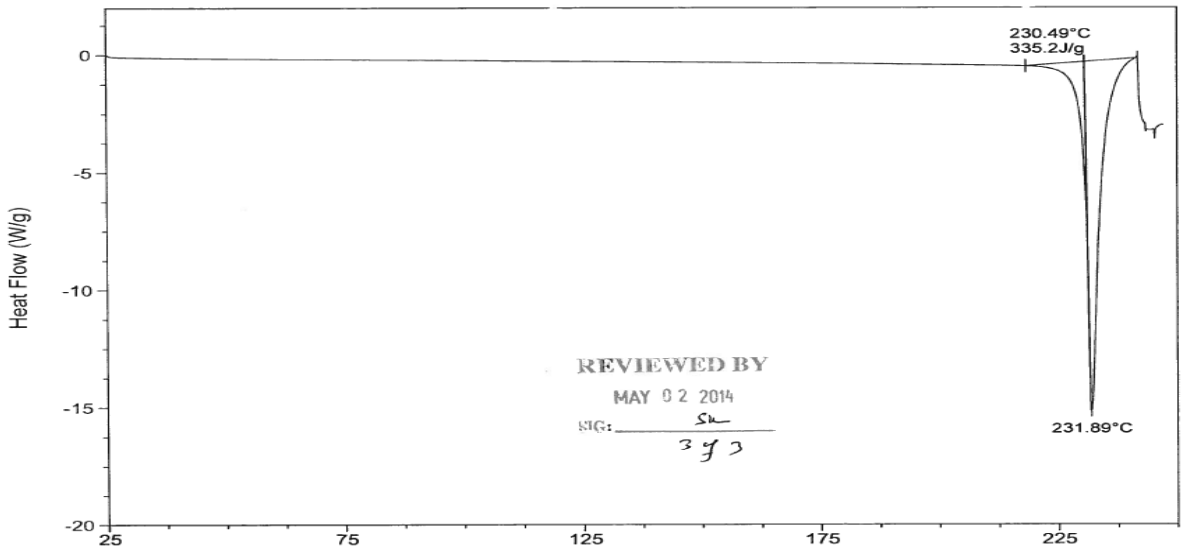

Figure A1.3: Differential Scanning Calorimetric Analysis for metformin HCl USP (Company B) showing the initiation of the phase transition at approximately the same temperature as material from Company A and confirming the crystalline nature of the material with a defined melting point

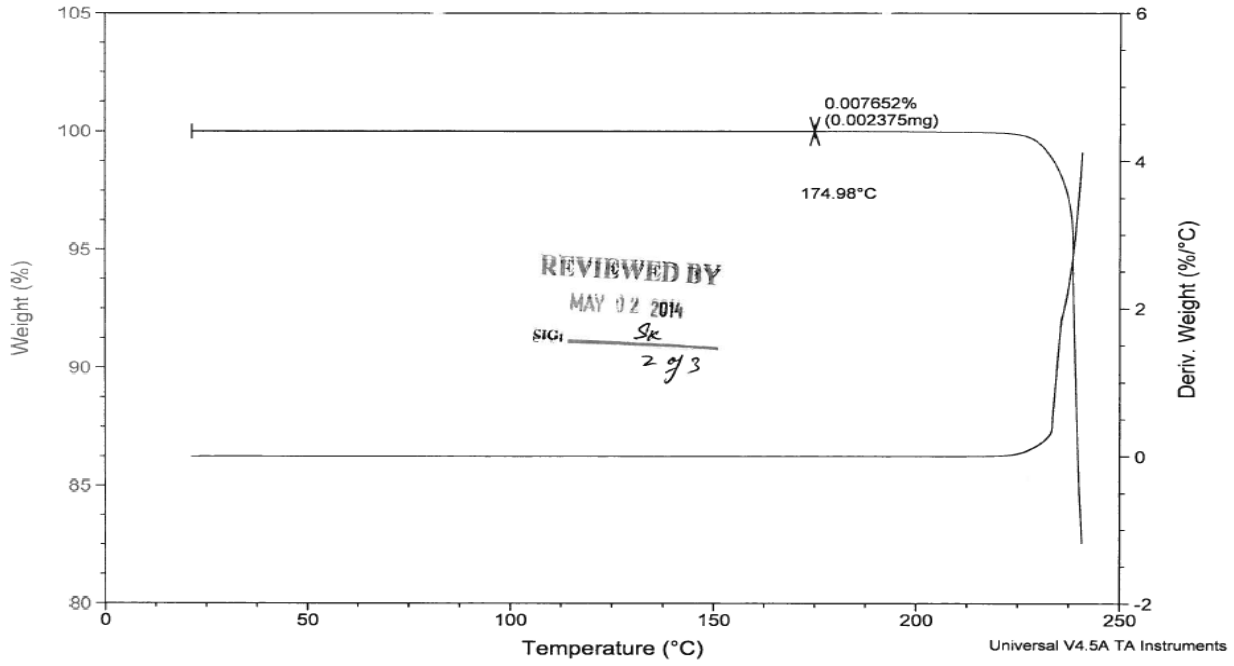

Figure A1.4: Thermo Gravimetric Analysis metformin HCl USP (Company A) clearly indicating a similar weight loss as material from Company B at the same temperature range

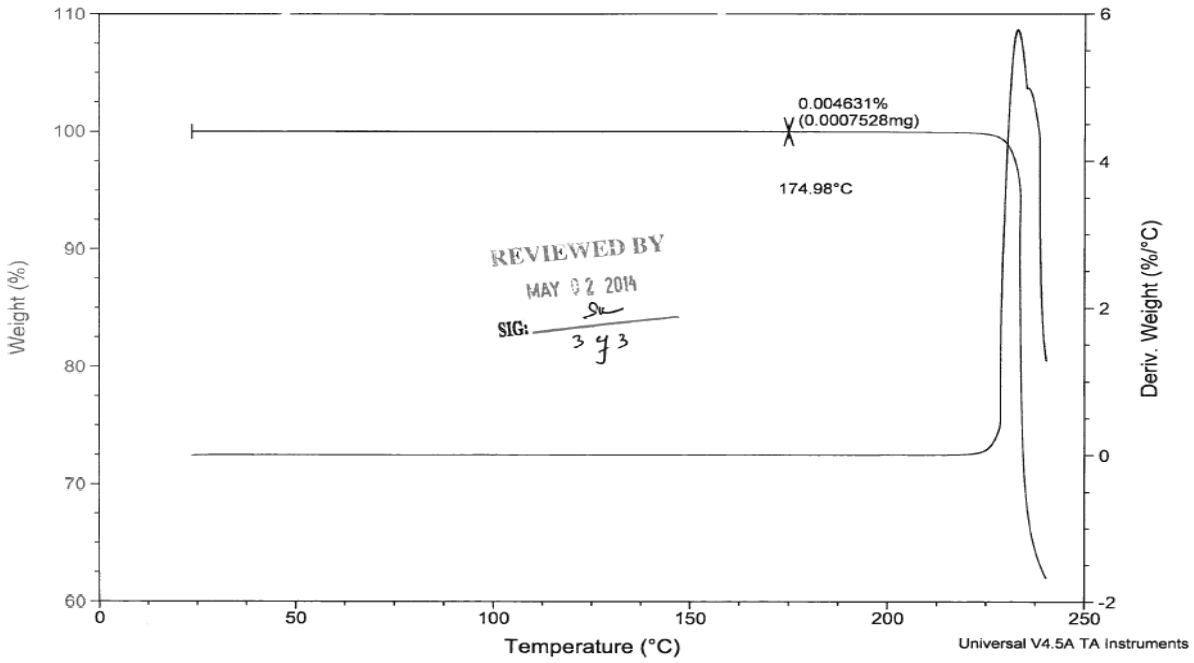

Figure A1.5: Thermo Gravimetric Analysis metformin HCl USP (Company B) clearly indicating a similar weight loss as material from Company A at the same temperature range

Appendix B

Gabapentin USP testing

Table A2.1: Additional C of A testing results for gabapentin USP API from Company X and Company Y used to evaluate variability within each source and between the two sources of material in chapter 4.

		Company X				Company Y			
Test	Specifications	Batch 1	Batch 2	Batch 3	Batch 4	Batch 1	Batch 2	Batch 3	Batch 4
Appearance	White to off-white powder	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	HPLC Retention Time: Corresponds to standard	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	IR Spectrum: Corresponds to Standard	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Polymorphic form III: NMT 5.0%	Conforms	Conforms	Conforms	Conforms	N/A	N/A	N/A	N/A
pH	6.8 - 7.4 (X) 6.5 - 8.0 (Y)	7.2	7.1	7.1	7.1	7.2	7.2	7.2	7.2
Residue on Ignition	NMT0.1%	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Heavy Metals	NMT0.002%	LT0.002	LT0.002	LT0.002	LT0.002	LT0.002	LT0.002	LT0.002	LT0.002
Water	NMT 0.5% (Y)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Chloride	NMT 0.01%	0.00	0.00	0.00	0.01	0.00	0.01	0.01	0.01
Related Compounds	GA RC2: NMT0.05%	BRT	BRT	BRT	0.03	BRT	BRT	BRT	BRT
Related Compounds	Unidentified impurity: NMT0.05% each	BRT	BRT	BRT	BRT	BRT	BRT	ND	BRT
Related Compounds (Limit of late Eluting impurities)	Any impurity: NMT0.10% each (X) NMT0.05% each (Y)	ND	ND	ND	ND	ND	ND	ND	ND
Total Related Compounds	Total Impurities: NMT0.5%	BRT	BRT	BRT	0.03	BRT	BRT	BRT	BRT
Assay	98.5 -101.5% (Anahydrous basis) (X) 98.0 - 102.0% (Anahydrous basis) (Y)	99.7	99.4	99.6	99.7	100.4	99.2	100.8	99.7
Bulk density	0.4 - 0.6 g/cc (X) 0.40 - 0.66 g/cc (Y)	0.6	0.6	0.6	0.6	0.51	0.51	0.52	0.48
Tapped density	0.6 - 1.0 g/cc	0.8	0.8	0.8	0.8	N/A	N/A	N/A	N/A
Residual Solvents	Ethanol: NMT0.2%	N/A	N/A	N/A	N/A	0	0	0	0
Residual Solvents	Methanol: NMT250 ppm	35	20	33	38	N/A	N/A	N/A	N/A
Residual Solvents	Isopropanol: NMT1000 ppm	64	37	61	66	N/A	N/A	N/A	N/A
Residual Solvents	Toluene: NMT100 ppm	0	ND	0	0	N/A	N/A	N/A	N/A
Residual Solvents	Acetone: NMT100 ppm	2	1	2	2	N/A	N/A	N/A	N/A
Partical Size	Percent smaller than 250 µm: NLT 95%	99	99	99	100	N/A	N/A	N/A	N/A
Partical Size	Percent smaller than150µm: NLT 45%	82	76	86	81	N/A	N/A	N/A	N/A

N/A – Criteria not included in C of A and therefore not tested

Table A2.2: Results of physical properties test beyond the C of A for gabapentin USP (Company X and Company Y)

	Company X	Company Y
Specific Surface Area	0.158 Square Meter per Gram	0.0384 Square Meter per Gram
Surface Weighted Mean Diameter	37.879 um	156.352 um
Volume Weighted Mean Diameter	114.124 um	254.367 um
Particle Size laser Diffraction (um) D 10 D 50 D 90 Minimum Maximum	 25 93 233 1 500	 93 206 495 12 900
Bulk Density (g/cc)	0.6	0.51
Tapped Density (g/cc)	0.73	0.64

Table A2.3: In – Process Granulation Blend results for batch 3 (Company X (copovidone NF/EP 35)) and batch 4 (Company Y (copovidone NF/EP 35))

	Company X (copovidone NF/EP 35)	STDEV	Company Y (copovidone NF/EP 35)	STDEV
Flow Index (mm)	18	3.1	18	1.2
Bulk Density (g/cc)	0.54	0.00	0.57	0.04
Tapped Density (g/cc)	0.67	0.00	0.72	0.04
Particle Size by Sieve (%) 20 mesh 40 mesh 60 mesh 80 mesh 100 mesh 200 mesh Fines	 36.0 23.2 8.1 5.4 12.9 6.5 7.7	 0.15 0.09 0.03 0.03 0.05 0.03 0.03	 26.4 22.4 9.2 5.6 5.4 15.8 14.4	 2.59 0.75 0.45 0.14 0.33 0.42 1.91

Table A2.4: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 3 (Company X (copovidone NF/EP 35))

	Start	20%	40%	60%	80%	End
Compression Force (kN)	47	47	47	47	47	47
Weight (mg)						
1	881.7	861.8	865.1	865.8	869.5	866.8
2	868.7	873.9	880.8	863.5	873.7	868.8
3	879.9	870.8	877.4	861.2	868.9	857.1
4	869.0	860.0	866.2	871.2	865.2	870.0
5	874.5	870.9	872.9	878.3	855.9	869.9
6	857.8	861.4	870.5	867.1	861.2	869.4
7	869.3	869.3	874.7	870.4	861.2	880.5
8	871.1	871.9	869.8	872.2	868.3	863.1
9	862.8	855.4	866.4	863.1	863.5	866.0
10	865.7	871.3	864.1	868.2	872.7	875.6
AVE	870.1	866.7	870.8	868.1	866.0	868.7
MIN	857.8	855.4	864.1	861.2	855.9	857.1
MAX	881.7	873.9	880.8	878.3	873.7	880.5
SD	7.3	6.4	5.6	5.1	5.6	6.4
CV (%)	0.8	0.7	0.6	0.6	0.6	0.7
Hardness (kp)						
1	19.8	20.4	24.1	25.0	25.3	23.5
2	20.3	17.5	20.2	23.4	23.3	22.7
3	22.6	23.2	21.7	23.7	22.6	19.6
4	18.8	19.0	23.1	22.7	22.9	21.4
5	20.9	20.1	20.0	21.7	20.9	22.6
6	20.3	22.4	23.3	21.8	23.7	21.5
7	20.3	19.5	20.8	22.3	21.0	21.2
8	22.3	21.1	22.2	20.9	23.0	22.6
9	19.2	21.2	21.9	21.8	23.0	22.7
10	20.8	22.5	23.1	23.6	21.4	24.3
AVE	20.5	20.7	22.0	22.7	22.7	22.2
MIN	18.8	17.5	20.0	20.9	20.9	19.6
MAX	22.6	23.2	24.1	25.0	25.3	24.3
SD	1.2	1.8	1.4	1.2	1.3	1.3
CV (%)	5.9	8.5	6.3	5.4	5.9	6.0
Thickness (ins)						
1	0.2550	0.2530	0.2530	0.2525	0.2530	0.2530
2	0.2535	0.2530	0.2515	0.2535	0.2525	0.2520
3	0.2530	0.2525	0.2555	0.2500	0.2530	0.2495
4	0.2530	0.2525	0.2520	0.2535	0.2515	0.2505
5	0.2510	0.2545	0.2535	0.2525	0.2515	0.2500
6	0.2535	0.2535	0.2530	0.2500	0.2525	0.2525
7	0.2545	0.2515	0.2540	0.2520	0.2535	0.2500
8	0.2535	0.2520	0.2530	0.2535	0.2520	0.2500
9	0.2520	0.2550	0.2560	0.2520	0.2510	0.2490
10	0.2530	0.2530	0.2500	0.2530	0.2505	0.2535
AVE	0.2532	0.2531	0.2532	0.2523	0.2521	0.2510
MIN	0.2510	0.2515	0.2500	0.2500	0.2505	0.2490
MAX	0.2550	0.2550	0.2560	0.2535	0.2535	0.2535
SD	0.0011	0.0011	0.0018	0.0013	0.0010	0.0016
CV (%)	0.4	0.4	0.7	0.5	0.4	0.6
Friability (%)						
4 mins	0.4	0.5	0.6	0.5	0.5	0.5
20 mins	2.0	2.4	2.3	1.9	2.4	2.2
Disintegration (Mins:Secs)						
Minimum	22:27	21:34	22:26	21:37	22:11	23:50
Maximum	24:28	22:48	24:48	23:29	22:24	24:09

Table A2.5: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 4 (Company Y (copovidone NF/EP 35))

	Start	20%	40%	60%	80%	End	Start
Compression Force (kN)	38.5	38.5	38.5	38.5	38.5	38.5	47
Weight (mg)							
1	868.1	872.7	868.6	863.1	876.2	861.2	872.1
2	868.1	873.9	869.6	870.1	855.2	868.4	874.1
3	868.3	862.3	872.0	872.0	869.5	866	864.7
4	851.2	866.4	865.5	856.7	864.0	867.5	877.4
5	870.7	860.4	863.5	858.2	869.5	861.5	873.8
6	855.8	862.3	871.6	858.5	863.6	866.6	868.0
7	877.2	877.5	861.7	867.2	863.0	863.7	872.3
8	858.8	851.9	868.0	868.2	868.5	871.5	873.8
9	867.3	860.5	862.6	864.7	873.6	863.2	864.4
10	868.4	859.3	878.2	862.2	865.1	869.6	880.6
AVE	865.4	864.7	868.1	864.1	866.8	865.9	872.1
MIN	851.2	851.9	861.7	856.7	855.2	861.2	864.4
MAX	877.2	877.5	878.2	872.0	876.2	871.5	880.6
SD	7.7	7.9	5.1	5.3	6.0	3.5	5.2
CV (%)	0.9	0.9	0.6	0.6	0.7	0.4	0.6
Hardness (kp)							
1	21.8	24.1	22.1	23.3	20.6	23.8	22.7
2	21.4	21.1	23.2	19.5	22.9	21.7	22.7
3	20.8	22.0	22.7	21.7	23.0	22.5	24.9
4	24.2	21.6	21.2	22.2	20.8	22.5	23.1
5	25.3	19.7	21.8	19.8	22.6	21.6	24.8
6	18.9	22.8	21.3	22.0	20.6	23.4	23.4
7	21.2	22.7	20.7	23.3	23.9	22.9	23.2
8	24.5	20.3	23.2	23.0	21.6	21.3	24.0
9	21.5	23.3	23.3	23.6	23.3	22.4	23.3
10	22.6	22.4	22.8	21.7	23.5	21.5	24.7
AVE	22.2	22.0	22.2	22.0	22.3	22.4	23.7
MIN	18.9	19.7	20.7	19.5	20.6	21.3	22.7
MAX	25.3	24.1	23.3	23.6	23.9	23.8	24.9
SD	1.9	1.4	0.9	1.4	1.3	0.8	0.9
CV (%)	8.8	6.2	4.3	6.5	5.7	3.8	3.6
Thickness (ins)							
1	0.2515	0.2530	0.2520	0.2525	0.2525	0.2515	0.2480
2	0.2490	0.2500	0.2535	0.2495	0.2535	0.2535	0.2505
3	0.2535	0.2520	0.2515	0.2515	0.2525	0.2535	0.2520
4	0.2525	0.2490	0.2545	0.2510	0.2520	0.2520	0.2510
5	0.2520	0.2505	0.2520	0.2520	0.2530	0.2515	0.2525
6	0.2550	0.2530	0.2515	0.2520	0.2525	0.2525	0.2485
7	0.2535	0.2510	0.2510	0.2510	0.2515	0.2530	0.2510
8	0.2560	0.2525	0.2520	0.2520	0.2530	0.2530	0.2510
9	0.2525	0.2505	0.2515	0.2525	0.2490	0.2505	0.2500
10	0.2535	0.2510	0.2515	0.2520	0.2530	0.2530	0.2500
AVE	0.2529	0.2513	0.2521	0.2516	0.2523	0.2524	0.2505
MIN	0.2490	0.2490	0.2510	0.2495	0.2490	0.2505	0.2480
MAX	0.2560	0.2530	0.2545	0.2525	0.2535	0.2535	0.2525
SD	0.0019	0.0013	0.0011	0.0009	0.0013	0.0010	0.0014
CV (%)	0.8	0.5	0.4	0.4	0.5	0.4	0.6
Friability (%)							
4 mins	0.5	0.6	0.5	0.6	0.6	0.6	0.6
20 mins	2.3	2.5	2.3	2.4	2.4	2.5	2.0
Disintegration (Mins:Secs)							
Minimum	22:17	22:47	22:14	21:55	20:42	22:58	24:18
Maximum	22:37	24:16	24:30	23:14	22:58	23:48	25:06

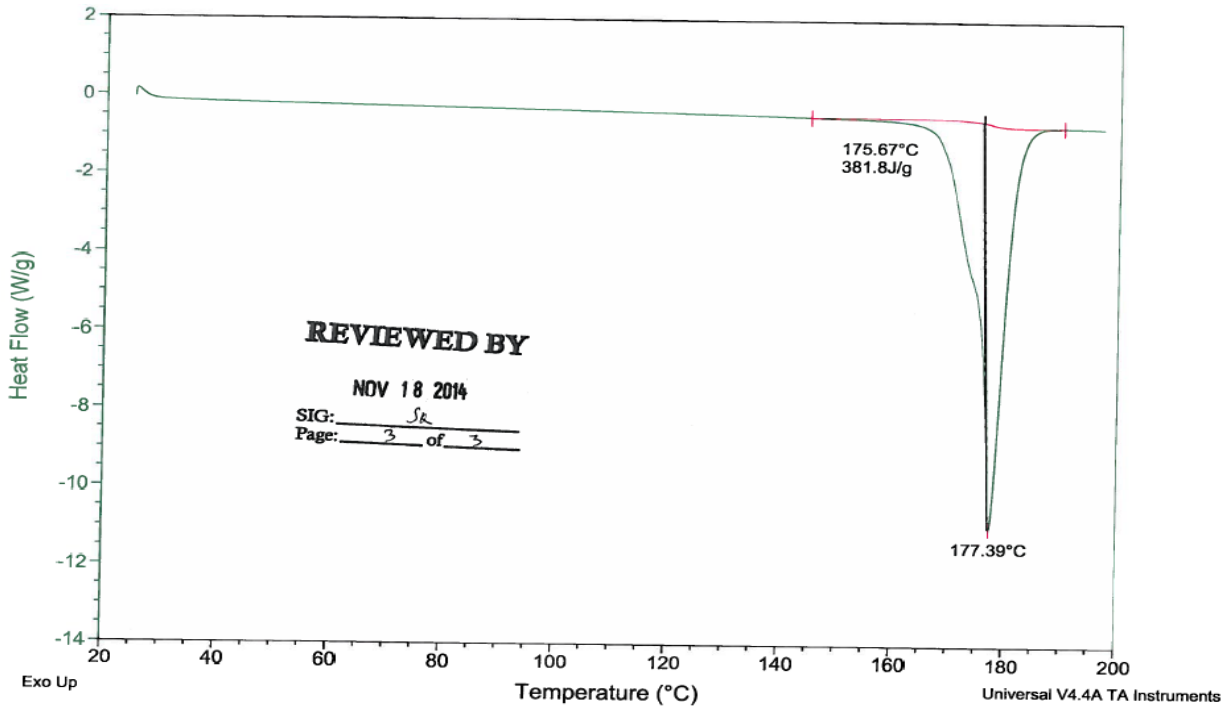

Figure A2.1: Differential Scanning Calorimetric Analysis for gabapentin USP (Company X) showing the initiation of the phase transition at the same temperature as material from Company Y and confirming the crystalline nature of the material with a defined melting point.

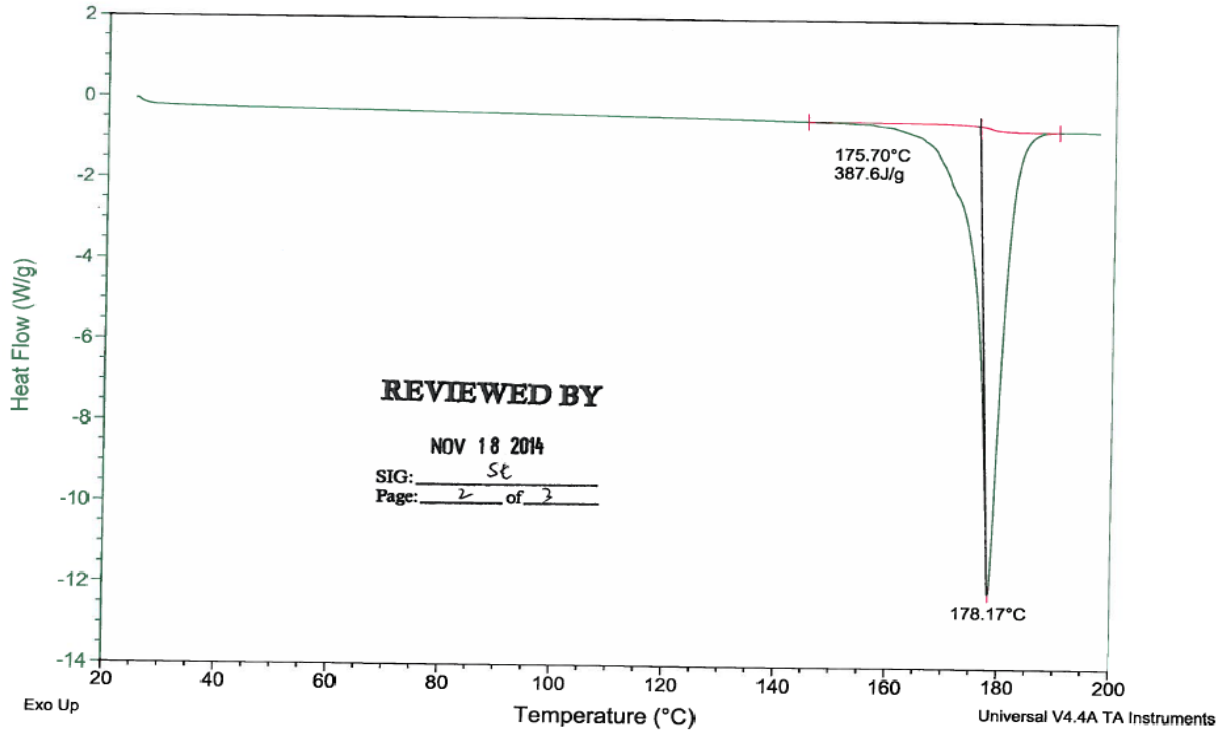

Figure A2.2: Differential Scanning Calorimetric Analysis for gabapentin USP (Company Y) showing the initiation of the phase transition at the same temperature as material from Company X and confirming the crystalline nature of the material with a defined melting point.

Appendix C

Copovidone NF/EP testing

Table A3.1: Additional C of A testing results for copovidone NF/EP 35 and copovidone NF/EP 20 used to evaluate variability within each source and between the two sources of material in chapter 4.

		Copovidone NF/EP 35				Copovidone NF/EP 20			
Test	Specification	Batch 1	Batch 2	Batch 3	Batch 4	Batch 1	Batch 2	Batch 3	Batch 4
Appearance	white or slightly yellowish powder	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Corresponds to ID B (USP)	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	IR Spectrum: Corresponds to Standard	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Appearance of Solution	Clarity: Sample solution is not more opalescent than reference suspension III Colour: Sample solution is not more intensely coloured than reference solution B5, R5, OR	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Aldehydes	NMT 500 ppm	0	245	135	0	0	219	0	18
Ethenyl Acetate	35.3 to 41.4 % (dried basis)	38.2	37.5	38.4	38	36.8	37.3	37.8	38.4
Heavy Metals	NMT 20 ppm	LT 20	LT 20	LT 20	LT 20	LT 20	LT 20	LT 20	LT 20
Hydrazine	1ppm	ND	ND	ND	ND	ND	ND	ND	ND
Impurities A	NMT 0.5%	BRT	BRT	BRT	BRT	0.1	0.1	0.1	0.1
Loss on drying	NMT 5.0	3.2	3	2.7	2.1	2.3	2.2	1.9	2.7
Monomers	NMT 0.1 %	0.1	0.1	0.1	0.1	0	0	0	0
Nitrogen	7.0-8.0 % (dried basis)	7.0	7.1	7.2	7.1	7.2	7.7	7.2	7.3
Peroxides	NMT 0.35 (400 ppm)	LT 400	LT 400	LT 400	LT 400	LT 400	LT400	LT 400	LT400
Sulphated Ash	NMT 0.1%	0	0	0	0	0	0	0	0.1
Viscosity (As K-value)	25.2-30.8 (dried basis)	26.0	27.8	25.7	25.7	25.4	27.0	25.7	26.3
Particle Size	D(v,0.1):NLT 18µm	34	38	35	35	59	31	32	28
Particle Size	D(v,0.5):NMT 135µm	85	85	85	83	128	93	96	88
Particle Size)	D(v,0.9):NMT 290µm	179	172	178	166	239	206	211	191

Table A3.2: Results of physical properties test beyond the C of A for copovidone NF/EP 35 and copovidone NF/EP 20

	Copovidone NF/EP 35	Copovidone NF/EP 20
Specific Surface Area	0.124 Square Meter per Gram	0.0697 Square Meter per Gram
Surface Weighted Mean Diameter	48.569 um	86.128 um
Volume Weighted Mean Diameter	91.938 um	136.905 um
Particle Size laser Diffraction (um) D 10 D 50 D 90 Minimum Maximum	 32 80 167 2 400	 48 125 245 7 300
Bulk Density g/cc	0.36	0.30
Tapped Density g/cc	0.43	0.38

Table A3.3: In – Process Granulation Blend results for batch 5 (Company X (copovidone NF/EP 20)) and batch 6 (Company Y (copovidone NF/EP 20))

	Company X (copovidone NF/EP 20)	STDEV	Company Y (copovidone NF/EP 20)	STDEV
Flow Index (mm)	18	2.0	18	1.2
Bulk Density (g/cc)	0.57	0.02	0.56	0.02
Tapped Density (g/cc)	0.72	0.02	0.71	0.02
Particle Size by Sieve (%) 20 mesh 40 mesh 60 mesh 80 mesh 100 mesh 200 mesh Fines	 20.3 18.0 10.2 7.4 6.5 21.1 16.2	 1.92 0.82 0.27 0.32 1.96 2.03 2.38	 23.9 19.7 10.1 6.9 6.7 17.6 14.2	 3.80 0.71 0.42 0.54 0.36 0.92 2.11

Table A3.4: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 5 Company X (copovidone NF/EP 20)

	Start	20%	40%	60%	80%	End	Start	Start
Compression Force (kN)	64	64	64	64	64	64	47	37
Weight (mg)								
1	875.7	869.0	875.6	874.3	869.6	883.2	882.2	874.8
2	866.1	873.1	867.3	876.8	874.4	876.5	892.7	883.5
3	876.0	869.8	864.3	868.4	875.9	867.5	874.0	882.5
4	877.2	880.2	869.9	872.2	867.1	871.3	882.3	879.6
5	876.0	873.6	876.2	864.8	871.9	871.8	886.5	880.0
6	867.5	866.8	871.6	873.0	866.9	879.4	876.4	869.7
7	874.7	869.8	867.9	857.1	864.8	869.5	876.8	877.8
8	879.3	876.8	865.3	876.3	874.4	872.0	876.7	876.4
9	869.1	870.1	870.2	874.8	871.4	865.6	876.1	875.2
10	871.5	870.0	871.5	875.0	873.2	874.5	877.7	878.3
AVE	873.3	871.9	870.0	871.3	871.0	873.1	880.1	877.8
MIN	866.1	866.8	864.3	857.1	864.8	865.6	874.0	869.7
MAX	879.3	880.2	876.2	876.8	875.9	883.2	892.7	883.5
SD	4.5	4.0	4.0	6.2	3.7	5.4	5.8	4.0
CV (%)	0.5	0.5	0.5	0.7	0.4	0.6	0.7	0.5
Hardness (kp)								
1	20.6	20.0	21.1	20.8	21.9	22.0	19.3	15.1
2	19.3	20.7	19.7	22.5	18.8	22.6	16.5	16.5
3	21.0	19.8	21.9	20.6	19.4	22.7	18.3	17.8
4	17.6	19.9	19.5	20.2	19.2	21.8	17.2	15.5
5	20.2	19.6	19.9	18.6	19.5	21.1	17.8	17.0
6	21.3	21.6	20.7	22.0	19.0	22.0	18.8	15.5
7	21.6	22.2	22.1	21.4	21.3	22.8	19.2	17.3
8	21.3	19.8	20.0	20.1	20.1	22.4	13.7	13.9
9	18.6	21.5	21.1	18.7	22.4	20.4	16.1	15.6
10	20.8	20.8	19.9	22.3	20.9	23.3	19.0	17.1
AVE	20.2	20.6	20.6	20.7	20.3	22.1	17.6	16.1
MIN	17.6	19.6	19.5	18.6	18.8	20.4	13.7	13.9
MAX	21.6	22.2	22.1	22.5	22.4	23.3	19.3	17.8
SD	1.3	0.9	0.9	1.4	1.3	0.9	1.8	1.2
CV (%)	6.5	4.4	4.5	6.6	6.4	3.9	10.1	7.5
Thickness (ins)								
1	0.2535	0.2540	0.2530	0.2560	0.2510	0.2525	0.2580	0.2565
2	0.2530	0.2545	0.2525	0.2510	0.2570	0.2530	0.2585	0.2585
3	0.2535	0.2545	0.2535	0.2540	0.2535	0.2545	0.2610	0.2615
4	0.2520	0.2510	0.2525	0.2505	0.2550	0.2520	0.2585	0.2590
5	0.2540	0.2570	0.2545	0.2535	0.2550	0.2535	0.2590	0.2590
6	0.2525	0.2500	0.2550	0.2535	0.2535	0.2545	0.2595	0.2595
7	0.2520	0.2545	0.2530	0.2550	0.2520	0.2530	0.2580	0.2630
8	0.2530	0.2560	0.2540	0.2520	0.2565	0.2535	0.2565	0.2605
9	0.2550	0.2535	0.2535	0.2540	0.2515	0.2540	0.2595	0.2630
10	0.2525	0.2545	0.2520	0.2530	0.2535	0.2530	0.2600	0.2600
AVE	0.2531	0.2540	0.2534	0.2533	0.2539	0.2534	0.2589	0.2601
MIN	0.2520	0.2500	0.2520	0.2505	0.2510	0.2520	0.2565	0.2565
MAX	0.2550	0.2570	0.2550	0.2560	0.2570	0.2545	0.2610	0.2630
SD	0.0009	0.0021	0.0009	0.0017	0.0020	0.0008	0.0012	0.0020
CV (%)	0.4	0.8	0.4	0.7	0.8	0.3	0.5	0.8
Friability (%)								
4 mins	0.8	0.7	0.8	0.6	0.7	0.7	0.8	0.9
20 mins	2.9	2.7	2.8	2.4	2.5	2.6	3.2	3.4
Disintegration (Mins:Secs)								
Minimum	23:02	22:36	21:50	22:30	22:02	22:05	23:15	22:44
Maximum	24:18	24:10	24:26	23:19	24:19	23:48	24:05	25:02

Table A3.5: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 6 Company Y (copovidone NF/EP 20)

	Start	20%	40%	60%	80%	End	Start	Start
Compression Force (kN)	47	47	47	47	47	47	38.5	60
Weight (mg)								
1	877.0	876.6	863.0	877.8	869.2	875.5	867.2	871.7
2	868.1	879.6	868.5	869.0	883.5	865.8	873.3	867.9
3	869.0	870.0	874.6	868.1	866.9	874.6	881.5	867.9
4	876.3	878.8	877.3	876.6	866.3	877.1	872.4	855.9
5	871.0	878.1	869.1	871.5	877.2	880.8	870.0	867.7
6	877.8	868.5	865.8	874.8	873.7	868.8	873.3	864.6
7	869.7	868.4	872.1	872.2	868.2	879.7	859.0	856.7
8	874.3	869.5	872.2	867.6	878.9	868.9	883.6	861.2
9	872.9	867.0	868.9	875.1	865.3	867.4	868.1	865.7
10	862.9	867.8	874.3	882.8	864.4	882.1	876.1	861.2
AVE	871.9	872.4	870.6	873.6	871.4	874.1	872.5	864.1
MIN	862.9	867.0	863.0	867.6	864.4	865.8	859.0	855.9
MAX	877.8	879.6	877.3	882.8	883.5	882.1	883.6	871.7
SD	4.7	5.1	4.3	4.8	6.6	6.0	7.1	5.2
CV (%)	0.5	0.6	0.5	0.6	0.8	0.7	0.8	0.6
Hardness (kp)								
1	19.9	18.4	20.3	20.0	18.9	20.6	16.5	22.8
2	21.2	19.9	20.8	21.5	19.0	22.0	17.6	21.6
3	19.0	19.6	18.8	19.3	20.1	20.0	17.5	22.7
4	17.8	19.6	21.8	19.4	18.8	19.4	16.6	23.5
5	20.1	19.2	19.7	20.7	20.4	21.1	19.6	21.9
6	20.5	20.7	19.5	21.8	21.7	22.0	16.8	21.5
7	19.2	19.0	19.7	19.0	19.4	18.9	18.6	22.9
8	20.5	18.8	19.6	21.1	19.6	19.9	16.7	21.7
9	19.4	20.7	22.3	20.5	20.4	19.8	15.6	21.2
10	23.0	20.9	18.7	21.2	20.5	20.2	18.1	21.0
AVE	20.1	19.7	20.1	20.5	19.9	20.4	17.4	22.1
MIN	17.8	18.4	18.7	19.0	18.8	18.9	15.6	21.0
MAX	23.0	20.9	22.3	21.8	21.7	22.0	19.6	23.5
SD	1.4	0.9	1.2	1.0	0.9	1.0	1.2	0.8
CV (%)	7.0	4.4	5.9	4.8	4.6	5.1	6.7	3.8
Thickness (ins)								
1	0.2535	0.2545	0.2555	0.2535	0.2505	0.2530	0.2595	0.2530
2	0.2565	0.2550	0.2545	0.2565	0.2540	0.2550	0.2595	0.2530
3	0.2555	0.2530	0.2525	0.2555	0.2545	0.2505	0.2590	0.2495
4	0.2540	0.2505	0.2545	0.2565	0.2555	0.2575	0.2580	0.2525
5	0.2545	0.2535	0.2560	0.2515	0.2530	0.2565	0.2555	0.2505
6	0.2560	0.2550	0.2515	0.2550	0.2550	0.2585	0.2545	0.2505
7	0.2555	0.2535	0.2560	0.2535	0.2530	0.2525	0.2610	0.2520
8	0.2550	0.2515	0.2530	0.2560	0.2535	0.2540	0.2580	0.2495
9	0.2560	0.2535	0.2540	0.2585	0.2530	0.2510	0.2595	0.2495
10	0.2575	0.2560	0.2525	0.2575	0.2545	0.2535	0.2565	0.2520
AVE	0.2554	0.2536	0.2540	0.2554	0.2537	0.2542	0.2581	0.2512
MIN	0.2535	0.2505	0.2515	0.2515	0.2505	0.2505	0.2545	0.2495
MAX	0.2575	0.2560	0.2560	0.2585	0.2555	0.2585	0.2610	0.2530
SD	0.0012	0.0017	0.0016	0.0021	0.0014	0.0027	0.0020	0.0015
CV (%)	0.5	0.7	0.6	0.8	0.6	1.0	0.8	0.6
Friability (%)								
4 mins	0.7	0.6	0.7	0.6	0.7	0.4	0.6	0.7
20 mins	2.6	2.4	2.7	2.6	2.7	2.3	2.9	2.3
Disintegration (Mins:Secs)								
Minimum	22:29	23:23	22:13	22:30	21:56	21:49	21:48	21:43
Maximum	23:52	24:32	24:40	23:38	23:52	23:20	23:41	24:05

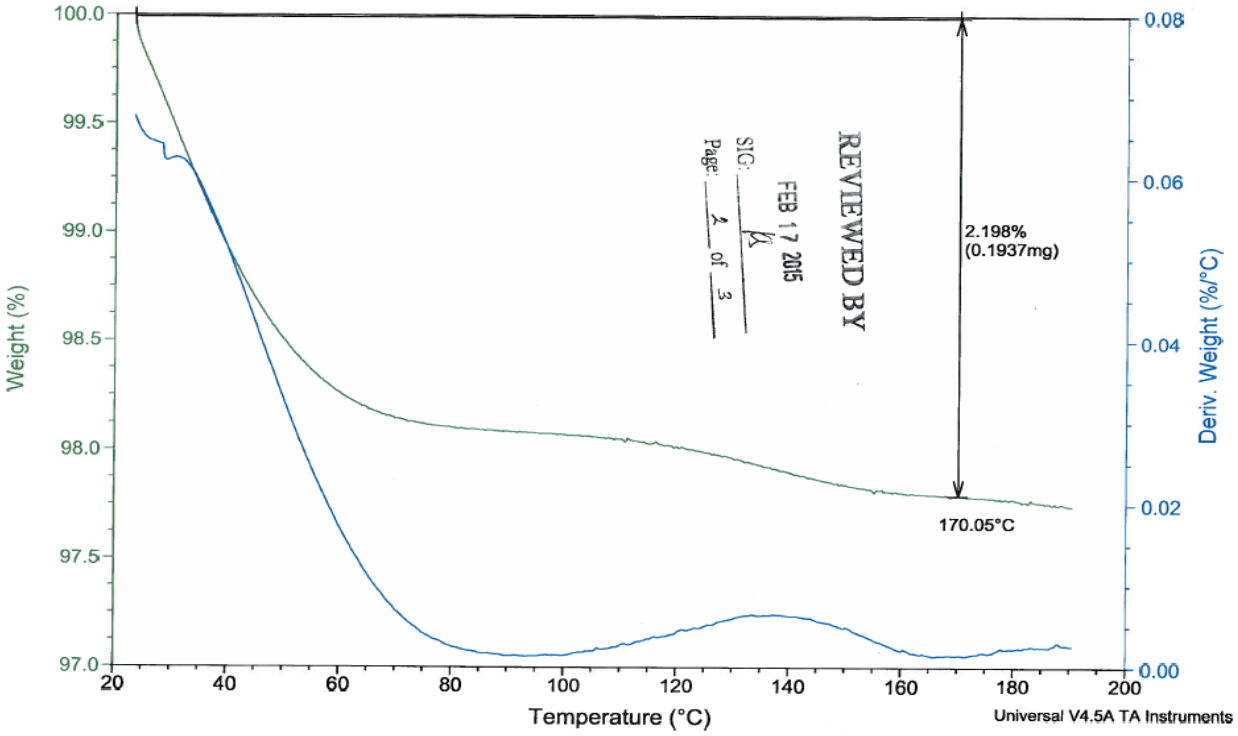

Figure A3.1: Thermo gravimetric Analysis for copovidone NF/EP 20 clearly indicating a similar weight loss as copovidone NF/EP 35 material at the same temperature range

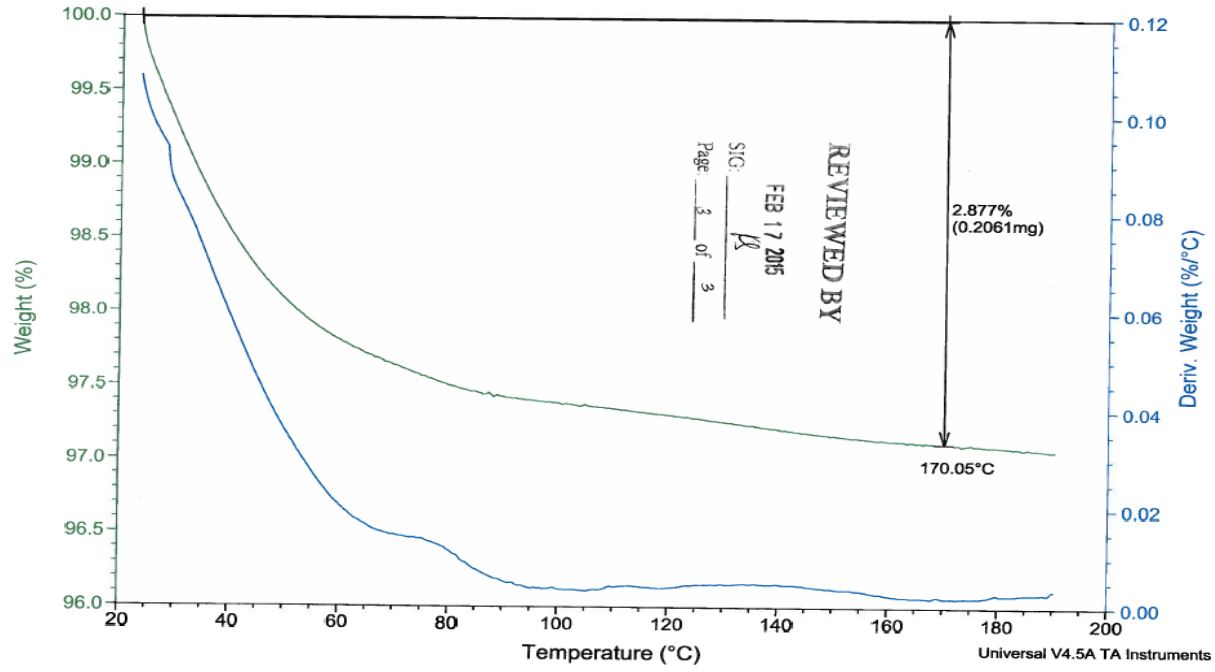

Figure A3.2: Thermo gravimetric Analysis for Copovidone NF/EP 35 clearly indicating a similar weight loss as copovidone NF/EP 20 material at the same temperature range

Appendix D

Fenofibrate EP/BP testing

Table A4.1: Additional C of A testing results for fenofibrate EP/BP API from Company J and Company K used to evaluate variability within each source and between the two sources of material in chapter 4.

		Company J				Company K		
Test	Specifications	Batch 1	Batch 2	Batch 3	Batch 4	Batch 1	Batch 2	Batch 3
Appearance	White to off white powder	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	UV Spectrum: Corresponds to Standard	N/A	N/A	N/A	N/A	Conforms	Conforms	Conforms
Identification	IR Spectrum: Corresponds to Standard	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Melting Point	79-82 °C	82	82	82	82	82	82	82
Halides (Expressed as Chlorides)	NMT 100 ppm	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100
Sulphates	NMT 100 ppm	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100
Acidity	Volume of 0.1 M NaOH Requiredd: NMT 0.2 mL	0.1	0.1	0.1	0.1	0.1	0	0
Loss on drying	NMT 0.5%	0.1	0.3	0.4	0.4	0.4	0.1	0.2
Sulphated Ash	NMT 0.1%	0.1	0.0	0.0	0.0	0.0	0.0	0.0
Heavy Metals	NMT 0.002 %	LT 0.002	LT 0.002	LT 0.002	LT 0.002	LT 0.002	LT 0.002	LT 0.002
Organic Volatile Impurities	Isopropanol: NMT 2000ppm	342	309	334	342	1103	1061	1061
Residual Solvents	Acetone: NMT 1000ppm	N/A	N/A	N/A	N/A	7	7	7
Residual Solvents	Chloroform: NMT 60ppm	N/A	N/A	N/A	N/A	7	8	8
Residual Solvents	Toluene: NMT 890 ppm	N/A	N/A	N/A	N/A	71	72	72
Residual Solvents	Butyl Acetate: NMT 1000 ppm	N/A	N/A	N/A	N/A	ND	ND	ND
Related Compounds	FF RC1: NMT 0.1%	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds	FF RC2: NMT 0.1%	ND	BRT	BRT	BRT	ND	ND	ND
Related Compounds	EP Imp. C: NMT 0.10%	N/A	N/A	N/A	N/A	ND	ND	ND
Related Compounds	EP Imp. D: NMT 0.10%	N/A	N/A	N/A	N/A	BRT	BRT	BRT
Related Compounds	EP Imp. E: NMT 0.10%	N/A	N/A	N/A	N/A	BRT	BRT	BRT
Related Compounds	EP Imp. F: NMT 0.10%	N/A	N/A	N/A	N/A	BRT	BRT	BRT
Related Compounds	FF RC4: NMT 0.2%	0.13	0.14	0.11	0.13	BRT	BRT	BRT
Related Compounds	FF RC5: NMT 0.10%	BRT	BRT	BRT	BRT	N/A	N/A	N/A
Related Compounds	FF RC6: NMT 0.10%	ND	ND	ND	ND	N/A	N/A	N/A
Related Compounds	FF RC7: NMT 0.10%	BRT	BRT	BRT	BRT	N/A	N/A	N/A
Related Compounds	FF RC8: NMT 0.10%	BRT	BRT	BRT	BRT	N/A	N/A	N/A
Related Compounds	Unidentified Impurity: NMT 0.10% each	BRT	BRT	BRT	BRT	BRT	BRT	BRT
Related Compounds	Total Impurity: NMT 0.5%	0.13	0.14	0.11	0.13	BRT	BRT	BRT
Assay	98.0 - 102.0 % (dried basis) (J) 98.5-101.0 % (dried basis) (K)	99.6	99.7	99.9	99.7	100.1	100.2	100.4
Bulk Density	0.5 - 0.7 g/cc	0.54	0.52	0.52	0.54	0.66	0.64	0.64
Appearance of Solution	Solution is clear and not more intensely coloured than reference solution BY6	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms

N/A – Criteria not included in C of A and therefore not tested

Table A4.2: Results of physical properties test beyond the C of A for fenofibrate EP/BP (Company J and Company K)

	Company J	Company K
Specific Surface Area	0.158 Square Meter per Gram	0.0365 Square Meter per Gram
Surface Weighted Mean Diameter	37.970 um	164.227 um
Volume Weighted Mean Diameter	114.270 um	269.791 um
Particle Size laser Diffraction (um)		
D 10	22	97
D 50	78	229
D 90	250	509
Minimum	0.8	10
Maximum	700	900
Bulk Density g/cc	0.47	0.61
Tapped Density g/cc	0.71	0.72

Table A4.3: In – Process Granulation Blend results for batch 7 (Company J (croscarmellose sodium NF/EP G)) and batch 8 (Company K (croscarmellose sodium NF/EP H))

	Company J (croscarmellose sodium NF/EP G)	STDEV	Company K (croscarmellose sodium NF/EP G)	STDEV
Flow Index (mm)	30	1.2	32	1.2
Bulk Density (g/cc)	0.59	0.03	0.57	0.05
Tapped Density (g/cc)	0.81	0.03	0.81	0.05
Particle Size by Sieve (%)				
20 mesh	24.3	4.74	27.9	8.02
40 mesh	18.5	2.49	18.0	1.45
60 mesh	8.4	0.67	7.7	0.40
80 mesh	3.8	0.42	3.2	0.30
100 mesh	2.0	0.35	1.8	0.15
200 mesh	9.6	4.82	19.0	4.96
Fines	33.4	2.00	22.7	4.00

Table A4.4: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 7 Company J (croscarmellose sodium NF/EP G)

	Start	20%	40%	60%	80%	End
Compression Force (kN)	5.3	5.3	5.3	5.3	5.3	5.3
Weight (mg)						
1	286.6	304.0	290.6	299.7	300.4	288.3
2	295.2	286.7	282.1	289.0	277.2	296.7
3	286.9	278.5	287.0	301.2	298.0	292.2
4	288.3	294.4	278.6	267.8	280.9	292.1
5	290.8	279.4	295.8	281.5	285.2	267.9
6	289.8	292.4	283.0	303.0	286.1	298.9
7	295.5	279.1	294.4	290.9	292.9	289.8
8	295.1	279.1	300.2	303.8	293.3	297.7
9	290.9	286.1	285.3	288.1	284.5	292.2
10	291.8	297.8	288.6	288.2	297.6	274.4
AVE	291.1	287.8	288.6	291.3	289.6	289.0
MIN	286.6	278.5	278.6	267.8	277.2	267.9
MAX	295.5	304.0	300.2	303.8	300.4	298.9
SD	3.3	9.1	6.8	11.2	7.9	10.1
CV (%)	1.1	3.2	2.3	3.9	2.7	3.5
Hardness (kp)						
1	5.2	5.1	3.6	4.8	6.6	4.5
2	6.2	7.2	5.6	5.0	5.5	6.4
3	5.8	7.2	5.4	6.8	6.7	3.8
4	5.1	6.4	5.2	7.6	6.4	5.9
5	5.4	6.1	6.2	5.0	6.2	3.4
6	6.6	6.6	6.3	5.9	5.2	7.0
7	4.6	5.8	4.7	7.1	4.8	6.4
8	5.9	3.9	6.8	6.0	3.1	4.9
9	6.3	6.9	4.1	5.4	5.0	4.2
10	6.1	7.1	6.1	6.0	6.1	5.4
AVE	5.7	6.2	5.4	6.0	5.6	5.2
MIN	4.6	3.9	3.6	4.8	3.1	3.4
MAX	6.6	7.2	6.8	7.6	6.7	7.0
SD	0.6	1.1	1.0	1.0	1.1	1.2
CV (%)	11.0	17.1	18.9	16.0	19.8	23.5
Thickness (ins)						
1	0.1695	0.1720	0.1700	0.1705	0.1695	0.1650
2	0.1715	0.1650	0.1670	0.1730	0.1710	0.1695
3	0.1685	0.1675	0.1665	0.1665	0.1690	0.1720
4	0.1690	0.1705	0.1730	0.1715	0.1665	0.1680
5	0.1695	0.1655	0.1665	0.1660	0.1685	0.1665
6	0.1680	0.1730	0.1695	0.1695	0.1715	0.1650
7	0.1705	0.1665	0.1740	0.1670	0.1710	0.1660
8	0.1700	0.1715	0.1740	0.1700	0.1705	0.1665
9	0.1710	0.1695	0.1695	0.1715	0.1680	0.1715
10	0.1675	0.1680	0.1700	0.1685	0.1700	0.1710
AVE	0.1695	0.1689	0.1700	0.1694	0.1696	0.1681
MIN	0.1675	0.1650	0.1665	0.1660	0.1665	0.1650
MAX	0.1715	0.1730	0.1740	0.1730	0.1715	0.1720
SD	0.0013	0.0028	0.0029	0.0024	0.0016	0.0027
CV (%)	0.8	1.7	1.7	1.4	0.9	1.6
Friability (%)						
4 mins	0.4	0.4	0.4	0.4	0.4	0.4
20 mins	Broken	Broken	Broken	1.0	1.4	2.4
Disintegration (Mins:Secs)						
Minimum	4:22	4:13	4:28	4:49	3:35	4:02
Maximum	7:18	6:25	7:04	7:18	5:20	5:55

Table A4.5: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 8 Company K (croscarmellose sodium NF/EP G)

	Start	20%	40%	60%	80%	End
Compression Force (kN)	5.3	5.3	5.3	5.3	5.3	5.3
Weight (mg)						
1	296.5	283.3	281.3	297.1	290.8	299.3
2	304.3	298.4	280.2	290.6	289.9	300.7
3	297.4	285.2	283.1	277.1	270.0	286.5
4	292.7	299.3	280.1	274.9	283.5	302.5
5	289.5	295.5	292.3	290.2	298.4	297.8
6	285.9	297.9	288.0	282.1	299.6	289.5
7	297.5	282.0	302.5	293.3	279.9	280.4
8	282.7	282.5	292.1	298.4	276.6	282.7
9	299.2	285.5	291.6	285.4	291.1	291.3
10	288.2	276.1	270.9	277.9	290.9	299.5
AVE	293.4	288.6	286.2	286.7	287.1	293.0
MIN	282.7	276.1	270.9	274.9	270.0	280.4
MAX	304.3	299.3	302.5	298.4	299.6	302.5
SD	6.7	8.4	8.9	8.5	9.4	8.0
CV (%)	2.3	2.9	3.1	3.0	3.3	2.7
Hardness (kp)						
1	6.7	4.0	5.9	6.0	3.5	6.9
2	4.7	4.7	6.5	5.1	4.3	3.8
3	5.0	3.5	4.8	4.8	6.7	6.0
4	4.8	4.7	4.5	5.4	4.2	6.9
5	5.6	5.5	5.7	3.2	6.1	6.0
6	7.4	5.3	5.5	7.3	6.1	5.9
7	5.5	4.0	6.7	3.1	7.3	3.6
8	6.4	6.1	6.7	5.6	4.1	6.4
9	5.8	6.0	4.8	5.7	4.4	6.1
10	3.7	5.1	5.5	6.2	5.3	6.3
AVE	5.6	4.9	5.7	5.2	5.2	5.8
MIN	3.7	3.5	4.5	3.1	3.5	3.6
MAX	7.4	6.1	6.7	7.3	7.3	6.9
SD	1.1	0.9	0.8	1.3	1.3	1.2
CV (%)	19.5	17.9	14.2	24.7	24.7	20.0
Thickness (ins)						
1	0.1730	0.1670	0.1705	0.1650	0.1670	0.1740
2	0.1695	0.1695	0.1680	0.1710	0.1680	0.1715
3	0.1675	0.1735	0.1715	0.1700	0.1750	0.1660
4	0.1690	0.1680	0.1730	0.1690	0.1770	0.1695
5	0.1665	0.1705	0.1705	0.1690	0.1685	0.1705
6	0.1705	0.1750	0.1715	0.1650	0.1685	0.1705
7	0.1665	0.1700	0.1720	0.1705	0.1695	0.1715
8	0.1710	0.1685	0.1695	0.1715	0.1680	0.1745
9	0.1705	0.1660	0.1690	0.1700	0.1715	0.1730
10	0.1710	0.1680	0.1685	0.1695	0.1700	0.1725
AVE	0.1695	0.1696	0.1704	0.1691	0.1703	0.1714
MIN	0.1665	0.1660	0.1680	0.1650	0.1670	0.1660
MAX	0.1730	0.1750	0.1730	0.1715	0.1770	0.1745
SD	0.0021	0.0028	0.0016	0.0023	0.0033	0.0025
CV (%)	1.3	1.7	1.0	1.3	1.9	1.4
Friability (%)						
4 mins	0.2	0.7	0.5	0.4	0.4	0.6
20 mins	1.1	1.4	Broken	1.3	Broken	Broken
Disintegration (Mins:Secs)						
Minimum	3:52	4:07	4:49	5:03	4:37	4:08
Maximum	6:06	6:40	6:38	6:49	6:54	5:07

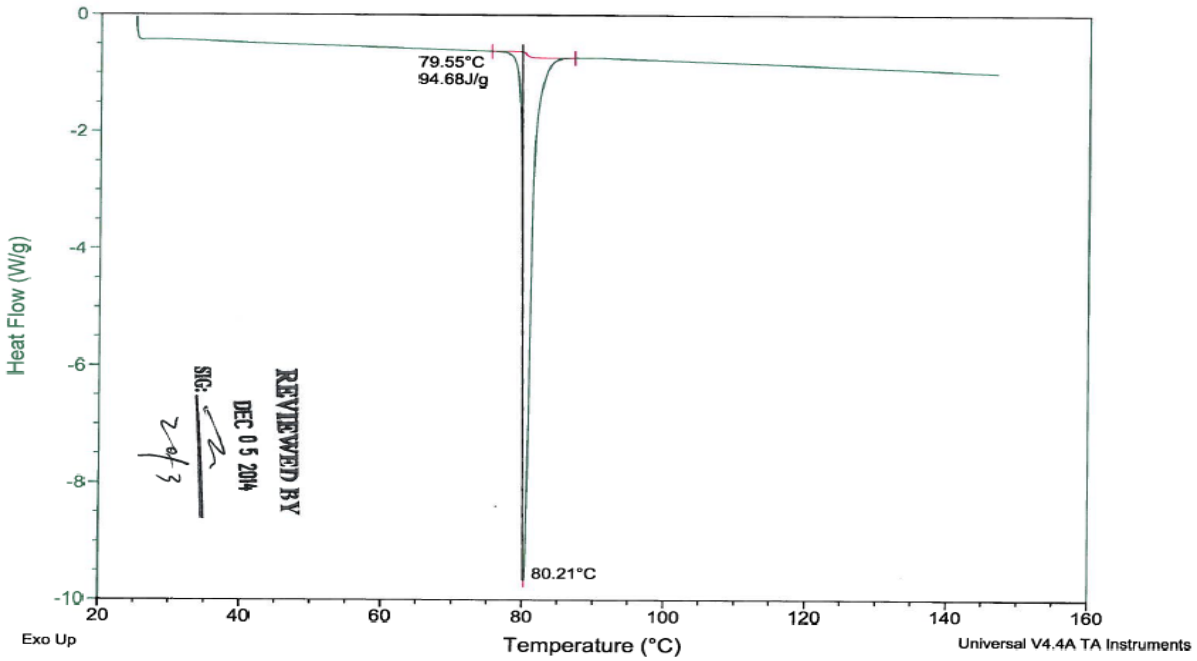

Figure A4.1: Differential Scanning Calorimetric Analysis for fenofibrate EP/BP (Company J) showing the initiation of the phase transition at the same temperature as material from Company K and confirming the crystalline nature of the material with a clearly defined melting point.

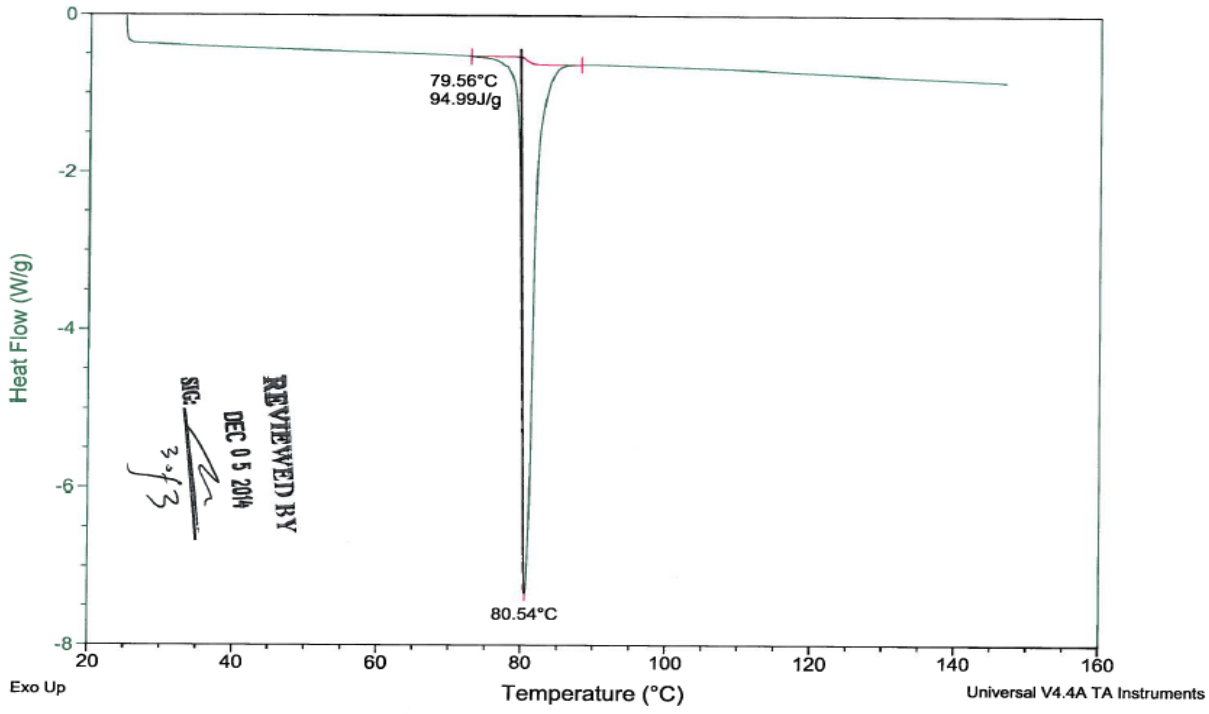

Figure A4.2: Differential Scanning Calorimetric Analysis for fenofibrate EP/BP (Company K) showing the initiation of the phase transition at the same temperature as material from Company J and confirming the crystalline nature of the material with a clearly defined melting point.

Appendix E

Croscarmellose Sodium NF/EP testing

Table A5.1: Additional C of A testing results for croscarmellose sodium NF/EP excipient from Company G and Company H used to evaluate variability within each source and between the two sources of material in chapter 4.

		Company G			Company H			
Test	Specifications	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 4
Apperance	A white orgreyish-white	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Reaction with Methylene Blue: Sample absorbs methylene blue	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	A reddish-violet colour develops at the interface	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Positive to test for Sodium	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
Identification	Positive to flame test for sodium	Conforms	Conforms	Conforms	N/A	N/A	N/A	N/A
pH	5.0 - 7.0	6.7	6.7	6.7	6.7	6.6	6.6	6.3
Load on drying	NMT 10.0 %	2.4	2.5	2.4	1.9	2.6	2.3	1.7
Sodium Chloride & Sodium Glycolate	NMT 0.5 %	0.15	0.2	0.21	0.4	0.2	0.2	0.1
Heavy Metals	NMT 20 ppm (G) NMT 10 ppm (H)	LT 20	LT 20	LT 20	LT 10	LT 10	LT 10	LT 10
Degree of Substitution	0.6 - 0.85 (dried basis)	0.77	0.75	0.75	0.73	0.74	0.74	0.83
Water - Soluble material	NMT 10.0 % (dried basis)	4.2	3.8	3.6	4.6	3.8	3.9	3.9
Settling Volume	10.0 - 30.0 mL	15	15	16	25	22	22	23
Sulphated Ash (EP)	14.0 - 28.0 % (dried basis)	16.5	16.8	16.7	19.8	19.5	19.1	21.6
Microbial Limits	Total Aerobic Microbial Count: NMT 1000 cfu/g	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100
Microbial Limits	Total Yeast and Mould Count: NMT 100 cfu/g	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100	LT 100
Microbial Limits	E.Coli: Absent in 1g	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Residual on ignition (NF)	14.0 - 28.0 % (dried basis)	19.3	19.7	19.7	N/A	N/A	N/A	N/A
Particle size	D(v,0.5): NMT 60µm	37	39	38	N/A	N/A	N/A	N/A
Particle size	D(v,0.9): NMT 155µm	85	89	85	N/A	N/A	N/A	N/A

N/A – Criteria not included in C of A and therefore not tested

Table A5.2: Results of physical properties test beyond the C of A for croscarmellose sodium NF/EP (Company G and Company H)

	Croscarmellose sodium NF/EP G	Croscarmellose sodium NF/EP H
Specific Surface Area	0.297Square Meter per Gram	0.169 Square Meter per Gram
Surface Weighted Mean Diameter	20.185 um	35.573 um
Volume Weighted Mean Diameter	47.163 um	54.363 um
Particle Size laser Diffraction (um) D 10 D 50 D 90 Minimum Maximum	 15 38 86 0.7 500	 18 43 108 10 200
Bulk Density g/cc	0.54	0.51
Tapped Density g/cc	0.68	0.65

Table A5.3: In – Process Granulation Blend results for batch 9 (Company J (croscarmellose sodium NF/EP H)) and batch 10 (Company K (croscarmellose sodium NF/EP H))

	Company J (croscarmellose sodium NF/EP H)	STDEV	Company K (croscarmellose sodium NF/EP H)	STDEV
Flow Index (mm)	32	0.0	32	1.4
Bulk Density (g/cc)	0.52	0.03	0.52	0.05
Tapped Density (g/cc)	0.76	0.07	0.76	0.06
Particle Size by Sieve (%) 20 mesh 40 mesh 60 mesh 80 mesh 100 mesh 200 mesh Fines	 24.9 15.1 6.4 2.5 1.3 9.4 40.2	 6.50 0.81 1.00 0.70 0.40 2.63 2.89	 25.0 14.8 6.0 2.6 1.7 11.8 37.8	 6.73 0.83 1.01 0.44 0.20 17.80 12.79

Table A5.4: Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 9 (Company J (croscarmellose sodium NF/EP H))

Compression Force	Start	20%	40%	60%	80%	End	Start
(kN)	7.4	7.4	7.4	7.4	7.4	7.4	5.3
Weight (mg)							
1	293.6	290.5	285.3	290.6	286.3	298.7	296.8
2	290.5	286.4	288.1	300.0	285.4	293.8	275.9
3	318.3	285.3	297.9	291.1	300.8	275.9	299.5
4	296.3	294.7	293.7	271.0	291.1	306.1	279.5
5	290.4	301.4	293.2	285.8	298.5	286.7	291.5
6	304.9	277.6	292.4	285.2	302.4	293.9	303.8
7	298.1	299.3	289.7	283.1	287.5	312.9	287.6
8	283.5	292.5	295.6	292.0	292.4	288.4	294.1
9	295.2	290.2	278.9	297.4	296.4	294.0	288.5
10	302.8	292.8	280.7	288.9	293.1	289.5	285.5
AVE	297.4	291.1	289.6	288.5	293.4	294.0	290.3
MIN	283.5	277.6	278.9	271.0	285.4	275.9	275.9
MAX	318.3	301.4	297.9	300.0	302.4	312.9	303.8
SD	9.6	6.9	6.3	8.1	6.0	10.3	8.7
CV (%)	3.2	2.4	2.2	2.8	2.1	3.5	3.0
Hardness (kp)							
1	5.0	6.7	6.7	6.4	5.1	7.3	3.8
2	5.6	5.6	7.0	6.0	5.4	5.5	3.3
3	7.5	5.4	5.6	6.1	4.5	6.6	5.8
4	6.4	8.0	6.4	5.0	6.7	4.5	3.4
5	4.2	6.6	6.7	5.8	6.1	7.1	4.8
6	3.3	3.5	5.9	3.6	6.6	5.3	3.8
7	4.2	5.4	5.4	5.0	6.3	4.8	4.1
8	5.5	5.8	6.0	6.0	4.2	5.8	4.4
9	3.4	6.4	5.2	5.8	5.0	6.2	5.8
10	5.4	6.1	6.5	6.0	2.9	6.4	4.6
AVE	5.1	6.0	6.1	5.6	5.3	6.0	4.4
MIN	3.3	3.5	5.2	3.6	2.9	4.5	3.3
MAX	7.5	8.0	7.0	6.4	6.7	7.3	5.8
SD	1.3	1.2	0.6	0.8	1.2	0.9	0.9
CV (%)	26.1	19.5	10.0	14.9	22.8	15.8	20.3
Thickness (ins)							
1	0.1700	0.1690	0.1720	0.1725	0.1720	0.1705	0.1725
2	0.1765	0.1750	0.1715	0.1700	0.1725	0.1725	0.1730
3	0.1700	0.1745	0.1670	0.1650	0.1670	0.1715	0.1700
4	0.1715	0.1745	0.1725	0.1680	0.1740	0.1680	0.1700
5	0.1665	0.1725	0.1730	0.1720	0.1685	0.1690	0.1700
6	0.1755	0.1670	0.1720	0.1715	0.1685	0.1655	0.1750
7	0.1665	0.1720	0.1695	0.1720	0.1740	0.1740	0.1705
8	0.1675	0.1710	0.1715	0.1675	0.1750	0.1755	0.1695
9	0.1700	0.1695	0.1715	0.1740	0.1720	0.1665	0.1740
10	0.1725	0.1705	0.1710	0.1740	0.1640	0.1695	0.1730
AVE	0.1707	0.1716	0.1712	0.1707	0.1708	0.1703	0.1718
MIN	0.1665	0.1670	0.1670	0.1650	0.1640	0.1655	0.1695
MAX	0.1765	0.1750	0.1730	0.1740	0.1750	0.1755	0.1750
SD	0.0035	0.0027	0.0017	0.0030	0.0036	0.0032	0.0020
CV (%)	2.0	1.5	1.0	1.7	2.1	1.9	1.2
Friability (%)							
4 mins	0.5	0.4	0.3	0.5	0.4	0.4	0.5
20 mins	1.6	1.1	0.8	1.5	2.4	1.1	Broken
Disintegration (Mins:Secs)							
Minimum	4:48	6:03	5:28	6:18	5:56	5:46	4:27
Maximum	7:23	7:02	6:54	7:22	7:08	7:42	6:08

Table A5.5 Individual CQAs results of weight, hardness, thickness, friability, disintegration and compression force for batch 10 (Company K (croscarmellose sodium NF/EP H))

	Start	20%	40%	60%	80%	End	Start
Compression Force (kN)	7.5	7.5	7.5	7.5	7.5	7.5	5.3
Weight (mg)							
1	296.6	302.4	295.0	287.9	283.3	299.8	292.7
2	295.8	282.2	301.0	297.8	290.8	270.0	300.6
3	281.7	295.4	293.7	303.6	286.5	297.6	281.7
4	285.3	280.2	272.9	295.5	279.5	283.6	287.0
5	284.8	293.0	301.3	287.8	305.1	284.1	301.4
6	293.3	293.3	289.7	291.9	296.5	277.2	294.9
7	280.4	283.2	291.3	288.2	301.5	283.3	300.8
8	295.5	274.2	290.2	291.5	283.3	297.0	292.6
9	270.5	289.3	309.2	278.2	291.8	291.0	299.9
10	289.8	285.5	283.2	292.1	276.9	281.1	288.4
AVE	287.4	287.9	292.8	291.5	289.5	286.5	294.0
MIN	270.5	274.2	272.9	278.2	276.9	270.0	281.7
MAX	296.6	302.4	309.2	303.6	305.1	299.8	301.4
SD	8.4	8.4	10.1	6.8	9.4	9.7	6.8
CV (%)	2.9	2.9	3.5	2.3	3.2	3.4	2.3
Hardness (kp)							
1	5.8	6.6	4.4	5.9	7.0	6.7	5.4
2	6.2	4.8	6.1	6.9	6.0	7.6	4.2
3	3.3	4.5	6.3	5.6	6.9	6.7	5.8
4	6.8	8.8	6.7	5.9	7.0	6.8	3.1
5	6.3	7.5	6.7	4.8	5.0	8.3	2.1
6	3.3	7.3	4.3	6.7	7.3	6.9	5.7
7	6.0	4.4	5.7	7.6	6.3	4.8	4.8
8	7.4	3.4	6.1	5.7	6.7	6.7	5.6
9	6.4	6.5	7.0	6.2	8.7	6.3	2.9
10	6.0	5.0	6.8	6.6	4.9	7.3	5.8
AVE	5.8	5.9	6.0	6.2	6.6	6.8	4.5
MIN	3.3	3.4	4.3	4.8	4.9	4.8	2.1
MAX	7.4	8.8	7.0	7.6	8.7	8.3	5.8
SD	1.4	1.7	1.0	0.8	1.1	0.9	1.4
CV (%)	23.8	29.0	15.9	12.8	17.0	13.3	30.5
Thickness (ins)							
1	0.1655	0.1670	0.1695	0.1715	0.1735	0.1720	0.1725
2	0.1705	0.1730	0.1700	0.1730	0.1695	0.1690	0.1765
3	0.1720	0.1715	0.1705	0.1680	0.1720	0.1705	0.1700
4	0.1640	0.1690	0.1635	0.1705	0.1705	0.1710	0.1725
5	0.1740	0.1665	0.1705	0.1695	0.1720	0.1685	0.1720
6	0.1715	0.1730	0.1710	0.1735	0.1705	0.1775	0.1755
7	0.1650	0.1675	0.1715	0.1710	0.1725	0.1740	0.1730
8	0.1715	0.1745	0.1655	0.1695	0.1665	0.1710	0.1705
9	0.1650	0.1695	0.1685	0.1715	0.1730	0.1685	0.1750
10	0.1725	0.1745	0.1690	0.1705	0.1760	0.1720	0.1705
AVE	0.1692	0.1706	0.1690	0.1709	0.1716	0.1714	0.1728
MIN	0.1640	0.1665	0.1635	0.1680	0.1665	0.1685	0.1700
MAX	0.1740	0.1745	0.1715	0.1735	0.1760	0.1775	0.1765
SD	0.0038	0.0031	0.0026	0.0017	0.0026	0.0028	0.0022
CV (%)	2.2	1.8	1.5	1.0	1.5	1.6	1.3
Friability (%)							
4 mins	0.4	0.4	0.4	0.3	0.6	0.6	0.5
20 mins	0.8	0.7	0.9	1.1	1.3	1.3	Broken
Disintegration (Mins:Secs)							
Minimum	5:44	4:54	5:06	6:44	5:02	5:32	5:56
Maximum	8:42	7:07	7:24	7:54	7:04	7:24	7:30

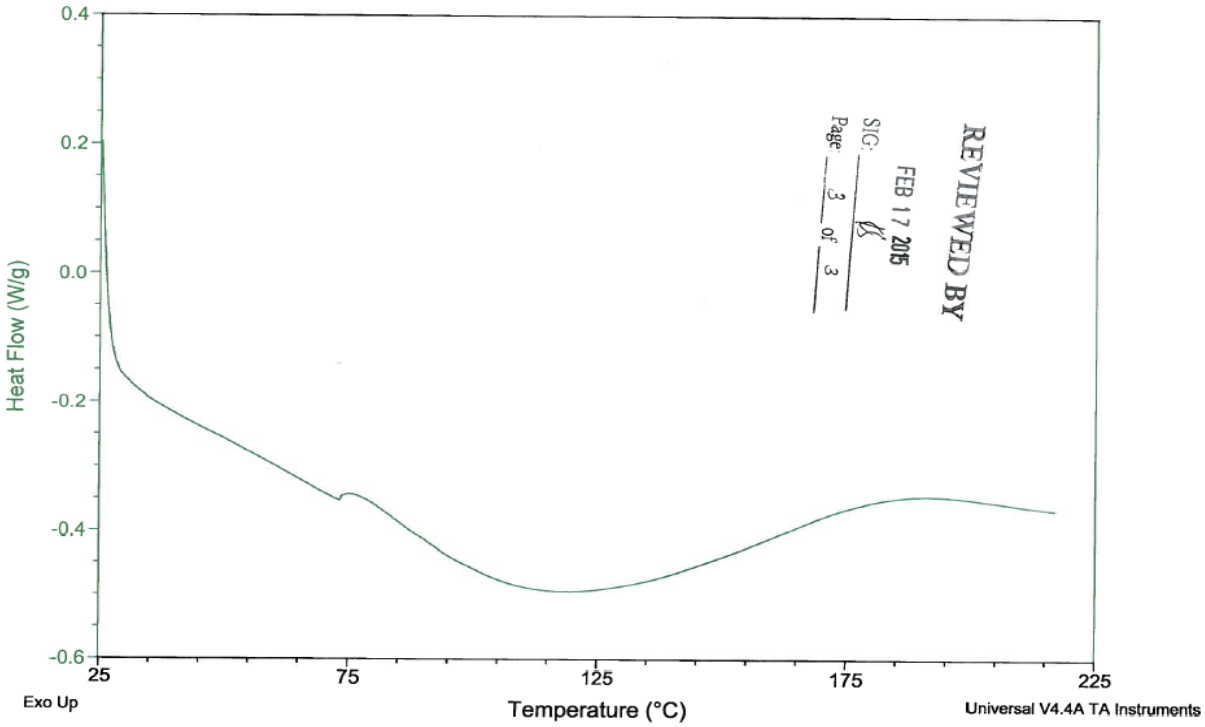

Figure A5.1: The DSC thermogram for croscarmellose sodium NF/EP (Company G) indicating comparable spectrum to that of croscarmellose sodium NF/EP (Company H) and confirming the amorphous nature of the material.

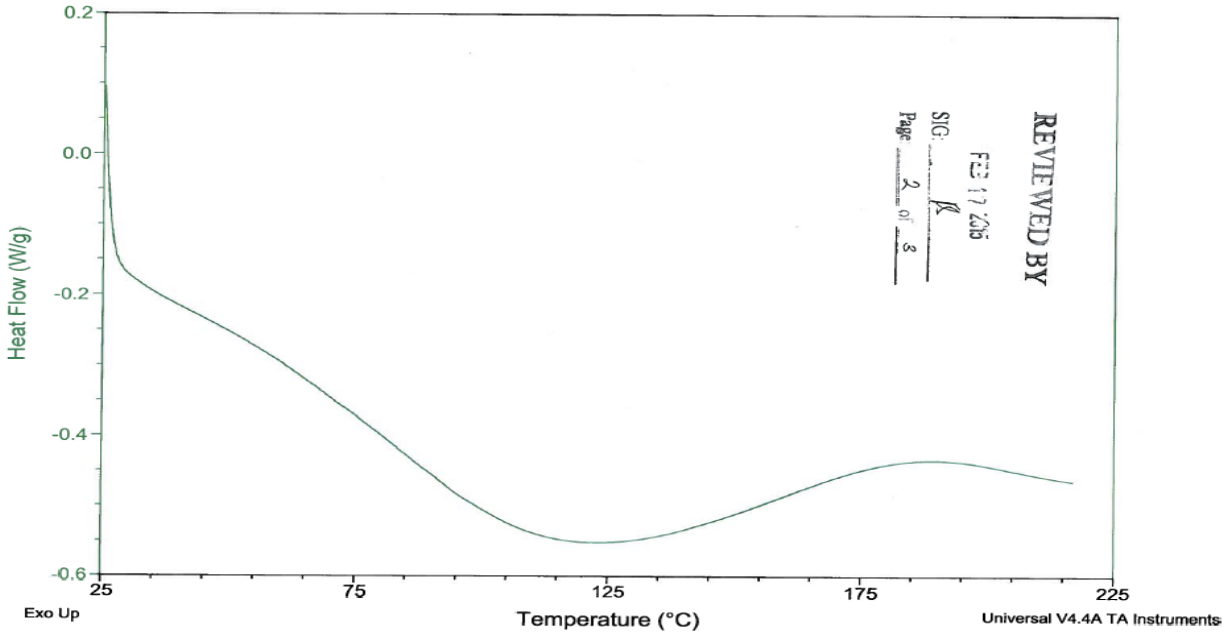

Figure A5.2: The DSC thermogram for croscarmellose sodium NF/EP (Company H) indicating comparable spectrum to that of croscarmellose sodium NF/EP (Company G) and confirming the amorphous nature of the material.

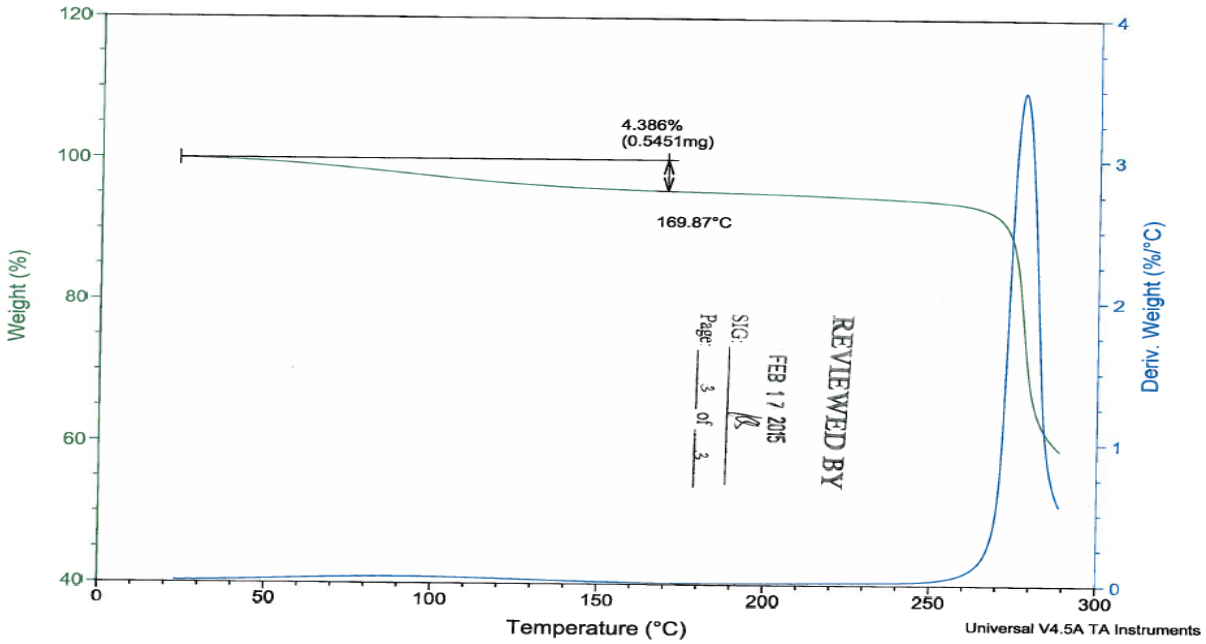

Figure A5.3: Thermo gravimetric Analysis for croscarmellose sodium NF/EP (Company G) indicating a similar weight loss as material from Company H at the same temperature range

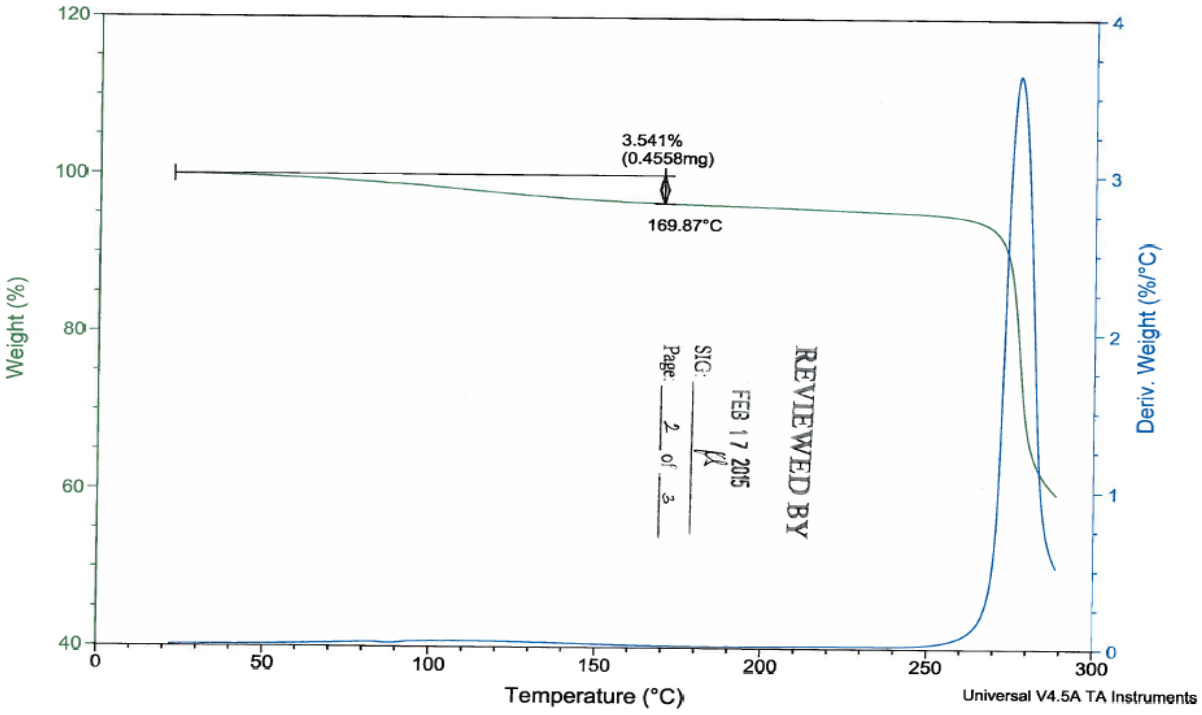

Figure A5.4: Thermo gravimetric Analysis for croscarmellose sodium NF/EP (company H) indicating a similar weight loss as material from Company G at the same temperature range

Appendix F

Release form from Hanson Research

Hanson

Release Form

22 February 2016

Hanson Research hereby grants Mohamed Ansari Chan the right to use, publish, and reproduce the image below ("Figure 1") for his master's thesis so long as the image is entitled "Hanson Flodex Test Instrument" and the instrument itself is referred to as the "Hanson Flodex" or the "Flodex" in the thesis.

Sara Hanson, Esq.
Director of Marketing
Hanson Research Corp.

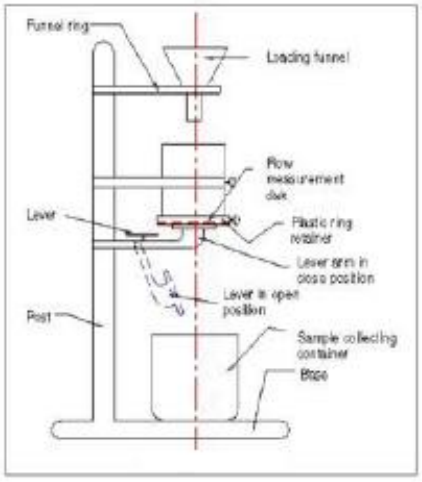

Figure 1: Hanson Flodex Test Instrument

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