NON-TRADITIONAL APPLICATION OF DRUG AND EXCIPIENT

by

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ABSTRACT OF THE DISSERTATION

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During formulation development, there are cases when, serendipitously, drug or excipients play a different role than intended one or a dual role. One of the examples of a non-traditional role is of a drug acting as a plasticizer. Plasticization tendency of APIs on polymers can be advantageous for hot melt extrusion, and film coating application. Due to the inherent plasticizing property of API, it can be mixed uniformly with other polymers using a V-blender or high shear mixer without the use of additional organic solvents during the formulation process. Divalproex sodium (DVS) is shown to possess plasticization tendency on Ethylcellulose(EC) using thermal, mechanical and rheological characterization of films of DVS and EC. Also, further characterization of the films using polarized microscopy, TGA, FTIR, Raman spectroscopy revealed the physical nature of the drug and polymer along with their interactions. The plasticization tendency was attributed to the presence of valproic acid, which is a component that is bound by coordinate bond with sodium valproate to form DVS. This study shows the non-traditional role of API as a plasticizer for a polymer (EC).

Some polymers can play a non-traditional role or dual role in formulation development; for example-a surfactant(poloxamer) can be used as plasticizer in hot melt extrusion, while Sodium Lauryl Sulfate, a wetting agent, can act as lubricant in a tablet formulation. Compression property of a sustained release polymer can aid the formulation scientist since it can be used alone or with less amount of compression aid to formulate a direct compression immediate release tablet or sustained release tablet dosage form. Affinisol® HPMC HME polymers were developed by Dow Chemicals to cater the need of Formulation Scientist for a low Tg HPMC for HME applications since the traditionally available grades have HPMC have much higher Tg and require the addition of plasticizer. Due to the low Tg of Affinisol® HPMC HME polymers, it is proposed that it may possess better compactability at low compression pressure. The study was undertaken to evaluate the compaction property of these polymers. Furthermore, powder properties were also examined for its proposed use as a dry binder or a direct compression sustained release polymer. Based on the compaction and powder properties of these polymers, these polymers can be used for the potential application as a dry binder or a direct compression sustained release polymer in tablet formulations.

DEDICATION

To my wonderful parents,

My mother who by her simple thoughts and actions has been my anchor

My father who has always instilled perseverance in me

To my mentor Dr. Tamara Minko,

For her selfless support and encouragement

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1. Introduction

Drug and excipients have been traditionally used for formulation development for their respective function as an active moiety to treat disorders and to facilitate the dosage form design, respectively. There have been cases where, drug or excipients play a different role than intended one or a dual role. One of the examples of a non-traditional role is of a drug acting as a plasticizer. One of the examples of a non-traditional role is of a drug acting as a plasticizer. Plasticization tendency of APIs on polymers can be advantageous for hot melt extrusion, and film coating application. Due to the inherent plasticizing property of API, it can be mixed uniformly with other polymers using a V-blender or high shear mixer without the use of additional organic solvents during the formulation process.

On the other hand, some excipients can play a dual role or a role that is different that their conventional use. Cases of such roles of drug and excipients facilitate formulation development activities by minimizing or reducing the usage of additional excipients. In this study following case studies will be discussed :

a. Characterization of Divalproex Sodium as a Non-traditional Plasticizer of Ethylcellulose (Non-traditional role of Drug)
b. Evaluation of Affinisol® HPMC polymers for direct compression process applications (Non-traditional role of Excipient)

2. Background

Extended drug release formulations have been widely accepted to enhance drug therapy by virtue of delivering drug in a controlled manner. Other advantages include protecting the drug against the harsh environment in the gastrointestinal tract, minimizing food effect, reducing any local gastrointestinal side-effects, improved patient compliance or life-cycle management of drugs. Mainly two types of oral extended drug release systems can be designed- matrix-controlled and membrane-controlled. In the matrix-controlled system, the release-controlling polymer is added in the matrix of the tablet, while, in membrane controlled system, a release controlling membrane over an immediate release core tablet controls the drug release. Matrix controlled system suffers from the drawback of burst release of drug, while precise control of drug release can be achieved using membrane controlled drug delivery system. Furthermore, matrix controlled systems exhibit drug release via diffusion and/or erosion, which is difficult to model, while membrane-controlled delivery systems exhibit drug release via diffusion only. Membrane-controlled delivery systems are usually developed in the form of tablet, multiparticulates(pellets) or rods, which are film-coated using a polymer based coating system (aqueous or organic). In addition to these systems, osmotic drug delivery systems are also a type of membrane coated drug delivery system that allow imbibing of water followed by drug release. However, since coating also affects drug-release, the role of plasticizer in coating systems utilized for osmotic drug delivery system is also discussed. Although each system has its own challenges and opportunities, the selection of an extended release system should be based on physiochemical and pharmacokinetic

properties of the drug of interest, dose strength, disease area, target population as well as other technical and business considerations.

It has been a little over three-decades since the first publication [1] and patent [2] on membrane coated tablets for sustained drug delivery. Since then this technology has been widely explored to formulate different types of drug delivery systems i.e. time-controlled, pH controlled, etc. These coating technologies are extensively in-use and involve traditionally used polymer, pore-former, plasticizer and a vehicle. The scope of this review is to focus on our acquired understanding of the role of plasticizer in the formation of the release controlling membrane, which is crucial for the in vitro and in vivo performance of the membrane coated drug delivery system.

Plasticizers are resins/polymers or small molecules- many time in liquid state that form secondary bonds with the polymer chains and spread them apart; thereby reducing the polymer-polymer secondary bonding and providing greater mobility for the macromolecules resulting in a soft and deformable polymer mass [3]. In pharmaceuticals, this attribute allows plasticizers to be used extensively for polymer film-coating and matrix based applications. Upon mixing with other polymers, plasticizers tend to get incorporated into the amorphous parts of polymers leaving crystalline part remains unaffected. Due to these interactions, it is expected that they will reduce the modulus, tensile strength, hardness, density, melt viscosity, glass transition temperature, electrostatic chargeability and a volume resistivity of a polymer, while simultaneously increasing its flexibility, elongation at break, toughness, dielectric constant and power factor [3, 4].

Coatings of various polymers have become feasible due to the use of plasticizers. Plasticizers with high compatibility, stability, lubricating properties at various temperature conditions, and resistant to leaching and migration are commercially available. Uses of these plasticizers have made coatings easy for polymers which have excellent drug diffusion properties but poor film forming properties. Moreover, uses of plasticizers have resulted in development of modified release formulations. Through this review article we have summarized various theories, types and applications of the plasticizers.

2.1. Theories of plasticization

Although plasticizers were in use since 19th century, theories of plasticization were not in existence until 1930-50. During the 1940s the lubricity theory and the gel theory were developed. The basic idea of lubricity theory was that plasticization involves filling the voids in the molecular space lattice and therefore leading to the formation of planes that are easy to glide on the application of shear [5]. Whereas the gel theory followed solvation-desolvation [6] and aggregation-deaggregation equilibria[7], Aiken proposed that a three dimensional gel network of plasticized polymer exists with two possibilities-dynamic equilibrium, which involves plasticizer molecules to diffuse through the polymer structure while opening and closing the polymer contacts while wandering in the polymer network, and static mechanism where plasticizer-polymer are associated for a mean that is greater as compared to the timescale of segmental motion [6]. To clarify the phenomenon of plasticization various other theories were proposed during this period. Manfred and Obrist in 1927 proposed plastization to be a disaggregation of the polymer molecules by the plasticizer. Later Doolittle formalized the gel theory supporting with

experimental results[8]. Moorshead proposed an empirical approach, reinstating the above-mentioned theories. He proposed that "polymer chains must be sufficiently long to have some strength even though the plasticizer forces move them apart, in highly cross-linked polymers and highly crystalline polymers the chains are held together by primary bonds and by crystalline forces. In both cases, forces are too strong to permit the plasticizer to penetrate into the polymer [9]. If the cohesive forces in the plasticizers and polymer are of same order then, the plasticizer can remain stable between the polymer chains. For a plasticizer, polar and polarizable groups improve tensile strength whereas non-polar groups provide flexibility to the plasticized polymer. Therefore, both polar and non-polar groups are essential for better compatibility and flexibility [10]. Although these theories didn't provide some critical phenomenon involved in plasticization, however they were used effectively by understanding basic phenomenon involved during the processes.

Later, in the 1950s, Fox and Flory put fourth Free volume theory, which gave a more precise explanation on plasticization. Free Volume theory explains some of the properties of plasticized polymer i.e. viscoelastic properties, which are very critical. Various findings concluded that between atoms and molecules there is nothing but free volume which explains the viscoelastic properties of the plasticizer [11]. Fox and Flory defined a free volume, at temperatures above the transition temperature, as the specific volume above the transition temperature minus the solid specific volume extrapolated to the same temperature above the transition temperature [11]. From the free volume theory, it can be implied that plasticizers with lower T_g are more efficient in reducing the T_g of the plasticized system [10]. Also, a branched plasticizer is more effective than a linear

plasticizer due to the availability of greater free volume owing to the branched structure [10]. These correlations provided more insight on the mechanism of plasticization. Due to these clarities, after the free volume theory, no more relevant theories have been proposed; however, some mathematical models were developed by Kanig [12], Wood [13], and Gordon and Taylor [14]. Later, DiMarzio and Gibbs proposed a new model by taking into consideration the intramolecular interactions of polymer and plasticizer via an iso-entropic model [15]. Lately, Mauritz and Storey have extended the standard free volume theory that considered diffusion of small molecules in an amorphous polymer above T_g to generalized one encompassing large molecules like plasticizers. It predicts plasticizer diffusion coefficients while requiring the input of minimum experimental parameters [16].

2.2. Types of Plasticizers

There are different ways of classifying plasticizers based on-physical state (solid or liquid), role (primary and secondary), molecular weight, and chemical structures. Plasticization could be achieved by two ways, externally by physical mixing of plasticizers with the polymers or internally by incorporating plasticizer molecules using chemical conjugation. Primary plasticizers can be used alone if they have suitable compatibility with the polymers and have ability to demonstrate required properties. On the other hand, primary plasticizers are also used along with secondary plasticizers to improve their efficiency. Ideality of the plasticizer changes with respect to the polymer. In this regard, compatibility plays a pivotal role in selecting the plasticizer. For instance, the combination of hydrophobic-hydrophobic and hydrophilic-hydrophilic plasticizer and polymer is favorable, factors such as hydrogen bonding and thermodynamic properties

also plays an important role in compatibility and phase separations. Additionally, the plasticizers with lower the molecular weight may diffuse or evaporate faster though the polymer as compared to high molecular weight plasticizers. With the advent of some new compounds that have shown plasticization tendency, external plasticizers can be differentiated into traditional and non-traditional plasticizer.

2.2.1. Traditional plasticizers

Plasticizers used, continuously, since past several decades in pharmaceutical industry are considered as traditional plasticizers. Some examples of traditionally used hydrophilic plasticizers are glycerol, triethyl citrate, glyceryl triacetate, triacetin, polyethylene glycol, and hydrophobic plasticizers are dibutyl sebacate, dibutyl phthalate, and diethyl phthalate. Plasticizers are obtained from natural sources or by derivatization of two different molecules. The derivatized forms are usually a combination of hydrophilic and hydrophobic molecules with the ester or ether linkages which gives an ideal plasticizing effect for hydrophilic as well as hydrophobic polymers. Some examples of these plasticizers are listed in Table 1. Hydrophilic plasticizers can be incorporated easily into aqueous dispersion and partition rapidly into the polymer than lipophilic plasticizers. Plasticizers should be allowed sufficient time while mixing to allow for complete plasticization of the polymer. Plasticizers which are highly hydrophilic in nature are known for leaching out early during drug release, which results in the formation of pores that causes the drug to release faster compared to using lipophilic plasticizers. From the formulation development point of view, this poses a challenge to optimize the suitable concentration since the concentration of plasticizer plays a very important role in controlling the drug release in addition to its inherent plasticization role.

Apart from the above-mentioned plasticizers, water (or humidity) can have a plasticization effect on film formation [17] or during drug release upon water uptake [18]. For instance, Lecomte et al. found that, due to the plasticization effect of water, percent elongation at break initially increased while the puncture strength decreased. [18]. Rujivipat and Bodmeier demonstrated that moisture causes superior plasticization for Eudragit® L compared to other traditional plasticizers such as triethyl citrate (TEC), when coated with Eudragit® L 30-D55 at 15% solid content with 20% TEC as a plasticizer. The elongation value of Eudragit® L100-55 increased from approximately 3% in the dry state to above 140% at the 84% relative humidity [19]. It should be noted that increase in moisture along with TEC resulted in greater plasticization compared to the proportional increase in the TEC concentration alone. Also, plasticizers like TEC allow for faster uptake of moisture or water and therefore indirectly aid in further plasticization. It was suggested that using dispersions with a lower solids content (less than 15%, w/w) can ensure higher local humidity during the coating process [20].

2.2.1.1. Commonly used plasticizers

2.2.1.1.1. Dibutyl Sebacate (DBS)

This is the first choice of plasticizer for non-aqueous and aqueous system due to its better plasticizing efficiency compared to other plasticizers. DBS is practically insoluble in water, which significantly reduces its leaching from the film, when exposed to aqueous media. This helps in avoiding drug release as well as maintains film integrity, which in turn provides efficient and reproducible control of drug release from the dosage form. Its boiling point is 344-349°C and its vapor pressure is 0.4 kPa at 180°C shows that it is less

volatile; this reduces its loss from the film, compared to other liquid plasticizers, during the curing step. However, due to its poor solubility, it requires greater time (7 hours) for plasticization of polymer in an aqueous polymer system [21]. DBS is frequently used as a plasticizer for ethyl cellulose, and Eudragits based formulations due to their high compatibilities. Moreover, due to its highly hydrophobic nature, it helps to reduce the vapor transmission into the formulation upon storage while retaining the mechanical properties and drug release properties of the formulations [22, 23].

2.2.1.1.2. Triethyl Citrate

Triethyl citrate is a triester of ethyl alcohol-citric acid and is a plasticizer of choice for aqueous system due to its water solubility. It has a viscosity of 35.2 cP at 25°C [24] and a vapor pressure of 1 mm Hg at 107°C [25]. Its commercial name is Citroflex®. Okarter and Singla studied the effect of plasticizer on the release of metoprolol tartrate from granules coated with Eudragit RS 30 D and concluded that plasticizers with higher water solubility-such as PEG400 and Propylene glycol showed higher release rate than with Tributyl Citrate (TBC) and TEC. Furthermore, TEC showed pH-independent release of drug while pH-dependent release was observed with Polyethylene Glycol (PEG) 400, Propylene Glycol (PG), and TBC [26]. Budavari et al. studied the migration of TEC from Acryl-Eze coating to the core. It was shown that in spite of moderate solubility of TEC, considerable migration was observed during 14 day storage. Results from storage at different humidity conditions showed that migration increases with increase in humidity due to the higher water adsorption [27].

2.2.1.1.3. Polyethylene glycol

Polyethylene glycols with various molecular weights have versatile applications in pharmaceutical industry. Some of its applications include solubilizers, stabilizer, binder, carrier, and plasticizer. Like other polymers, the physical state of PEG is depended upon its molecular weight, for instance PEG 400 is a liquid state plasticizer while, PEG 6000 is a solid-state plasticizer with a melting point of 55-69°C [24] which also effects significantly on its plasticization effect. Yuan et al. concluded that the lower the molecular weight of PEG the more effective it is in decreasing the glass transition temperature of the plasticized polymer [28]. They also found that, the slope of the increase of percent elongation of the plasticized was found to decrease with PEG molecular weight. Compared to PEG 1000 and 3350, PEG 400 was found to provide better film mechanical properties with cellulose acetate polymer [28].

2.2.1.1.4. Triacetin

Triacetin (TRI) is a triester of acetic acid and glycerol and has a viscosity of 17.4 cP at 25°C and boiling point of 258°C [24]. It has been shown to have the higher plasticization efficiency compared to other plasticizers such as acetyl triethyl citrate (ATEC), tributyl citrate (TBC), and acetyl tributyl citrate (ATBC) with Eudragit L100 -55 as polymer. Also, it showed greatest effect on reducing the brittleness of the polymer, which was attributed to their differences in molecular size and subsequent greater ability to interact with the polymer chains as compared to the aforementioned plasticizers [29]. One of the major limitations to its use as a plasticizer is that it evaporates or degrades even at ambient conditions; the loss being almost 10 % upon 90 days of storage. [29]. The

evaporation of TRI from the films can be attributed to the higher vapor pressure which is 133 Pa at 100°C. [24]. This characteristic limits its use in drug delivery formulations which are intended to store for longer periods of time at ambient temperatures.

2.2.2. Non-traditional plasticizers

In addition to the traditionally used plasticizers which are very widely studied, certain Active Pharmaceutical Ingredients (APIs) or excipients have been shown to act as plasticizers without the use of typical plasticizer. For instance, the glass transition temperature of Eudragit RS films were lowered in the presence of Methylparaben [30], ibuprofen, chlorpheniramine maleate (CPM) [30, 31] and metoprolol tartrate[31], which is usually seen upon the use of plasticizers. It is evident from X-ray diffraction studies that, due to the presence of ibuprofen into the film formulation, the polymer chains were highly disordered [30]. Similarly, ibuprofen up to 20% w/w was also shown to be lowering the glass transition temperature of ethylcellulose hot melt extrudates as well as co-evaporates. It is worth noting that the plasticizing efficiency of the same degree, as traditionally used plasticizers, was achieved with ibuprofen. Infrared spectroscopy indicated the presence of hydrogen bonds between ibuprofen and ethylcellulose. This is attributed to the proximity of solubility parameters of ibuprofen and ethyl cellulose which were in the range of (19.5-21.1 $Mpa^{1/2}$) [30, 32].

2.3. Selection of plasticizers

Plasticizers have been used selectively for the development of numerous drug delivery systems such as buccal, transdermal, ocular, gastro retentive, tablet, and reservoir devices. Choice of the plasticizer plays a vital role in the performance of these

formulations. Apart from being biocompatible, other properties such as non-leaching, flexibility, stability, and resistance to the critical factors such as heat and moisture determines their suitability for the particular formulation. Although several plasticizers have been used traditionally, the plasticizing effect varies with respect to different polymers. The choice of plasticizer for pellet coating depends primarily on the type of polymer, compatibility, processability and its effect on the drug release. In the following sections, we have discussed most recent criteria's which have been preferred during selection of plasticizers.

2.3.1. Plasticization efficiency

While selecting plasticizers, the plasticization efficiency should be compared in order to choose the plasticizer that requires the least concentration to achieve the desired plasticization. Plasticization efficiency is a function of glass transition temperature and is defined as the decrease in glass transition temperature per unit increase in the concentration of plasticizers. The effect of plasticizer concentration on the glass transition temperature during plasticization is complicated by the ambiguous nature of glass transition in polymers. Depending on structure, the glass transition causes freezing of the segmental mobility, or local mobility of microsites or mobility of the whole molecule [33]. Assuming no interactions between plasticizer and polymer certain points should be borne in mind while selecting the plasticizers. The ability of plasticizer to reduce the glass transition temperature (plasticization efficiency) of plasticizer depends on the flexibility of the plasticizer molecule. Theoretically, the more the flexibility, the greater the reduction in the glass transition temperature of the plasticized polymer. Also, at equal flexibility among plasticizers, the plasticization efficiency decreases with increase in

molecular mass [33]. Plasticizers with long chains are better plasticizers compared to small molecules. It should be noted that these generalizations are valid for one phase polymer-plasticizer system only. If there is incompatibility at any concentration, increase in plasticizer concentration beyond this level may not affect the glass transition temperature i.e. glass transition temperature remains nearly constant [33].

To determine the plasticization efficiency, the glass transition temperature of the various ratios of plasticizer and polymer, after sufficient mixing, should be determined. The addition of 20% of triethyl citrate, triacetin, acetyl triethyl citrate or acetyl tributyl citrate was able to lower the T_g of the plasticized films of Eudragit RS 30D from 48°C to below 22°C [34]. The glass transition temperature of Eudragit RSPO was found decrease by 2.70 ° C and 1.31° C for each percentage of TEC and Chlorpheniramine maleate, respectively, present in the polymer [35]. In pharmaceuticals, often, a blend of polymers is used to achieve desired drug release profile. In such cases, the interaction of plasticizer and matrix polymers is caused by polarization of charges in molecular fragments, hydrogen bonding and Lewis acid-base interactions [36]. However, the presence of another polymer in most cases is unlikely to affect interactions because a plasticizer is evenly distributed and acts independently with the polymer components [36].

2.3.2. Compatibility

2.3.2.1. Based on phase diagram

Phase equilibrium is used to evaluate the phase state of a complex system. Polymer-plasticizer systems are described by the principles of phase equilibrium for reversible systems. A phase diagram of amorphous polymer-plasticizer consists of an area of

complete mutual mixing, phase segregation, metastability (an area where the two incompatible phases can coexist without any visible segregation for a long time). For crystallizing polymer-plasticizer system, the phase diagrams are complicated by the crystallization processes. The rates of crystallization can significantly alter and depends on pressure, temperature as well as the presence of impurities [37]. The phase diagrams represent the interactions between polymer and plasticizers as governed by the equations of state (Pressure-volume-temperature). However, the generation of such equations is quite challenging and can only be achieved for selected systems [37].

2.3.2.2. Based on Flory-Huggin's Interaction parameter

The phase diagram represents the regions of compatibility and incompatibility, usually at the atmospheric pressure. But it is important to predict the compatibility with respect to other external factors such as pressure, using any thermodynamic criterion. Mixing of polymer and plasticizer (as a solvent) as a process determined by a combination of entropy and enthalpy factors is given by Flory-Huggins theory [37]. Gibb's free energy of mixing equation describes this process [38, 39].

$$\Delta G = RT\left(n_1 \ln \emptyset_1 + n_2 \ln \emptyset_2 + \emptyset_2 \emptyset_2 \chi \left\{n_1 + n_2 \frac{V_2}{V_1}\right\}\right) \qquad \textbf{Equation 2-1}$$

where n_1 is the number of moles of plasticizer, n2 is the number of moles of polymer, Φ1 is the volume fraction of the drug, Φ2 is the volume fraction of the polymer, V_1 is the volume of plasticizer, V_2 is the volume of polymer, R is the gas constant, and T is the absolute temperature and χ is Huggins the interaction parameter. X is a non-dimensional

value representing the difference between the interaction energy of plasticizer molecule immersed in a pure polymer and the interaction energy of the same molecule in a pure plasticizer [37]. As per the Flory Huggin's equation, the first two terms, which are for the configurational entropy of mixing, will always be negative. Therefore, if the value of χ is small, the free energy of mixing will be negative implying a spontaneous process. The critical value of χ that is sufficient for the compatibility of a polymer with a large molecular mass with a plasticizer is 0.5 [37].

This theory assumes that the molecules are spherical and the long-chain polymer molecules differ in the arrangements from the spherical molecules. The polymer-plasticizer interaction differs from the ideal entropy of mixing with the addition of the interaction parameter [37].

2.3.2.3. Based on chemical structure and polarity

Chemical structure and polarity are the two major factors determining the solvation of polymers by plasticizers. As the thumb rule of "Like dissolves like", generally, the similarity in polarity between the bonds in the polymer and plasticizer implies nearly similar energy of interaction, resulting in compatibility and vice versa [37].

The flexibility of the polymer chain influences the solvation by plasticizers. Flexible chains demands lower energy and can easily diffuse into solution accompanied by an increase in entropy. Crystalline polymers also dissolve much slowly than amorphous polymers, since more energy is required to break the bonds to separate the chains [37].

If some polymers are prone to crosslinking during processing, it might decrease its compatibility with the plasticizer [37].

2.3.2.4. Based on solubility parameter

The solubility parameter is the measure of the cohesive energy of a molecule. If the cohesive energy of two substances is similar, there is a greater possibility of compatibility. The solubility parameter can be estimated by theoretical methods like group addition method and various experimental procedures [37]. Table 2.4 lists the Glass transition temperature (T_G) of the plasticized film of ethylcellulose at 25%w/w level of plasticizers and Solubility Parameters of various plasticizers. The Glass transition temperature (T_g) and Solubility Parameters of ethylcellulose are 130.0 °C and 20.0 $MPa^{0.5}$, respectively [40]. Veset et al. showed that except glycerin, polyethylene glycol 400, and propylene glycol, other plasticizers listed were compatible with the ethylcellulose. Plasticizers with similar solubility parameter as that of ethylcellulose (20 $MPa^{0.5}$) had a prominent effect on T_g suppression and a good correlation was found between solubility parameters and T_g; however, solubility parameter was loosely correlated with tensile strength and modulus of elasticity [40]. The increase in plasticizer concentration did result in lowering of the tensile strength and modulus of elasticity [40].

Hence, it is advisable to utilize more than one approach to select a plasticizer for the controlled release membrane system.

2.3.3. Processability

It is essential that after incorporation of plasticizer in the coating dispersion, the coating dispersion can be coated on pellets or tablets. Following are some of the practical approaches, which can be helpful in formulating a film coated product.

2.3.3.1. Determination of Minimum Film-formation Temperature (MFT)

The minimum film-forming temperature (MFT) is the lowest temperature required for film formation i.e. coalescence of colloidal particles when applied on a substrate as a thin film. Tg and MFT are apparently similar parameters with a difference that Tg is a fundamental property of the material while MFT is an ill-defined parameter, which reflects latex morphology and even particle size in some cases [41]. It was shown by Paulsson and Singh that Tg can, however, be used as a first approximation for the MFT [41]. It can be estimated by commercially available minimum film-forming temperature bar equipment. Below MFT, a polymeric dispersion will form an opaque, discontinuous material upon solvent evaporation; however, a clear continuous film will be formed at temperatures above the MFT. Furthermore, drying at temperatures above the MFT provides adequate capillary force for coalescence to occur [42]. On the other hand polymer solutions (organic) do not exhibit an MFT and therefore will form a film even at room temperature. It has been shown that plasticizer type and plasticizer concentration have an effect on MFT [42].

Kojima et al. measured T_g and MFT of HPMCAS systems containing various amounts of TEC. They observed that the MFT was around 20°C less than T_g. It is worthwhile to note that the measurement of MFT was carried out in presence of water; whereas, T_g was measured in absence of water. Water too might have accounted for greater plasticization resulting in a lower MFT [43].

2.3.3.2. Film formation studies

Films of coating dispersion are usually casted on a Teflon plate and allowed to dry at a suitable temperature. These films are evaluated for glass transition temperature, water uptake, and morphology. One of the very common properties of plasticizers is to reduce the glass transition temperature of the polymers which imparts them greater flexibility and processability. Similarly, for the glass transition temperature of films prepared with Aquacoat® decreased initially with an increase in plasticizer concentration until it reaches a plateau; after this level, there is an insignificant change in the glass transition temperature with further increase in plasticizer concentration [44]. Therefore, plasticizer concentration above certain range is inconsequential. Manufacturer recommends 24% concentration of plasticizers such as dibutyl sebacate, Myvacet® (acetylated monoglycerides), triacetin (GTA or glyceryl triacetate), acetyltriethyl citrate (ATEC) and triethyl citrate for Aquacoat® coating system [44]. In addition to the plasticizer concentration, it is important to understand the water uptake properties of the film on exposure to the moisture or humidity since it effects on glass transition temperature, leaching of plasticizer and formation of pores in film. While coating, the formulator should be mindful of the glass transition temperature of the plasticized system since, a product temperature much above the glass transition temperature might result in a tacky

film that may lead to sticking on walls and agglomerations. If for any reason the temperature cannot be minimized, anti-tacking agents like talc or titanium dioxide can be helpful.

Morphologically, the film should be smooth, flexible with enough tensile strength to withstand mechanical shocks while coating. Addition of anti-tacking agents in small quantity assists in producing a non-tacky film; however, increase in amount will result in film cracking due to the brittle nature of the anti-tacking agents. Quantitatively, the films should be compared for puncture strength, percentage elongation and tensile strength using a material testing instrument. Plasticization of Eudragit L100-55 from organic solution using water soluble plasticizer like TEC, TRI, ATC, TBC, and ATBC showed that water soluble plasticizers-TEC and ATEC showed 4 times elongation and TRI showed 6 times elongation. This can be explained by the ability of water-soluble plasticizer to diffuse and interact with the chains of plasticizer and increase the polymer's mobility. Water insoluble plasticizer-TBC resulted in less than 8% elongation at 30% plasticizer concentration compared to 20% in the film [29]. Similar trend was obtained for modulus for elasticity, where it was found to decrease significantly with increase in concentration of water-soluble plasticizers (TEC, ATEC, TRI), however the decrease was insignificant beyond 10% concentration for water-insoluble plasticizers (TBC, ATBC) [29]. Tensile strength of the film was found to be insignificantly different for water soluble and insoluble plasticizers, with the tensile strength decreasing with increasing plasticizer level up to 30% [29]

2.3.4. Effect on drug release

Usually, water-soluble plasticizers tend to leach out when exposed to dissolution medium and thereby create pores, which allow for faster drug release. The increase in the concentration of water -soluble plasticizers causes more pore formation resulting in a very fast release. Water permeation through films prepared using tributyl citrate (lipophilic plasticizer) was half of that of polyethylene glycol 400 (hydrophilic plasticizer) during gastric residence testing [17]. In contrast to reports that water soluble plasticizers leach out and increase the drug release, Dias et al. showed that the drug release rate did not increase with water soluble plasticizers like TEC and Triacetin from polymer-based organic solvent based coating system. They proposed that it might be due to the higher mechanical strength of the solvent-coated ethyl cellulose films, from which, leaching could have very less impact on the mechanical properties of the film [45]. Also, leaching of plasticizer from such solvent cast films is slower compared to pseudo-latex cast films due to the higher film density of the former [46]. As indicated in Figure 2.1 and Figure 2.2, pellets coated using TEC showed approximate zero-order drug release after a lag time of an hour. On the other hand, those coated using poorly soluble plasticizer-DBS, show a two-phase profile. Release during the up to almost an hour (first phase) is fast and contributed by the drug diffusion through water-filled pores after the migration of the water soluble pore former similar to that with TEC. In the second phase the drug release decreases as the remaining film of ethylcellulose and plasticizer shrinks in the free volume created by the loss of drug and pore former; thereby reducing the permeability[21]. Therefore, the choice of solvent (aqueous or organic) along with the nature of plasticizer (hydrophilic or lipophilic) affects the drug release.

2.4. Applications of plasticizers in membrane film coating

2.4.1. Film coating on tablets or pellets filled in capsules

Generally, film coating of tablets is performed in a perforated pan coating machine, while coating of multi-particulates is performed in a fluid bed processor equipped with a wurster column. The same polymer coating systems are used for coating tablets or multi-particulate system. Nonpareil substrates (e.g. sugar spheres, microcrystalline cellulose spheres (cellets®) or pellets from the extrusion-spheronization process can also be film-coated to provide sustained or delayed release profile. The size of the finished product (pellet) should not exceed the target pellet size of 2.4 mm if the capsule content is labeled for sprinkle-use. However, the size of 1.5 mm was recommended for modified release generic products [47]. Film coating can be performed with an organic solvent and aqueous system, the type of solvent (aqueous or organic) can have a major influence on the resulting film structure and subsequent release kinetics [48], some of these properties are discussed in following sections.

2.4.2. Film formation from non-aqueous system

Non-aqueous coating systems are popular since the majority of release controlling polymers like ethylcellulose, and methacrylate based polymers (Eudragits) are soluble in organic solvents and can be coated effectively. Film formation from non-aqueous coating system involves the polymer solutions undergoing sol to gel transitions upon solvent evaporation to finally form the polymeric films [48]. The film-forming mechanism of non-aqueous coating systems allows for a strong and continuous coatings. During drug release processes having robust membrane property is crucial since drug diffusion takes

place either by swelling of core and membrane or by drug diffusion without swellings. In either case, the addition of plasticizer, indeed, improves the strength of the film and provides flexibility to withstand any hydrostatic pressure that develops during the drug release. Also, the addition of plasticizer improves the processability by reducing attrition due to particle collision or collision to the equipment surface. Generally, ethyl cellulose based films are known to be rigid, which requires a higher amount of plasticizer in order to form a flexible film; on the other hand, eudragit based films are inherently flexible in nature, requiring lesser plasticizer. Films from aqueous dispersions have been found to be brittle in comparison to solvent-cast films [49]. This is of significance for delayed release systems like colonic drug delivery system, where the membrane has to sustain coating for a greater amount of time till it reaches the colon and then to withstand the mechanical stress in water scarce colonic environment. For instance, beads coated at 20% plasticizer level for acetyl tributyl citrate with ethylcellulose in ethanol, showed the drug release profile was slower than those coated with Aquacoat® with similar plasticizer and sodium lauryl sulfate composition. Also, no curing effect was seen with organic solvent-based coating [50]. Hyppölä et al, showed that for ethylcellulose in ethanol solution, up to 20% of dibutyl sebacate or Myvacet® (acetylated monoglycerides) were found to be the most efficient plasticizers based on tensile tests and thermal analysis [51]. It was observed that, at 10% plasticizer level of dibutyl phthalate, organic solutions of Eudragit RS100 and Eudragit RL100 prepared in Isopropanol:Acetone (4:3) solvent mixture, the product temperature was found to have much lesser effect on drug release compared to aqueous based coating system of Eudragit RS 30D and Eudragit RL 30D, at the product temperature range studied [52]. Bando and McGinity showed that films casted with

Eudragit L100 and S100(1:1) plasticized with TEC demonstrated significantly higher tensile strength and lower percent elongation from organic cast than that from aqueous cast films. Also, leaching of the TEC from the aqueous films was rapid and the TEC was found to diffuse from the films within one hour at pH 6.0, while the diffusion from organic cast films was minimal.[53].

On an average, organic solvent-based polymers system allow a three times faster spray rate for the same amount of polymer aqueous-based dispersions. Also, it offers lower expenditure on process validation and optimization compared to polymer aqueous-based systems[52]. This can significantly lower the cost of drug product development. However, due to environmental and safety concerns, aqueous systems are being explored nowadays.

2.4.3. **Film formation from Aqueous system**

Aqueous systems have an advantage over non-aqueous systems from the environmental and safety point of view [48]. However, coating process with aqueous polymer dispersions is affected by different factors, such as temperature, pH, addition of electrolytes and other polymers that can lead to coagulation of the dispersion [48]. Some of the parameters that can affect film formation from aqueous systems are curing time and type of curing.

2.4.3.1. Curing

The film formation from aqueous coating dispersion involves curing -the fusion of colloidal particles together to form a thin continuous film under appropriate temperature

conditions and plasticizer concentration [48]. Since fusing involves compatibility between the polymer and a plasticizer, it is crucial to choose an efficient and compatible plasticizer in order to form a smooth and continuous film. While coating above MFT ensures film formation while coating, a curing step is often required for some polymers to complete the coalescence process after coating. The curing temperature should be sufficiently high to allow the fusing of the colloidal particles. Humidity conditions also help in curing due to the plasticizing ability of water molecules. In practice, the airflow is reduced during curing stage to avoid any damage to the film. While coating, if the airflow is too high, then the Tg, and hence MFT, of the sprayed latex will change with moisture content, and eventually result in a poor film if the MFT rises above the product temperature [41].

Eudragit polymers that require curing include Eudragit RL/RS and Eudragit NE/NM from their aqueous dispersions. The curing conditions for Eudragit RL/RS from the 30% dispersion is 45-50-°C and 10-15% RH with water spray rate of 240 ml/kg for 30 min, while that for Eudragit NE/NM from 30 % dispersion is 40-45°C and 40-50% RH with a water spray rate of 10-14 g/min/m^3 for 30 min [54, 55]. Wu and McGinity have demonstrated that addition of the enteric polymer, Eudragit® L 100-55 to Eudragit® RS 30D, in ratio 1:3, along with 17.5% TEC minimized the change in dissolution rate of theophylline from pellets coated with during storage at 40°C for 4 days [56]. Interestingly, the T_g of the polymer of the plasticized film was found to increase to 44°C from 20°C after addition of Eudragit L100-55. This was attributed to the decrease in the molecular mobility of the Eudragit® RS polymer [56]. Similarly, ethyl cellulose based aqueous dispersion (Aquacoat®) has been found to have curing effect i.e. decrease in drug

release on curing [57]. If the curing step does not completely fuse the colloidal particles, then it has been observed that the drug release decreases on storage due to the progressive fusing process.

Wesseling et al. observed that curing for 1 hour at 60°C was found to have a drug release profile similar to that after 7-day storage. This can be attributed to the progressive fusing taking place during storage. This was confirmed by the 28-day storage sample that showed slightly slower drug release compared to the initial drug pattern. It was also found that 8 h curing was sufficient to eliminate any prospective slowing of drug release on storage [57]. For determining a curing temperature for a coating system, sufficient experiments should be performed.

2.4.3.1.1. Static vs dynamic curing

Studies have shown that dynamic curing (in a coating equipment like coating pan or fluid bed processor) is far more efficient than static curing (in a tray dryer) since the entire surface of all the pellets is exposed. Gendre et al. (Figure 2.3) demonstrated that 24 hr of static curing and 4 hr of dynamic curing, both performed at 60°C and ambient relative humidity were equivalent in terms of drug release properties, porosity, water content, structural rearrangement of polymer chains and crystalline distribution [58].

While curing, rapid drying rates are generally considered desirable; however it may have adverse effects on the resulting film since the rapid loss of water may not allow for the development of the capillary pressure necessary, which may inhibit deformation and coalescence [41]. Bhattacharya and Wurster found that with higher temperature and longer curing, the drug release from Eudragit® RS was found faster. It was shown that

there was an increase in pore volume with increased curing times for Eudragit® RS free films. It was concluded that these changes were because of the loss of plasticizer molecules during drying process, leading to the formation of molecular-scale voids and channels [59]. Therefore, volatility of the plasticizer should be considered while choosing a plasticizer. Out of liquid plasticizers, DBS has lesser volatility compared to TEC and Triacetin, and therefore exhibits lesser plasticizer loss during curing or storage [21]. Higher airflow may also cause spray-drying and loss of process efficiency, which can eventually cause faster drug release. Extreme care must be taken to reduce the fluidization of pellets in the fluid bed processor or tumbling of coated tablets in the coating pan so that there is a least mechanical shock.

Alternatively, static curing has an advantage of avoiding mechanical stress; however, it might have a tendency to form agglomerates during curing. Apart from the polymer, there are other excipients like surfactants, dispersing agents, etc., which are added to disperse the polymer particles. These excipients might interact with the API and disrupt proper film formation. Schmid et al. showed that cetyl alcohol, a stabilizing agent in Aquacoat ECD 30 was found to form a eutectic mixture with ibuprofen, which caused sticking tendency on ibuprofen crystals while coating [60].

2.4.4. Aqueous polymeric dispersions

To make coating procedures easy and environment friendly, various aqueous based polymers dispersions are available. Some of those are discussed in the following sections.

2.4.4.1. **Kollicoat MAE 30 DP**

Kollicoat MAE 30 DP is a 30% aqueous dispersion of polyvinyl acetate polymer in a polyvinyl pyrrolidone and sodium lauryl sulfate solution. It is an enteric polymer, which, inherently, has a tendency to form a brittle and non-tacky film due to the higher glass transition temperature of 113°C [17]. Hydrophilic plasticizers are preferred due to their incorporation in aqueous dispersion since, the use of hydrophobic plasticizers leads to a porous film due to non-homogeneous incorporation. The incorporation could, however, be improved by preparing a microemulsion of the hydrophobic plasticizer in water prior to addition to the polymeric dispersion [17]. It was found that the T_g of the plasticized film at 15% plasticizer concentration was above 60°C, making it non-tacky. Interestingly, water was found to act as an efficient plasticizer, for methylacrylate ester polymer, reducing the T_g below 0°C with only 10% plasticizer [17]. This observation indicates that the release rate can be affected by the water uptake of the plasticizer; this concludes that hydrophilic plasticizers show faster release rate compared to the hydrophobic counterparts.

2.4.4.2. **Aquacoat® ECD**

It is available as a 30% aqueous dispersion containing ethyl cellulose. It does not contain plasticizer; therefore plasticizer has to be incorporated externally. It is recommended that plasticizer should be mixed for at least 30 minutes before spraying with around 24% of plasticizer concentration for Aquacoat ECD [44]. The increase in plasticizer concentration above this concentration did not show any significant change in the glass transition of the plasticized system [44]. Moreover, the mechanical properties of aquacoat

films plasticized with triethyl citrate, triacetin, tributyl citrate, acetyltributyl citrate, acetyltriethyl citrate, dibutyl sebacate, dibutyl phthalate and diethyl phthalate in dry and wet conditions were found to be similar [49].

Although drug release profiles from Aquacoat® ECD coated formulations are pH-independent, the types of excipient in the films may affect the pH independent properties. For instance, Wesseling and Bodmeier showed that in certain cases pH can also influence the dissolution from Aquacoat® ECD based film. The buffer of pH 7.4 can cause dissociation of sodium lauryl sulfate present in Aquacoat® ECD, which subsequently allows rapid penetration of the dissolution medium through the incompletely coalesced film; whereas in 0.1 N HCl, since sodium lauryl sulfate remained predominantly unionized, there is no effect on drug release [50].

2.4.4.3. **Surelease®**

In contrary to the dispersion discussed in the previous section which does not have plasticizer, Surelease® is a fully formulated and optimally plasticized system of ethylcellulose supplied at 25% w/w solids content and available with various plasticizers. Surelease® grade E-7-19040 containing medium chain triglyceride and oleic acid as a plasticizer is more popularly used in pharmaceutical industry. Surelease® formulated with oleic acid (OA), or in combination with medium chain triglycerides (OA-MCT), or dibutyl sebacate (OA-DBS), as plasticizers showed very little difference in physical properties of the dispersions and thermal behavior of the casted films [61]. This could be attributed to the similar plasticizing effect of OA-MCT, and DBS in combination with OA.

Studies with two formulations of Surelease®, i.e., Surelease® grade E-7-7050 and E-7-7060 containing dibutyl sebacate (DBS) and glyceryl tricaprylate/caprate (GTC) as plasticizers, respectively, demonstrated that films containing GTC were harder and elastic than those containing DBS plasticized Surelease®. Also, the drug release was found to be lower for Surelease® plasticized with GTC compared to DBS at equal coat levels [62]. This indicates that Surelease® using GTC could be the suitable approach for extended release application. On other hand, hydrophilic polymers like methylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC), or polyethylene glycol are added to hydrophobic coatings for increasing the permeability and hence control the drug release properties [63].

2.4.4.4. **Eudragit RS/RL 30 D**

Bodmeier and Paeratakul found that Aquacoat films leach more water-soluble plasticizers than Eudragit RS30D films [46], which indicate that Eudragit RS30D is more hydrophobic in nature than Aquacoat. Sadeghi et al showed that mechanical properties of the Eudragit RL films were influenced by the type of solvent, plasticizer and its concentration in the coating liquid [64]. For instance, in organic solvents, an increase in the concentration of plasticizer decreased the tensile strength and modulus of elasticity, while, in aqueous dispersions, tensile strength decreased at 10% concentration from no plasticizer level but increased when increasing the plasticizer concentration from 10% to 20%. Modulus of elasticity was found to decrease with increase in plasticizer concentration irrespective of the type of solvent. Plasticized films with PEG 400 showed better mechanical strength compared to those with triethyl citrate [64]. It is proposed that this might be due to the interaction between carbonyl groups in trimethylammonioethyl

methacrylate chloride segment of Eudragit RS and hydroxyl groups of PEG 400 [65]. In the same way, the potential for interaction of PEG 400 with Eudragit RL would be even more due to a higher percentage of trimethylammonioethyl methacrylate chloride segments [64]. The film properties of Eudragit RS 30D were significantly affected by the type of plasticizers due to their plasticization efficiency significantly affecting the film properties of Eudragit RS 30D. Water-soluble plasticizers like triethyl citrate and triacetin had higher elongation and lower puncture strength values, while water insoluble plasticizers had lower elongation and higher puncture strength. [49].

In addition to the type of solvent and plasticizer, curing temperature and humidity also plays a very important role in monitoring the film properties. Curing at 60°C for 24 hours showed no effect on films with 10% PEG 400 or TEC and films with 20% plasticizer prepared from organic solution, while films prepared from aqueous dispersion and containing 20% plasticizer tensile strength and elastic modulus increased significantly ($p<0.05$) after curing [64]. Film coating on diclofenac sodium pellets with Eudragit® RS and RL 30D dispersions (Evonik GmbH, Germany) in the ratio of 4:1 with 20% TEC was performed to study the effect of curing conditions (temperature, time and humidity) on the drug release. Using response surface methodology, similar results could be obtained at 50°C with low relative humidity and long curing time (24 h) or with medium relative humidity (20–50% RH) and short curing time (4–8 h). On the flip side, curing at high humidity and long curing time, the drug release increased. This shows that curing at high humidity and high temperature can be detrimental in terms of drug release [66].

2.4.4.5. **Eudragit L30-D 55**

Eudragit L30-D55 is available as 30% aqueous dispersion of Eudragit L100-55, which is an enteric polymer dissolving at pH above 5.5. Triethyl citrate has been the choice of plasticizer for Eudragit® L30-D55, where it requires lower TEC levels for film formation than Eudragit® S100:L100 [53]. However, for electrostatic dry coating, it was found that use of PEG400 was found to provide good powder adhesion and successful coating, which was attributed to the greater reduction in glass transition temperature by PEG400 than TEC [67] Eudragit L100-55 has been shown to have profound moisture induced plasticization compared to other enteric polymers, which enables pellet coated with it to be successfully compressed into tablets without membrane breakage [19].

2.4.5. **Dry powder coating**

Although, aqueous and organic based polymer coatings have been used for a long time, they are time-consuming, costly, and environmentally unsafe. In order to reduce the time and cost while being environment-friendly, solvent less or low solvent-usage coating have been explored for single unit as well as multiparticulates. In this process, the polymer is sprayed along with plasticizer using a centrifugal granulator, fluidized bed, or tablet-coating machine followed by curing step using water or hydroxypropyl methylcellulose solution and then heating [68]. In this process, the amount of coating material required is higher to protect formulation from gastric pH, and the coating time required is significantly less as compared to conventional coating processes [68].

Mechanism of film formation for powder coating involves essentially the same sequence of steps as conventional solvent based coatings (Figure 2.4). The sequence involves- pretreatment of the coating material, application of the coating material on the substrate, considering the coating material adheres to the substrate during formation of film. The formation of film includes evaporation of any volatile material used and subsequent coalescence of the coating solid by application of heat and humidity.

Generally, powders having a particle size below 100μm (D_v 50) are suitable for powder coating [69]. Along with the particle size of the pre-plasticized polymer powder, the appropriate ratio of coating powder to substrate particle size should be considered to ensure appropriate adhesion and visual appearance [69]. For pretreatment, the particle size of dry powder should be less than 1% of the substrate [69]. This allows for uniform distribution of the material on the surface of the substrate. After distribution of the coating material on the substrate, it is exposed to higher heat and humidity conditions to allow for coalescence of the coating solids. The temperature is often more than the glass transition temperature in order to allow sufficient mobility of the polymer molecules. Exposing to higher humidity conditions provides water, which acts as a plasticizer that hastens the coalescence process. For reducing the processing temperature of the powder coating and decrease the curing time, plasticizers are crucial for polymers with very high Tg (>60 °C) [69]. Addition of plasticizer- either before coating (pretreatment of polymer with plasticizer by physical mixing) or spraying plasticizer while spraying dry polymer, helps in decreasing the glass transition temperature by plasticization of the polymer. To improve the process of dry powder coating, polymer-plasticizer fine particles can be prepared using spray drying of polymer-plasticizer solution and used further for dry

coating application [70]. Since spraying pure plasticizer can result in agglomeration of the pellets, plasticizers can be diluted with a 10% aqueous HPMC solution [71]. Spraying the plasticizer, while coating, might also assist in providing a sticky surface for the coating solids to stick to the surface as well as amongst it. Addition of a subcoat of 2-3% on the uncoated substrate helps in the adhesion of coating solids to the substrate by lowering the interfacial energy [72]. Low melting polymers like polyethylene glycol 3350 or Pluronic 127 and cetylstearyl alcohol can be used for subcoating [73]. Furthermore, keeping higher processing temperature for low melting point subcoat allows for better adhesion of the coating solids on the substrate with a subcoat [69]. After adhering to the surface of the substrate, spreading of the coating material in rubbery state (above glass transition temperature) is also crucial. Therefore, the contact angle between the subcoat material and the coating solids in rubbery state should be determined while selecting a suitable subcoat and polymer material. For thermoplastic materials like the coating solids, distribution on the substrate depends on the molecular weight of the polymer and the curing temperature [69].

The mechanism of formation of film by dry coating process can be summarized by (a) coalescence of the coating solids, (b) leveling of the coating solids by densification, removal of the empty spaces and smoothening and (c) eventual cooling of the layer resulting in hardening of the coating [69]. The coalescence of the coating solids occurs due to heat and is aided by the presence of an enormous quantity of plasticizer, which lowers the glass transition temperature and minimum film formation temperature. The leveling and smoothening occurs by the gentle interaction of the semi-fluid layer with the

equipment walls and other substrates. The semi-fluid layer then cools off due to decrease in temperature resulting in hardening of the coating.

Compared to conventional coating techniques, dry coating formulation contains a higher concentration of plasticizers, lower glass transition temperature of the pre-plasticized polymers and lower particle size [69]. In one of the studies, talc (30% of the dry weight of polymer) was pre-blended to Hypromellose Acetate Succinate (HPMCAS) in order to enhance the surface smoothness of the film as well as to prevent sticking. Addition of another plasticizer-acetylated monoglyceride (AMG) to triethyl citrate in a 3:2 ratio, proved helpful in promoting wettability of HPMCAS, due to the lowering of contact angle with the polymer, and reducing agglomeration during powder coating. The concentration of TEC and AMG used in this study were 30% and 20%, respectively, based on the dry weight of the polymer [68]. During the curing step, water or solution of HPMC was sprayed to facilitate film formation. Therefore, this technique cannot be considered solvent free; however, it significantly reduces the use of solvent. At equal coating levels, conventional film coating process provided much better enteric protection compared to dry coating technique. Upon storing at an elevated temperature for up to 6 months the enteric protection of the dry coated beads and tablets was comparable to conventional coating process [68].

The drug release showed faster release from the dry coating process compared to conventional film coating procedures. From the processing point of view, the outlet temperature should be maintained around the glass transition temperature in order to promote the powder adherence through capillary forces of the liquid plasticizer and coalescence. Also, like conventional film coating, curing temperature should be

maintained a few degrees more than the glass transition temperature to facilitate film formation.

2.5. **Film coating of multi-particulates compressed into tablets**

Due to the ease of administration and patient's compliance, tablets have been the most popular dosage of administration; however, multi-particulates are gaining popularity for certain applications due to some distinct advantages. The advantage of multi-particulate pellets over unit dosage forms like tablets and capsules is their uniform spread throughout the gastrointestinal tract, avoiding the risk of high local drug concentrations and hence toxicity, avoiding premature drug release from enteric coated tablets in the stomach as a result of rapid gastric transit time [74]. Moreover, administration of the multi-particulate pellets will essentially eliminate the dependence of the drug effect on gastric emptying since the individual units being sufficiently small (less than 1 mm in diameter) can pass through the pylorus opening [75].This may help reduce variations in drug plasma concentrations during fasted and fed conditions. In comparison to capsule, compressed multiparticulate tablets, also referred as Multi-Unit Particulate System (MUPS), reduces the cost of production; compared to unit dose tablet, it reduces the variability in bioavailability and risk of local irritation, also safeguards against tampering, easier esophageal transport, a higher dose can be administered, higher patience compliance, and ability of being scored in order to provide flexible dosing regimen [74].

Since the role of membrane coating on pellet is vital in obtaining the controlled drug release over time, maintaining its integrity during coating, and tablet compression is crucial. The primary requirements for pellets to be compressed into tablets are that the

outer membrane should not crack or fuse into a non-disintegration matrix during compaction and should disintegrate rapidly into individual pellets in the gastrointestinal fluid [76]. Therefore, greater plasticization is required during coating process to ensure the integrity of the release controlling membrane. From the regulatory point of view, USFDA guidance on "Tablet scoring: nomenclature, labeling, and data for evaluation" states that "the dissolution profile on pre-compressed beads versus post-compressed whole and split tablet portions should meet similarity factor (f2) criteria to ascertain the integrity of beads during compression" [77]. Therefore, it is advisable to conduct the dissolution of pre-compressed beads and post-compressed beads and demonstrate similarity prior to the regulatory filing of beads-based products for marketing in the United States. The guidance also recommends demonstrating satisfactory splittability and compliance of the split tablets with the USP <905> guidance [77, 78].

Along with the optimization of the level of plasticizer, the addition of cushioning agents like microcrystalline cellulose, due to its fibrous structure and better compressibility, provides cushioning to the pellets during compression. It was shown that excipients that caused the least damage to the pellets of Eudragit RS with theophylline as a drug, in the order: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate [79]. Disintegration agents like crospovidone, croscarmellose sodium, etc. ensure rapid disintegration and hence reproducible dosage form performance. Vergote et al. showed that addition of 50% (w/w) drum-dried corn starch/Explotab®/paraffinic wax beads to the formulation provided better protection than lactose monohydrate granules and microcrystalline pellets while maintaining the acceptable disintegration properties [80]. Comparison between microcrystalline cellulose

granules and Avicel PH 101 as a cushioning agent showed that larger size microcrystalline cellulose granules caused more deformation of the pellets but less damage to coating in comparison to Avicel PH 101 [81]. Also, the substrate should be plastic enough to withstand changes in shapes during compression. Since, microcrystalline cellulose pellets (Cellets®) has a plastic fracture, it is preferred in comparison to sugar spheres. Traditional tableting ingredients like lubricants are added to avoid any picking or sticking to the die and punches [82]. Polymers used for release controlling film coating are either cellulose or acrylate based. These polymers can be used in aqueous or non-aqueous systems.

Lehmann et al have shown that elongation of more than 75% was obtained with acrylic polymers, Eudragit®RL/RS. Also, the release pattern of disintegrating tablets was found to be very similar or nearly the same as that of uncompressed pellets [83]. Some of the marketed products based on MUPS system are shown in Table 2.5.

2.6. **Formulation of osmotic drug delivery system**

The simplest design of osmotic drug delivery system consists of drug along with or without osmagent coated with semi-permeable membrane. The system imbibes water, and forms a saturated solution inside the coated system that releases drug through the pore, in a controlled manner [89]. Polymers like cellulose acetate, cellulose, diacetate, cellulose triacetate, ethyl cellulose eudragits, etc. that are permeable to water but impermeable to solute are used [89]. Since plasticizer also impacts the permeability of the semi-permeable membrane, it is crucial to study the effect of plasticizer in coating systems for osmotic drug delivery system. Hence, it is essential that the integrity of the

semi-permeable membrane be maintained while resisting osmotic pressure internally and shear during gastrointestinal transit, externally. This is essential to maintain a uniform drug release from the dosage form. Shokri et al. studied the effect of different concentration of plasticizer (glycerin and castor oil) along with cellulose acetate as polymer on the drug release. The semi-permeable membrane with only 0.5% castor oil was found to crack in the dissolution medium after few hours due to high internal hydrostatic pressure (Figure 2.5) [90]. These studies indicate that to obtain robust membrane, the plasticizer concentration in the membrane should be optimized.

The nature of plasticizers also affects the drug release profiles. For instance, the drug release was found to be faster with hydrophilic plasticizer-glycerin compared to hydrophobic plasticizer-castor oil [90]. This is due to the fact that hydrophilic plasticizer leaches readily while increasing the porosity of the semi-permeable membrane, which allows it to imbibe water faster than semi-permeable membranes containing hydrophobic plasticizers. Similar results were obtained with hydrophobic plasticizer triacetin and hydrophilic plasticizer-PEG 200 too [91]. Increasing in the concentration of hydrophilic plasticizer in the semi-permeable membrane increased drug release, while the drug release decreased while increasing hydrophobic plasticizer concentration [90].

2.7. Safety and regulatory perspective on the use of plasticizers

Although, the generally used plasticizers possess GRAS(Generally Regarded As Safe) status, United States Food and Drug Administration (USFDA) has laid down the Maximum Acceptable Daily Dose (MADD) of excipients in the Inactive Ingredient Database. The list is updated, if required, based on current research data. An applicant

has to demonstrate compliance of the excipient levels in the formulation to this database. Exceeding the MADD requires the applicant to demonstrate the safety of the ingredient using different means like citing an already approved product with higher levels of those excipients or toxicological studies, which can be quite expensive and time-consuming. Therefore, it is important for the formulators to adhere to the MADD of plasticizers during formulation development. Table 2.6 lists the animal toxicity data (LD_{50}) of the commonly used plasticizers. Safety aspects of the commonly used plasticizers are discussed below:

2.7.1. **Dibutyl phthalate**

It was found that Phthalates are rapidly metabolized and excreted, therefore, the presence of phthalate ester metabolites reflect the exposure of parent diester. Dibutyl phthalate has been shown to have reproductive system-related adverse effects in human and rodents(Food and Drug Administration, 2012). EPA-recommended oral Reference Dose (RfD) for DBP is 0.1 mg/kg/day based on the adverse effects observed in animals. In December 2012, USFDA published a guidance "Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products". Moreover, USFDA recommended avoiding usage of dibutyl phthalate, which is a widely used plasticizer, citing toxicity concerns (Food and Drug Administration, 2012). Hence, the regulatory agency requested to reformulate the already marketed products, like Asacol®, by removing dibutyl phthalate. In 2013, Asacol (mesalamine) delayed release tablets 400 mg was discontinued by Warner Chilcott and was replaced by a new formulation of Delzicol (mesalamine) delayed release capsules 400 mg, which contains 4 tablets of 100 mg mesalamine [92,

93]. In Delzicol®, dibutyl sebacate was used as a plasticizer instead of dibutyl phthalate used in previously marketed Asacol® formulation.

2.7.2. Acetyl Tributyl Citrate (ATBC)

ATBC is extensively metabolized in to many metabolites. Monobutyl citrate is the major urinary metabolite of ATBC. Although, ATBC could be hydrolysed to butanol, it has not been documented as a metabolite. The No Observed Adverse Effect Level (NOAEL) of ATBC is 100 mg/kg bw/day [94].

2.7.3. Triethyl Citrate

It has been found that triethyl citrate hydrolyses in vivo to citric acid and ethanol, which are well-defined compounds with low toxic potential. The rate of hydrolysis of triethyl citrate appears to be slower in human serum compared to rat serum [94].

2.7.4. Dibutyl Sebacate

On ingestion, dibutyl sebacate is metabolized by pancreatic lipase. It follows the same route of metabolism as fats [95].

2.7.5. Polyethylene Glycol

Polyethylene glycol has been widely used for pegylation, a process of attaching polyethylene glycol to a biomolecules in order to enhance their in-vivo residence time [96]. USFDA currently allows maximum of 8649 mg of PEG 400[97] in an oral dosage unit, which shows the relatively less toxic nature of the plasticizer. There is scarcity of literature on the pharmacokinetics of PEG. It is not known to be metabolized in humans

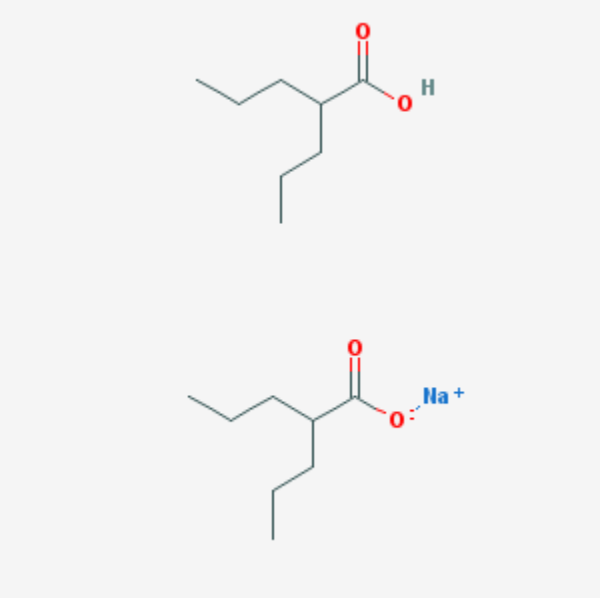
and there have been no known pharmacological actions or confirmed toxicity as a result of the limited absorption [98].

2.7.6. Propylene Glycol

Propylene glycol is shown to rapidly absorb and cleared from body with a relatively short half-life (2.4-5.2 hours) [99]. It is shown that propylene glycol is first oxidised to lactaldehyde by alcohol dehydrogenase, then further oxidized to lactate by aldehyde dehydrogenase. The resulting lactate is further metabolised to pyruvate, carbon dioxide, and water. Furthermore, Lactate also participates in glucose formation through gluconeogenic pathways [99]. A low LD_{50} of 0.02 g/kg shows the its relatively toxic profile compared to other currently used plasticizers[24]. Considering the toxic potential of propylene glycol, European Medicines Agency proposed a change in labeling on the package inserts of products containing propylene glycol[99]. However, the quantities of propylene glycol used as plasticizers in oral membrane controlled dosage forms are relatively small.

2.8. Drug properties-Divalproex Sodium

Divalproex sodium is a coordination complex of sodium valproate and valproic acid. It has a pK_a of 4.6, with a solubility of 1 mg/ml at pH 1.0 and 200 mg/ml at pH 6.8 [100]. Valproic acid is clear, colorless to pale yellow, slightly viscous liquid, and sparingly soluble in water, whereas sodium valproate is a white crystalline, hygroscopic, and highly soluble in water and alcohol [101].



Chemical structure of Divalproex Sodium

Divalproex sodium has been used as an anticonvulsant to treat seizures, bipolar disorder, and migraines. It is available in tablet and capsule dosage forms to treat these conditions.

2.9. Powder compression models

2.9.1. Heckel equation

The Heckel equation assumes that the compression of powder mimics a first order chemical reaction kinetics; in which, the pores in the initial powder are the reactants and the densification of the bulk is the product. It was initially developed for metals but now has been used for other materials [102]. This relationship can be given by Equation 2-2, where D is the relative density, k is the proportionality constant and P is the applied pressure.

$$\frac{dD}{dP} = k(1 - D) \qquad \textbf{Equation 2-2}$$

Integrating the equation for density change from D_0 to D while increasing pressure from zero to maximum pressure (P), the equation becomes Equation 2-3.

$$Ln\left(\frac{1-D_0}{1-D}\right) = kP \qquad \textbf{Equation 2-3}$$

Heckel studied some metal powders and found that the proportionality constant 'k' is inversely related to the ability of the material to deform plastically. James found that, on isostatic compaction on metal powders, the slopes were different at higher compression pressure than initial [103]. Studies with materials of different porosities revealed that the low porosity material yielded straight line over the entire pressure range compared to high porosity material [104].

Softer metals like tin and, lead showed straight lines with no curvature, except at very low porosities. Also, materials known to deform plastically like alkali halides and sodium bicarbonate showed little or no curvature [105]. Therefore, the reasons of the initial curvature can be summarized as below:

(a) Packing by particle sliding and rearrangement at low compression pressure
(b) Densification by brittle fracture at low compression pressure followed by plastic deformation at the higher pressures
(c) Deagglomeration of agglomerates of fine particles at low compression pressure

(d) Elastic compaction of a nearly nonporous material [105].

There are two ways to apply Heckel equation to the compaction data in two ways: (a) the "in-die" Heckel plot and (b) the "out-of-die" Heckel plot [106]. For "out-of-die" approach, compact dimensions are measured after ejection, while for "in-die" approach, the dimensions are estimated using apparatus like instrumented tablet press or compaction simulator. Generally, "in-die" approach is used due to generation of faster results and relative ease of data collection. However, in this study, an "out-of-die" approach was chosen to perform compactability analysis since "out-of-die" results represent only plastic deformation and not elastic deformation. Literature shows that "in-die" heckel plot analysis fails to accurately describe the compaction properties of pharmaceutical powders[106].

2.9.2. Kawakita equation

The Kawakita equation describes the relationship between the degree of volume reduction of the powder and the applied pressure [107]). The Kawakita equation is given by Equation 2-4.

$$\frac{\mathbf{P}}{\mathbf{C}} = \frac{\mathbf{P}}{\mathbf{a}} + \frac{\mathbf{1}}{\mathbf{ab}}, \qquad \mathbf{C} = \mathbf{1} - \frac{\boldsymbol{\rho}_{\mathbf{b}}}{\boldsymbol{\rho}_{\mathbf{a}}} \qquad \textbf{Equation 2-4}$$

where ρ_a, ρ_b, C, and P are the compact apparent density, powder bulk density, degree of volume reduction and compression pressure, respectively. The constant "a" and "b" represent compressibility index and resistant forces to compression, respectively [108]

Kawakita equation, generally, holds for soft. fluffy and medical powders [107]. It is imperative to measure the initial volume(Bulk volume) of the powder since any error in the measurement can lead to deviations in the modelling results. This equation can be applied for tapping compaction too; in this case, the compaction pressure term is replaced by number of taps[107].

2.10. Powder properties

Density(Bulk, tapped and true) measurement, flowability and moisture content of the powder are critical for the pharmaceutical excipients to be utilized as a binder/filler for direct compression application.

2.10.1. **Bulk and Tapped density**

Bulk and tapped density are measured by pouring samples in a graduated cylinder without disturbing the powder bed. The uneven powder bed was leveled carefully using a stainless steel spatula. This initial volume was recorded as bulk volume (V_b) and the bulk density (ρ_B) was calculated as per the Equation 2-5. The cylinders were tapped in increments of 250 taps using a Tapped Density tester until the bed volume remained unchanged from the previous reading. The final volume is recorded as Tapped Volume (V_T). The Tapped density (ρ_T) is calculated using Equation 2-6 .

$$\boldsymbol{\rho_B = \frac{W}{V_B}} \qquad \textbf{Equation 2-5}$$

$$\rho_T = \frac{W}{V_T}$$ **Equation 2-6**

2.10.2. Flowability

Flowability is a key parameter that ensures uniform filling of the die during compression leading to consistent tablet weight. There are different parameters that can indicate the flowability of the powder. Four commonly used methods to test powder flow are angle of repose, compressibility index or Hausner ratio, flow rate through an orifice and shear cell.

Table 2.1 Flow Properties and Corresponding Angles of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25-30
Good	31-35
Fair-aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate, vibrate	46-55
Very poor	56-65

Very, very poor	>66

Compressibility index or Carr's index and Hausner's ratio are simple fast and popular method of predicting flow characteristics. It has been proposed as an indirect measure of bulk density, size and shape, surface area, cohesiveness and moisture content. Carr's index and Hausner's ratio can be determined using Equation 2-7 and Equation 2-8, respectively [109].

$$\textbf{Carr's Index} = \left(\frac{V_B - V_T}{V_B}\right) \times 100 \qquad \textbf{Equation 2-7}$$

$$\textbf{Hausner's ratio} = \left(\frac{\rho_T}{\rho_B}\right) \qquad \textbf{Equation 2-8}$$

Table 2.2 Scale of flowability based on Compressibility index (Carr's index) and Hausner Ratio

Flow Property	Compressibility Index (%)	Hausner Ratio
Excellent	≤10	1.00-1.11
Good	11-15	1.12-1.18
Fair	16-20	1.19-1.25

Passable	21-25	1.26-1.34
Poor	26-31	1.35-1.45
Very poor	32-37	1.46-1.59
Very, very poor	>38	>1.60

Adapted from [109]

2.10.2.1. Angle of Repose

Powder was passed at 45° angle from a funnel until the tip of the heap of powder reaches the bottom tip of the funnel. The circumference(C) and the height of the heap (h) were noted and the angle of repose was calculated as per Equation 2-9.

$$\textbf{Angle of Repose} = \tan^{-1}\left(\frac{2\pi h}{C}\right) \qquad \textbf{Equation 2-9}$$

2.10.2.2. Loss on drying (Unbound moisture content)

Unbound moisture can cause drug degradation for water sensitive drugs; therefore, excipients with low unbound moisture content are preferred for direct compression. Unbound moisture content can be determined using moisture analyzer. The test

temperature should be able enough to be able to remove the unbound water without charring the sample.

2.11. Tablet properties

2.11.1. Tablet Hardness

Tablet should possess sufficient mechanical strength to withstand coating, packaging, shipping and handling. Mechanically weaker tablets can result in excessive friability, reduced dose and loss of cosmetic aesthetics resulting in patient non-compliance.

The mechanical strength of a tablet is a function of inter-particle bonding area and bonding strength [110]. Creation and elimination of bonding area is affected by compaction conditions, mechanical properties and particulate properties (such as particle size and shape) [110]. Amongst the deformation mechanisms, plastic deformation is the most important mechanism for creating larger bonding area. Bonding strength is determined by the chemical nature of the materials involved [110].

2.11.2. Friability

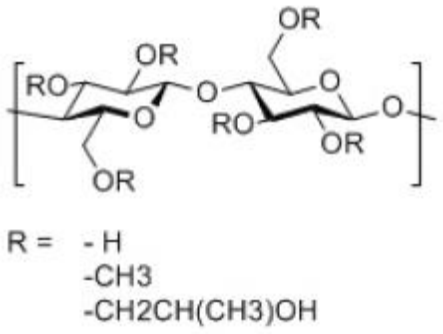
Friability test is carried out to determine the loss of mass during subsequent handling of tablets i.e. coating, storage or transport. Friability is a measure of the physical integrity of tablets. Weaker tablets and tablets with sharp edges show higher friability. Friability of tablet is determined using a Friabilator. Sample weight is determined by the unit mass of the tablet. For tablets with a unit mass equal to or less than 650 mg, sample of whole tablets corresponding to 6.5 g is taken, whereas for tablets with a unit mass of more than 650 mg, sample of 10 whole tablets is taken.. The tablets should be carefully dedusted

prior to and after the testing. Tablets should be accurately weighed and placed in drum and rotated for 100 revolutions (4 min at 25 rpm). The Friabilty is calculated as per Equation 2-10. The sample is deemed to fail the test if any tablet is found to be broken at the end of the test.

$$\textbf{Friability} = \left(\frac{\textbf{Initial weight of sample} - \textbf{Final weight of sample}}{\textbf{Initial weight of sample}}\right) \times \mathbf{100} \quad \textbf{Equation 2-10}$$

2.12. Affinisol® HPMC polymers

AFFINISOL™ HPMC HME, was introduced by Dow Chemicals to overcome the high glass transition temperature, high melt viscosity, and low degradation temperature challenges for hot melt extrusion applications. It has a significantly lower T_g and melt viscosity as compared to other available grades of HPMC. Furthermore, they have been shown to improve wetting and dissolution of poorly soluble drugs [111]. **Error! Reference source not found.** shows the chemical structure of HPMC. It has Methoxyl,% and Hydroxypropoxyl,% substitutions of 22.0-27.0 and 25.0-32.0, respectively.



Chemical structure of HPMC

Figures

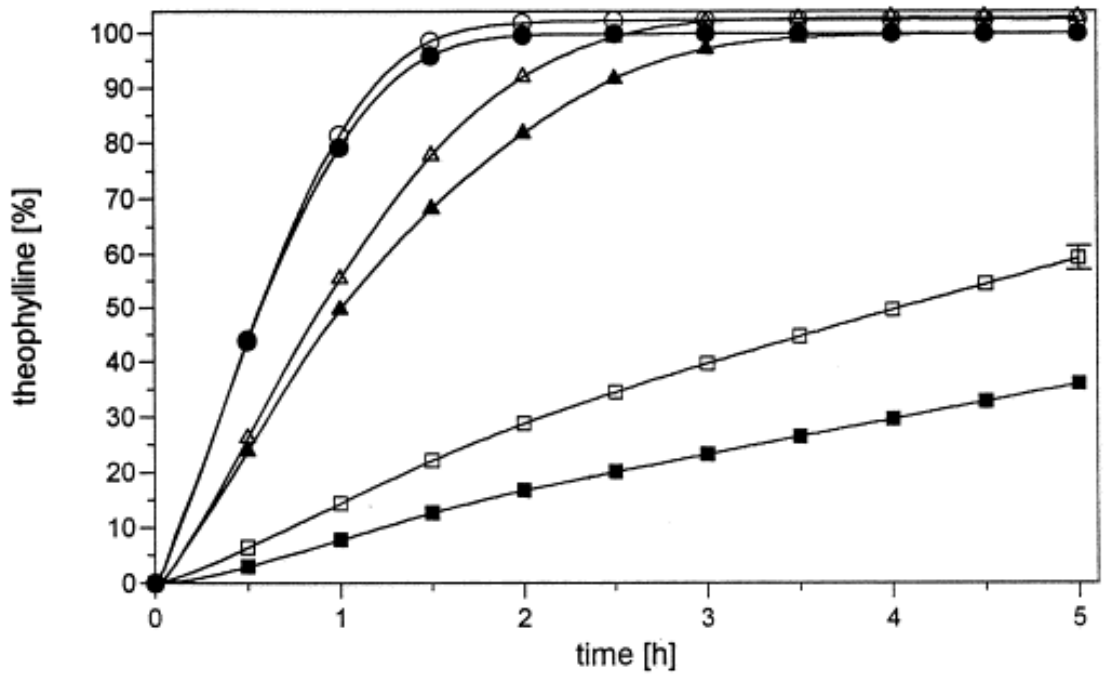


Figure 2.1 Effect of the pore former content in combination with water soluble and fairly water soluble plasticizers in the coatings on the release of theophylline. Film: 90, 80, 70% ECD (11.0% TEC, Diethyl Phthalate(DEP)); 10, 20, 30% HPMC. Curing: TEC: 1 h, 90°C, DEP: 1 h, 100°C. Release conditions: Type II; 0.1 N-HCl; 37°C; (mean±S.D.;n=2). 11.0% TEC: ■ 10% HPMC; ▲ 20% HPMC; • 30% HPMC. 11.0% DEP: □ 10% HPMC; △ 20% HPMC; ○ 30% HPMC. Adapted from [21]

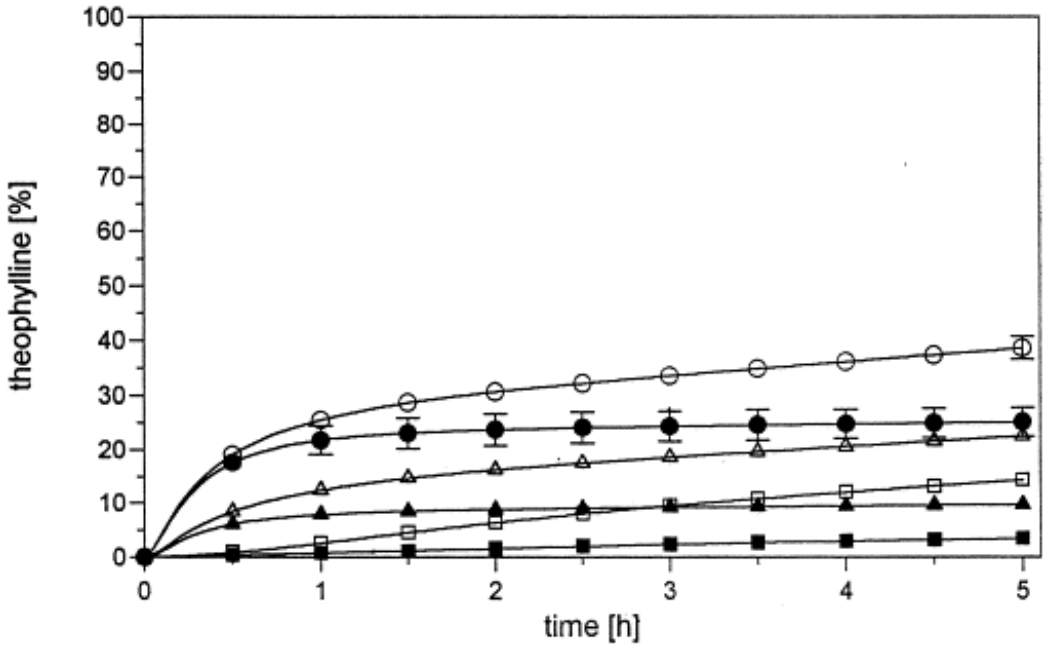


Figure 2.2 Effect of the pore former content in combination with very fairly water soluble and water insoluble plasticizers in the coatings on the release of theophylline. Film: 90, 80, 70% ECD (12.5% DBP, DBS); 10, 20, 30% HPMC. Curing: DBP: 1 h, 80°C, DBS: 1 h, 80°C. Release conditions: Type II; 0.1 N-HCl; 37°C; (mean±S.D.;n=2). 12.5% DBP: □ 10% HPMC; ▵ 20% HPMC; ○ 30% HPMC. 12.5% DBS: ■ 10% HPMC; ▲ 20% HPMC; • 30% HPMC. Adapted from [21]

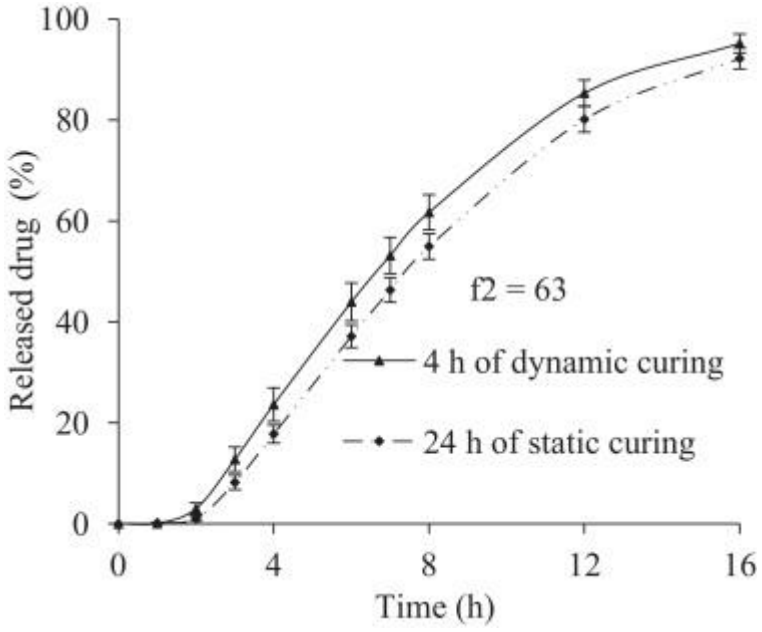


Figure 2.3 Influence of curing conditions on drug release properties from coated tablets after 24 h of static curing and 4 h of dynamic curing, both carried out at 60°C and ambient relative humidity. (Adapted from [58])

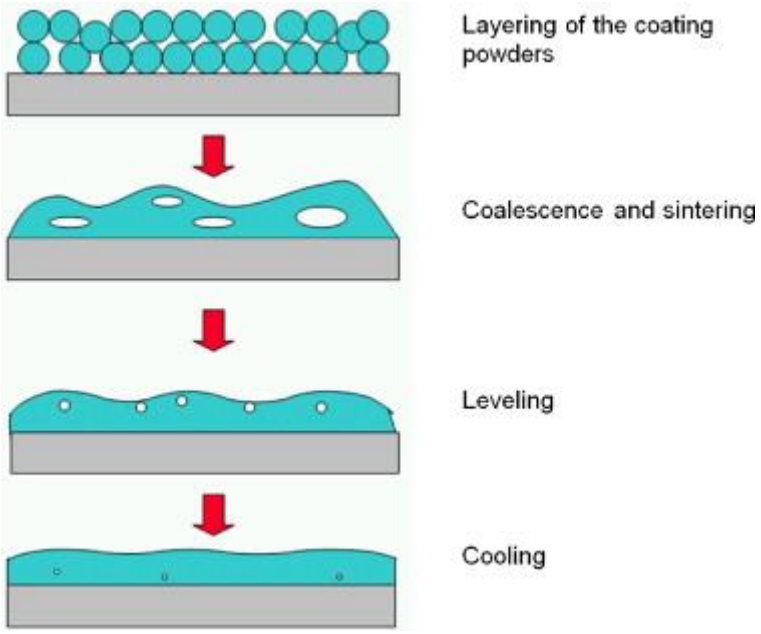


Figure 2.4 Schematic of film formation in dry powder coating systems. (Adapted from [69])

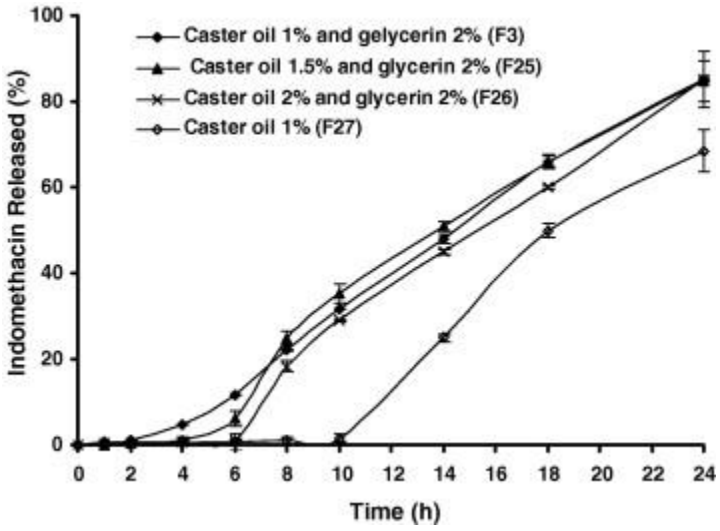


Figure 2.5 Release profiles of indomethacin from formulations containing different percents of glycerin (0% and 2%) and caster oil (0.5%, 1%, 1.5% and 2%) in the SPM formulation (F24 containing 0.5% castor oil was cracked and broken during dissolution process).(Adapted from [90])

Tables

Table 2.3 Common Plasticizers Used in Pharmaceutical Dosage Forms Type Examples

Chemical class	Example(s)
Citrate esters	triethyl citrate, tributyl citrate, acetyl triethyl citrate, acetyl tributyl citrate
Phthalate esters	dibutyl phthalate
Fatty acid esters	dibutyl sebacate
Glycol derivatives	polyethylene glycol, propylene glycol
Others	triacetin, mineral oil, castor oil, vitamin E TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate)

Table 2.4 Glass transition temperature (T_g) of the plasticized film of ethylcellulose at 25%w/w level of plasticizers and Solubility Parameters of various plasticizers

Plasticizer	**T_g (°C)**	**Solubility Parameter ($MPa^{0.5}$)**
Oleic acid	45.2	16.0
Dibutyl sebacate	49.6	18.8
Dibutyl phthalate	58.1	19.0
Medium chain triglyceride	62.0	20.0
Diethyl phthalate	67.7	20.5
PEG 400	70.0	23.0
Triethyl citrate	74.4	20.4
Triacetin	79.6	20.0
Propylene Glycol	91.1	25.8

Glycerin	128.5	33.8

(Adapted from [40])

Table 2.5 Marketed MUPS (Multi-Unit Particulate System) products

Product	Company	Drug	Strengths	Plasticizer used
LOSEC® MUPS[84]	AstraZeneca	Omeprazole magnesium equivalent to Omeprazole	10, 20, 40 mg	Triethyl citrate
Antra® MUPS[85]	AstraZeneca	Omeprazole magnesium equivalent to Omeprazole	10, 20 mg	Triethyl citrate
PREVACID® SoluTab™[86]	Takeda	Lansoprazole	15 mg, 30 mg	Triethyl citrate
TOPROL XL® [87]	AstraZeneca	metoprolol succinate equivalent to metoprolol tartrate	25, 50, 100, 200 mg	Polyethylene glycol
Beloc® ZOK[88]	AstraZeneca	metoprolol succinate equivalent to metoprolol tartrate	25, 50, 100, 200 mg	Polyethylene glycol

Table 2.6 Animal toxicity data **(**LD_{50}) of commonly used plasticizers

Plasticizer	Animal tested	LD_{50}
Acetyl Tributyl Citrate	Rat	5.8 g/kg[24]
Triethyl Citrate	Rat	5.9 g/kg[24]
Dibutyl Sebacate	Rat	16 g/kg[24]
Triacetin	Rat	3 g/kg[24]
Polyethylene Glycol 400	Mouse	28.9 g/kg[24]
Propylene Glycol	Rat	0.02g/kg[24]

3. SPECIFIC AIMS

Specific Aim 1: Divalproex Sodium as a Non-traditional Plasticizer of Ethylcellulose (Non-traditional role of Drug)

The objective of the research was to demonstrate the plasticization properties of divalproex sodium (DVS) on ethyl cellulose (EC), which could prove beneficial for film fabrications or hot melt extrusion based formulations. Films containing 10 - 50% w/w DVS in EC as dry weight of polymer were prepared using solvent evaporation method. In order to prove the plasticization effect of DVS on EC, mechanical and rheological and thermal characterization using texture analyzer, hybrid rheometer, and differential scanning calorimetry (DSC), respectively, were performed. Also, stability studies at45°C/75% RH for 2 weeks (open condition) were carried out to determine any changes in the glass transition temperature of the films. It was found that there was a decrease in average peak load, melt viscosity and glass transition temperature (T_g) while increase in elongation, with increase in concentration of DVS in the films. These results demonstrate the plasticization tendency of DVS on EC, Films showed reasonable physical stability (similar T_g) at 45°C/75% RH for 2 weeks (open condition), attributable to the similar solubility parameters of DVS and EC.

Specific Aim 2: Characterization of films of divalproex sodium and ethylcellulose to investigate the plasticization effect of divalproex sodium on ethylcellulose

The objective of the research was to characterize the films of DVS and EC to investigate the mechanism of plasticization of DVS on EC. Films containing 10 - 50% DVS as dry weight of polymer were prepared were characterized using thermogravimetry (TGA), X-ray diffractometry (XRD), polarized microscopy, Fourier Transform Infrared (FTIR) spectroscopy and Raman spectroscopy. TGA studies revealed the interaction between valproic acid- a constituent of divalproex sodium and ethylcellulose. Owing to the liquid nature of valproic acid and the interaction with ethylcellulose, the plasticization tendency of DVS on EC, can be attributed to the presence of valproic acid (fatty acid). XRD studies showed amorphous nature of the films; however, polarized microscopy revealed the presence of scattered undissolved sodium valproate crystals. FTIR and Raman spectroscopy results proved the presence of hydrogen bonding between DVS and EC. The stability studies showed no change in crystallinity as evident from the XRD profile of the films after storing at 45°C/75% RH for 2 weeks (open condition).

Specific Aim 3: Evaluation of Affinisol® HPMC polymers for direct compression process applications (Non-traditional role of Excipient)

Affinisol® (Hydroxypropylmethyl cellulose) polymers with low glass-transition temperature are usually processed by Melt Extrusion. Low glass transition temperature of polymer is proposed to show better compressibility at lower compression pressure. This study evaluates the compaction properties and powder properties of Affinisol® Powder by the determination of physical properties like bulk/tapped density, angle of repose and loss on drying. An out-of-die compactability study was carried out and evaluated using Kawakita and Heckel compaction models along with axial expansion post-compression. Also, effect of compression force on hardness of the compact was evaluated. Moreover, friability and lubricant sensitivity studies were also carried out. The results of the evaluation of powder properties showed that the tested polymers had acceptable flow properties and low moisture content compared to other HPMC polymers. Compactability study showed lower yield pressure of Affinisol® compared to HPMC E15. This is evident by higher hardness of compact at lower compression pressure (up to 66 MPa) compared to HPMC E15. Furthermore, the friability of Affinisol® tablets compressed at 0.6 metric ton was found to be much lower than HPMC E15 tablets compressed at the same compression pressure. The plastic nature of the polymers caused more than 30% lost of compressibility due to lubrication. Differential Scanning Calorimetry (DSC) studies confirmed low glass transition temperature of the polymers, which can be attributed to other higher degree of substitution. Overall, Affinisol® HPMC polymers can be proposed as a binder or controlled release matrix former for direct compression.

4. DIVALPROEX SODIUM AS A NON-TRADITIONAL PLASTICIZER OF ETHYLCELLULOSE

4.1. Introduction

Plasticizers are low molecular weight resins/polymers or small molecules, which are generally used to facilitate the device development processes by reducing the glass transition temperatures of the polymers. The majority of plasticizers are in the liquid state and form secondary bonds to polymer chains and spread them apart; thereby reducing the polymer-polymer secondary bonding and providing greater mobility for the macromolecules. Such phenomenon plasticization, results in a soft and deformable polymer mass [3]. In pharmaceuticals, this attribute allows it to be used extensively for film-coating and hot melt extrusion applications.

Plasticizers are incorporated into the amorphous parts of polymers leaving the crystalline part unaffected. It is expected that a plasticizer will reduce the modulus, tensile strength, hardness, density, melt viscosity, glass transition temperature, electrostatic chargeability and a volume resistivity of a polymer, while simultaneously increasing its flexibility, elongation at break, toughness, dielectric constant and power factor [3].

Traditional plasticizers such as triethyl citrate, dibutyl sebacate, and triacetin have been used widely; additionally certain active pharmaceutical ingredients (API) or excipients have been also shown to act as plasticizers. For instance, methylparaben [112], ibuprofen, chlorpheniramine maleate (CPM) [112,113] and metoprolol tartarate [113] were found to decrease the glass transition temperature of Eudragit RS films.

Plasticization tendency of APIs on polymers can be advantageous for hot melt extrusion, and film coating application. During hot melt extrusion, the plasticization of the polymer by API lowers the processing temperature, which in turn helps in reducing thermal exposure on the thermally sensitive excipients such as antioxidants. API acting as a plasticizer helps in increasing the API loading since additional plasticizer is not required. Due to the inherent plasticizing property of API, it can be mixed uniformly with other polymers using a V-blender or high shear mixer without the use of additional organic solvents during the formulation process. During the coating process, a coating system containing the API, acting as a plasticizer, and polymer can be coated on non-pareil beads or tablets without the need of a traditional plasticizer. Addition of plasticizer imparts smoothness and flexibility to the coat, which provides a smooth substrate for subsequent enteric or sustained release coating. Such non-pareil beads may be compressed to form tablets without causing the rupture of the film coat due to the enhanced flexibility imparted by the plasticization effect of the API. On the contrary traditional liquid plasticizers require them to be sprayed as a solution on to the API-polymer mixture in a high shear mixer followed by drying the granules. For example, to use lipophilic plasticizers like dibutyl sebacate, organic solvents will be required to form a solution, which can cause safety concerns. Therefore, identification of APIs acting as a plasticizer aids in formulation development.

Divalproex sodium is a coordination complex of sodium valproate and valproic acid. It has a pK_a of 4.6, with a solubility of 1 mg/ml at pH 1.0 and 200 mg/ml at pH 6.8 [100]. Valproic acid is clear, colorless to pale yellow, slightly viscous liquid, and sparingly soluble in water, whereas sodium valproate is a white crystalline, hygroscopic, and highly

soluble in water and alcohol [101]. Divalproex sodium has been used as an anticonvulsant to treat seizures, bipolar disorder, and migraines. It is available in tablet, capsule and syrup to treat these conditions. It was noticed that on the addition of divalproex sodium to water, the coordination complex readily dissociates into sodium valproate and valproic acid. Since sodium valproate is highly soluble in water, it dissolves in the aqueous phase, while valproic acid due to its poor solubility forms an oily phase over the aqueous phase. This shows that divalproex sodium cannot be used with aqueous granulation or coating coating processes. Therefore, only non-aqueous granulation or coating is feasible to avoid potential content uniformity issues segregation of valproic acid and sodium valproate in presence of water. Melt extrusion of divalproex sodium with ethylcellulose can achieve sustained release without using non-aqueous solvents and without additional plasticizer. Hence its use as a plasticizer as well as an API along with highly acceptable polymers such as various cellulose derivatives to develop novel formulations will potentially benefit the pharmaceutical field.

During preformulation studies of divalproex sodium with different polymers, it was found that films composed of divalproex sodium and ethyl cellulose were smooth and flexible in nature. This observation led to this investigation of divalproex sodium as a non-traditional plasticizer of ethylcellulose.

4.2. Materials and Methodology

4.2.1. Materials

Divalproex sodium (Manufactured by Sci Pharmatech, Inc, Taiwan) was gifted by G&W PA Laboratories (Sellersville, PA). Ethylcellulose (Ethocel Standard 10 Premium) with

viscosity 9-11 mPa.s and ethyoxyl content of 48-49.5%wt was gifted by Colorcon, Inc (West Point, PA). Ethyl alcohol 200 proof (ACS/USP grade) was purchased from PHARMACO-AAPER (Brookfield, CT).

4.2.2. Preparation of DVS/EC films

Films of DVS and EC were prepared using solvent evaporation method. DVS and EC stock solutions at 5% w/w concentration were prepared by dissolving them separately in ethanol. From the respective stock solutions, mixtures of API and polymer solutions with 10, 20, 30, 40, and 50% w/w DVS of the dry weight of EC were prepared, while mixing. After mixing for 10 min, the solution was poured in an aluminum plate and dried overnight at 35°C to completely evaporate the solvent and achieve the constant weight to form films. The solid content of the mixture solution was kept similar in order to obtain films with similar thickness. Films were stored in polyethylene bags at ambient conditions until further used. The thickness of the rectangular films for texture analysis was measured with a digital thickness gauge (Mitutoya, IL) in mm up to two decimal places.

4.2.3. API content analysis

Approximately 10-30 mg of sample was dissolved in the ethanol. Aliquots were analyzed using HPLC, which was adapted from USP method for Divalproex Sodium Delayed-Release Capsule monograph. Briefly, samples of different dilutions (1.6 – 240 μg/mL) were prepared in acetonitrile: deionized water (1:1 v/v). The column used was Symmetry® 4.6 x 75 mm, C-18, 3.5 μm. The mobile phase consisted of buffer: acetonitrile (2:3 v/v), where the buffer was 6.8 g/L of monobasic potassium phosphate

adjusted to pH 3 with phosphoric acid. The flow rate was kept at 1.2 mL/min. The column temperature was maintained at 30 °C, while the sample temperature was maintained at 27 °C. The injection volume was 80 µL. UV detection was performed at a wavelength of 210 nm. The run time was kept at 7 min. The analysis was performed on a Waters® HPLC system using Breeze® data integration software. Percent API content were determined by using Equation 4-1.

$$\%\textbf{API content} = \left(\frac{\textbf{Actual drug loading}}{\textbf{Theoretical drug loading}}\right)\textbf{x 100} \qquad \textbf{Equation 4-1}$$

4.2.4. Mechanical properties of film

Brookfield Texture Analyzer attached to 4500 g load cell with tension module was used to test the Peak load and % Elongation of films. Rectangular films 10 mm x 50 mm were cut and clamped on both sides with a flat faced grip with the target test distance of 38 mm. Films were extended at the rate of 0.1 mm/sec and were extended until they break. % Elongation was calculated from the elongation length using the initial length of the film (distance between the clamps) i.e. 38 mm. Other parameters such as peak load, elongation length, and the load vs time (seconds) profile are reported. The test was carried out in duplicate for each film.

4.2.5. Rheological studies

Rheological studies were conducted to demonstrate the plasticization effect of DVS on films as a result of change in melt viscosity. A hybrid rheometer with an oven heating assembly (Discovery DHR-3, TA instruments, DE, USA) was utilized for the analysis. Films were chosen for melt viscosity studies since powdered sample or compressed

sample may not be uniform. Furthermore, air bubbles from the powder may get entrapped between the plates leading to aberrant results. The films were placed between the parallel plates and a dynamic oscillation temperature sweep was performed from 150 to 200 °C at 5°C/min. The velocity was 0.02 rad/sec. The shear rate, velocity, torque, and stress were 1.25 1/s, 0.02 rad/sec, 3.25946 Pa and 10.0 µN.m, respectively. Since the glass transition temperature of ethylcellulose is 133 °C, a higher temperature was chosen to initiate the study to allow for melting of the polymer.

4.2.6. Differential scanning calorimetry (DSC)

DSC analysis of DVS, EC and prepared films was performed using Q200 ™ DSC differential scanning calorimeter (TA Instrument, New Castle, DE). Weighed samples (5-10 mg) were placed in T_{zero} aluminum pans and crimped with a T_{zero} lid. DSC thermograms were obtained at the heating rate of 10 ºC/min from 30 to 160 ºC comparing with the similar blank pan as a reference and continuous nitrogen flow was maintained to obtain inert atmospheres. Indium was used as a reference standard and Universal analysis software (TA Instrument, New Castle, DE) was used for the data analysis.

4.2.7. Stability studies

Stability studies were performed at 45 °C/75% RH(Relative Humidity) in humidity chamber for 2 weeks by placing samples separately in aluminum bags and covering with perforated Parafilm®. Humidity condition (75% RH) was created manually using a saturated solution of sodium chloride. After two weeks, samples were characterized using DSC and observed for glass transition temperature change. Results of samples before and after 45 °C/75% RH for 2 weeks at open condition were compared. A paired t-test was

used to compare the experimental Tg values before and after stability using Microsoft® Excel 2010 ($\alpha = 0.05$).

4.3. Results and Discussion

4.3.1. API content

API content was found to be between 95-105% of the theoretical amount. The optimum API loading efficiencies are attributed to the no loss of API or polymer during film fabrications. These results also indicate that API was stable during film fabrication. Results of API content analysis are summarized in Table 4.1.

4.3.2. Mechanical properties

Rectangular films of 0.11 -0.12 mm were used to study mechanical properties. The average peak load and average elongation of ethylcellulose films containing different concentrations of the DVS are as shown in Figure 4.1 and Figure 4.2, respectively. It can be seen that the peak load decreases whereas the average elongation increases, with an increase in API concentration. This could be due to the increase in elasticity of ethylcellulose film upon addition of divalproex sodium. Similarly, increase in elasticity of ethylcellulose was also noticed upon addition of traditional plasticizers like triethyl citrate and dibutyl sebacate. However, at 20% plasticizer concentration, the elongation (%) of the films containing divalproex sodium was found to be 3.5%, which was much higher than that found with traditional plasticizers like triethyl citrate, dibutyl sebacate, triacetin, myvacet and diethyl phthalate [114].

4.3.3. Rheological studies

Rheological profiles of different films plotted as viscosity as a function of temperature are presented in Figure 4.3. Plasticization of polymer leads to decrease in the melt viscosity of the polymer. It could be noticed that for all the films, the melt viscosity was found to decrease progressively with increase in temperature. The initial melt viscosity at 150°C was found to decrease with increase in the concentration of divalproex sodium in the films. This provides further evidence of the plasticization of ethylcellulose by divalproex sodium. Earlier studies performed also indicate the decrease in melt temperatures of the films [115], which supports our conclusions.

4.3.4. Differential scanning calorimetry (DSC)

DSC thermograms indicating glass transition temperature of ethyl cellulose films with and without divalproex sodium are as shown in Figure 4.4. It was observed that the glass transition temperature of ethylcellulose decreases progressively with increase in the concentration of divalproex sodium in the films. The glass transition temperature decreased from 133°C of pure ethylcellulose to 110°C at 10% DVS concentration. At 20% concentration, the glass transition temperature of ethylcellulose films containing divalproex sodium showed glass transition temperature of 97°C, which is comparable to that obtained with triacetin [114]. At 50% DVS concentration, the T_g of ethyl cellulose was found to be 75 °C, which is comparable with the plasticization efficiency of traditional plasticizers like triethyl citrate, assuming that the effective concentration of valproic acid available for plasticization is approximately half of divalproex sodium added i.e. 25% if 50% of divalproex sodium is added [40]. Since no melting peak was

observed in the thermograms, the physical nature of API can be assumed to be amorphous; however, crystallinities below 2% cannot generally be detected with DSC [116]. These studies support that DVS has similar plasticizing effect as other well-known plasticizers.

4.3.5. Stability studies

DSC thermograms (Figure 4.5) of the stability samples indicated a single glass transition temperature, which did not change significantly after storing the samples at stability conditions ($p=0.4955>0.05$). This indicates that the films are physically stable at the given storage condition similar to that of initial condition samples and there is no phase separation when exposed to stability conditions. The stability of the DVS-EC films might be due to the similar solubility parameter of DVS and EC. Therefore, choice of plasticizer based on solubility parameter of the polymer is recommended.

4.4. Conclusion

In the current study, the mechanical, thermal and rheological characterizations clearly demonstrate that DVS was able to plasticize EC films. Stability studies indicated that there is no change in the plasticization tendency of DVS on EC on storage for 2 weeks in open condition at 40°C/75% RH. This study can prove to be useful for developing a sustained release melt extruded formulation of DVS using EC as release sustaining polymer since DVS can also act as a processing aid to reduce the extrusion temperature owing its ability to plasticize ethylcellulose.

Tables

Table 4.1 DVS content(%) of films

DVS concentration as dry weight of EC (%) in films	DVS content (% of label claim)
10	95.9
20	103.1
30	96.1
40	102.3
50	99.0

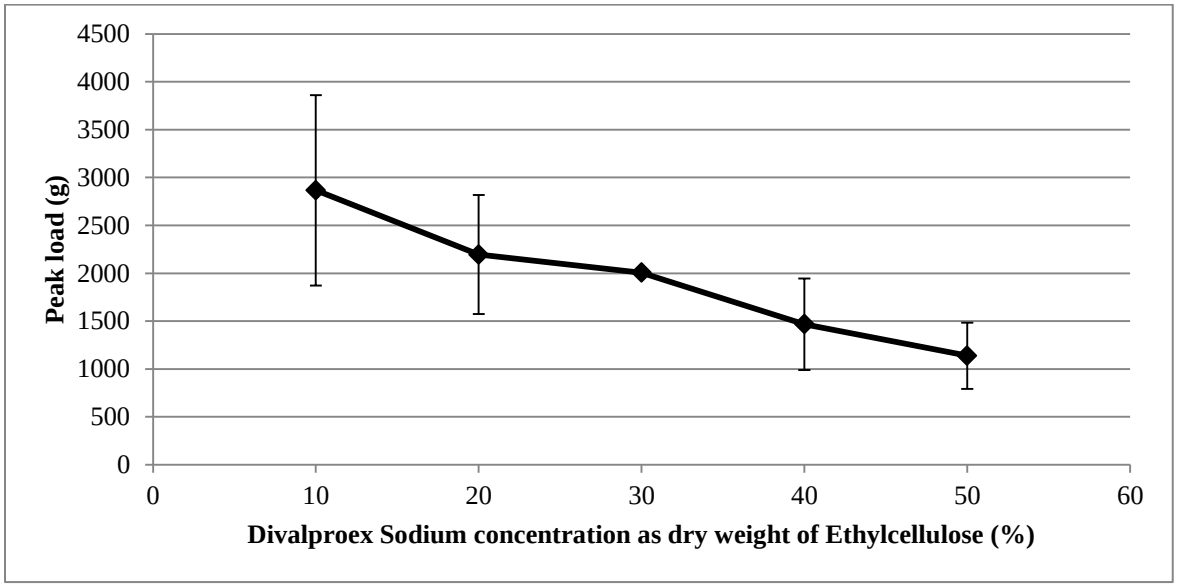


Figure 4.1 Peak load for films containing different concentration of divalproex sodium in ethylcellulose (data represents mean±s.d., n=3)

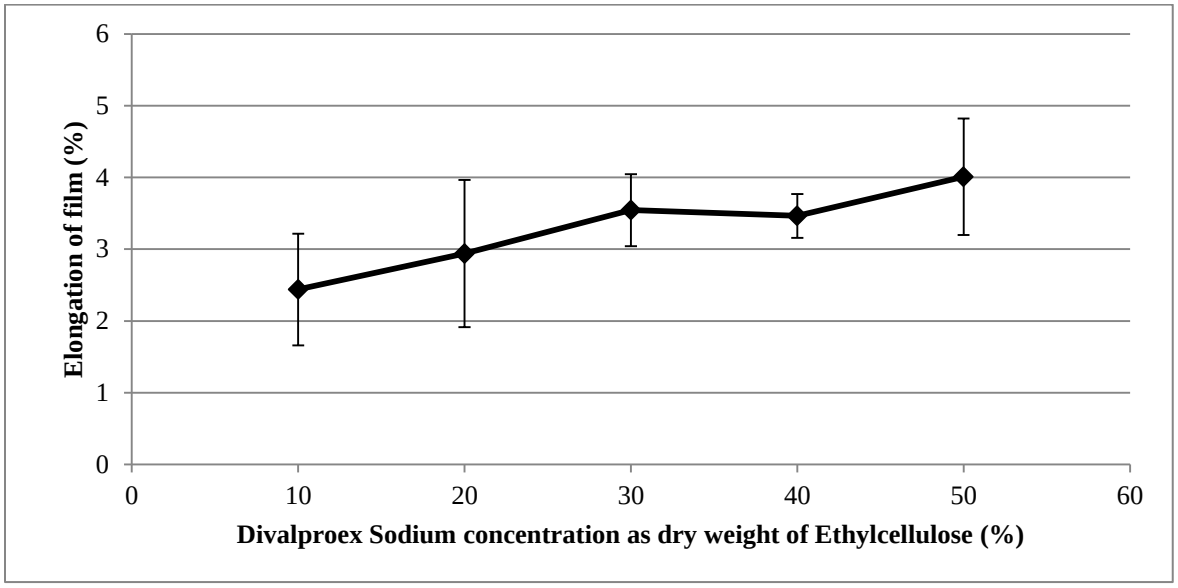


Figure 4.2 Elongation of films containing different concentration of divalproex sodium in ethylcellulose (data represents mean±s.d., n=3)

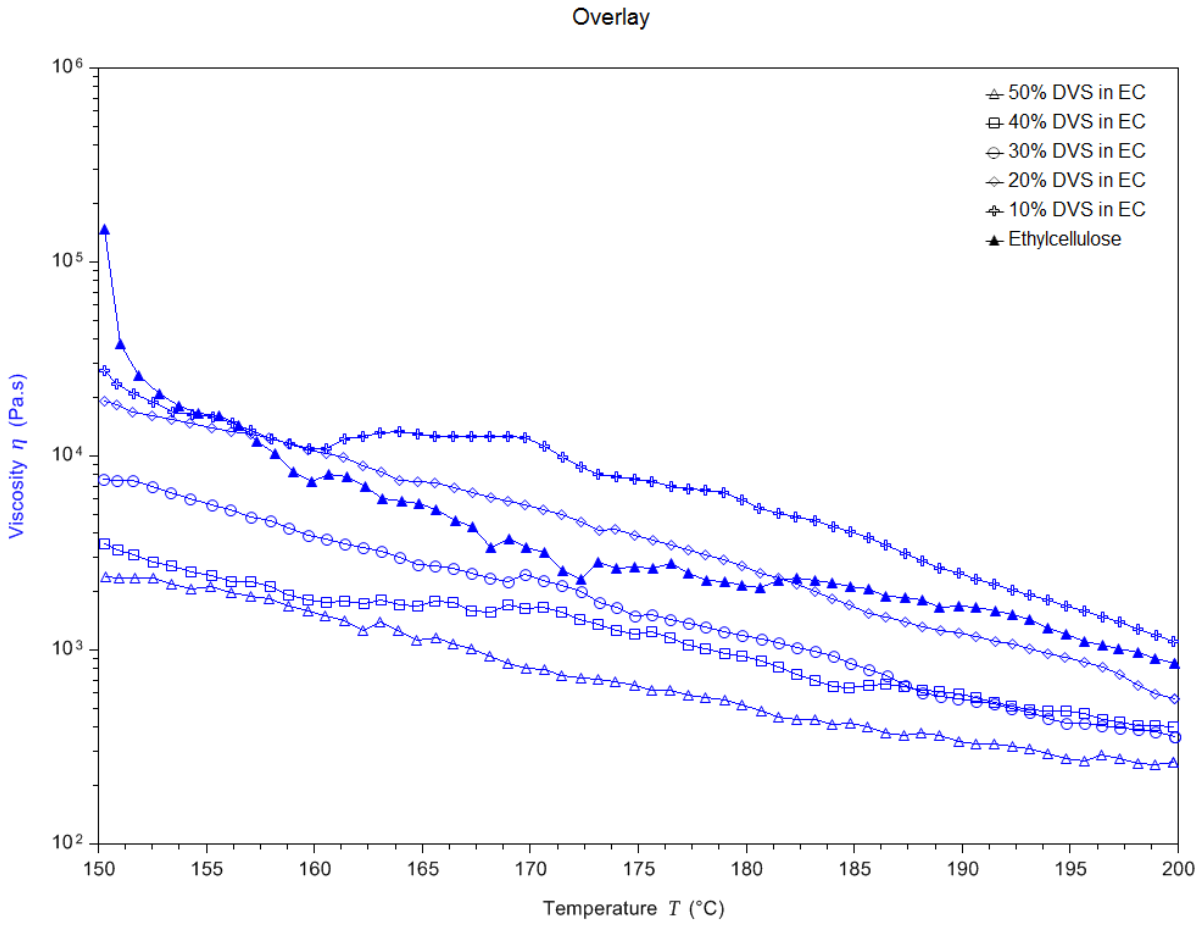


Figure 4.3 Melt viscosity of ethylcellulose and films containing different concentration divalproex sodium as a function of temperature

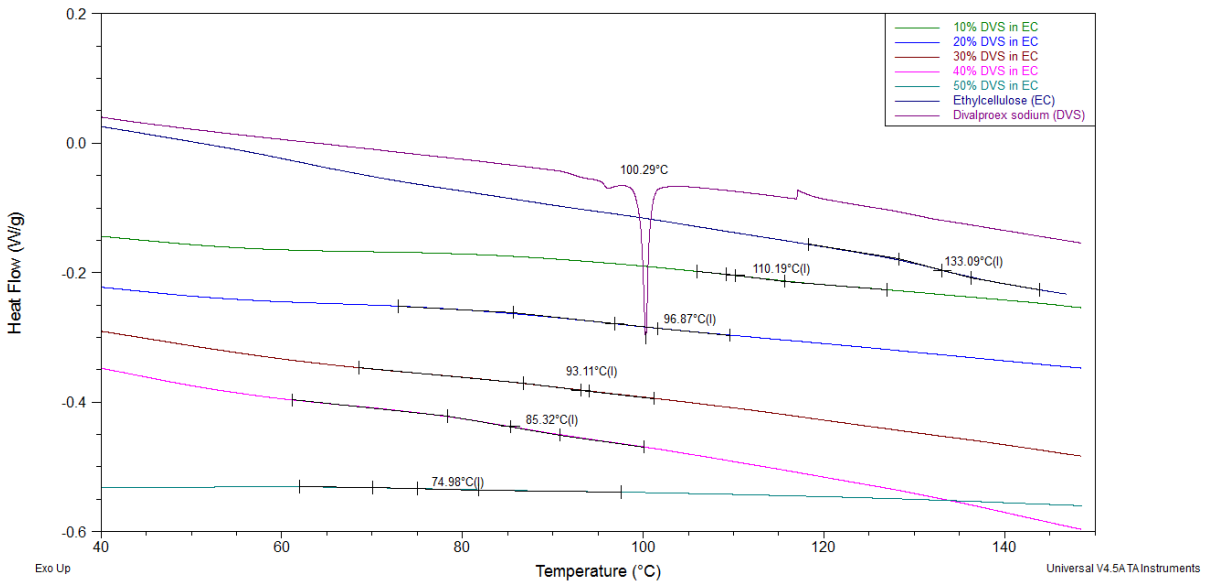


Figure 4.4 DSC thermogram of divalproex sodium, ethylcellulose and ethylcellulose films containing different concentration divalproex sodium

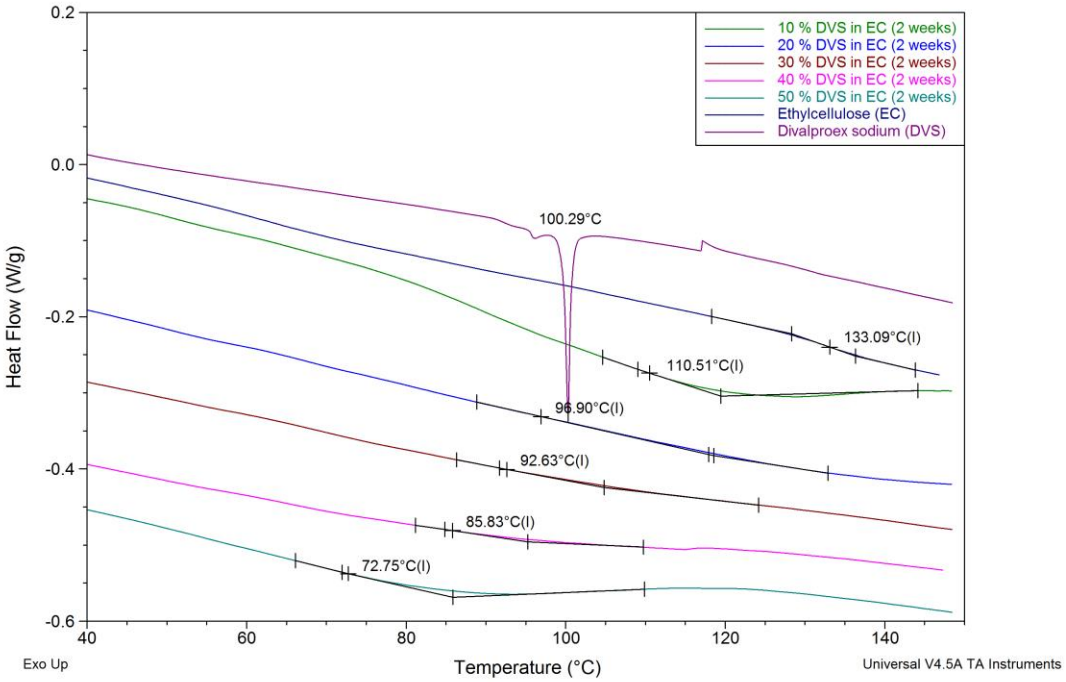


Figure 4.5 DSC thermogram of divalproex sodium, ethylcellulose and ethylcellulose films containing different concentration of divalproex sodium (2 weeks, 45°C/75% RH, open)

5. CHARACTERIZATION OF FILMS OF DIVALPROEX SODIUM AND ETHYLCELLULOSE TO INVESTIGATE THE PLASTICIZATION EFFECT OF DIVALPROEX SODIUM ON ETHYLCELLULOSE

5.1. Introduction

Plasticizers are low molecular weight resins/polymers or small molecules, which are generally used to facilitate the device development processes by reducing the glass transition temperatures of the polymers. The majority of plasticizers are in the liquid state and form secondary bonds to polymer chains and spread them apart; thereby reducing the polymer-polymer secondary bonding and providing greater mobility for the macromolecules. Such phenomenon plasticization, results in a soft and deformable polymer mass [3].

Divalproex sodium is a coordination complex of sodium valproate and valproic acid. It has a pK_a of 4.6, with a solubility of 1 mg/ml at pH 1.0 and 200 mg/ml at pH 6.8 [100]. Valproic acid is clear, colorless to pale yellow, slightly viscous liquid, and sparingly soluble in water, whereas sodium valproate is a white crystalline, hygroscopic, and highly soluble in water and alcohol [101].

In the previous chapter, we showed that divalproex sodium can plasticize ethylcellulose. It was noticed that on the addition of divalproex sodium to water, the coordination complex forming divalproex sodium readily dissociates into individual constituents-sodium valproate and valproic acid. Since sodium valproate is highly soluble in water, it dissolves readily in the aqueous phase, while valproic acid due to its poor solubility forms an oily phase over the aqueous phase. This observation led to a hypothesis that

valproic acid, which is a small molecule liquid fatty acid, may cause plasticization of ethylcellulose similar to other small molecule plasticizers like triacetin, triethylcitrate, etc. Therefore, studies were undertaken to study the interaction of DVS and ethylcellulose in the films to investigate the role of valproic acid in plasticizing ethylcellulose.

5.2. Material and Methodology

5.2.1. Preparation of DVS/EC films

Films of DVS and EC were prepared using solvent evaporation method. DVS and EC stock solutions at 5% w/w concentration were prepared by dissolving them separately in ethanol. From the respective stock solutions, mixtures of API and polymer solutions with 10, 20, 30, 40, and 50% w/w DVS of the dry weight of EC were prepared, while mixing. After mixing for 10 min, the solution was poured in an aluminum plate and dried overnight at 35°C to the constant weight to form films. The solid content of the mixture solution was kept similar in order to obtain films with similar thickness. Films were stored in polyethylene bags at ambient conditions until further used.

5.2.2. X-ray Diffraction

DVS-EC films were characterized using Shimadzu X-Ray Diffractometer (Cu Kα, Shimadzu, Columbia, MD) with accelerating voltage and anode current set as 40 kV and 30 mA, respectively. XRD patterns were recorded over the range 10-40° 2θ using a step size of 0.02°, counting time of 1s/step, and the scanning rate of 2° 2θ/min.

5.2.3. Polarized Microscopy

DVS-EC films were observed under a Nikon microscope Eclipse 80I attached to DS-Fi1 camera using NIS-Element-BR(Melville, NY) using a polarizer under 40x magnification to determine the physical nature of DVS in the films. Films were observed for presence of undissolved crystals of sodium valproate or other impurities.

5.2.4. Thermogravimetric analysis

A Q500 ™ TGA (TA Instrument, New Castle, DE) instrument was used to determine the percentage weight loss of the DVS, EC and 50% DVS (dry polymer weight) in ethylcellulose. Samples (3–10 mg) were placed into open aluminum crucibles. The samples were heated from 65°C to 450°C with a heating rate of 20°C/min and a nitrogen gas purge of 60 mL/min.

5.2.5. Fourier transform infrared (FT-IR) spectroscopy analysis

FT-IR spectra (4000–650 cm^{-1}) were acquired with a Perkin Elmer Spectrum 100 FTIR spectrometer equipped with Universal ATR (Perkin Elmer Inc., Wellesley, MA) to understand the chemical interactions between DVS and EC. Samples were placed on the crystal surface and tightened using the screw of the pressure arm. IR Spectrums of films without DVS and with DVS were obtained by running 32/64 scans and compared using Spectrum E5. For analyzing DVS and EC, individual tablets were compressed on Carver Press to form a solid die that could be placed between the crystal surface and pressure arm.

5.2.6. Raman spectroscopy

The Raman spectra were collected to study the polymorphic form of the film. The Raman spectra were collected using Raman Rxn System Model # RXN1-785, Kaiser Optical Systems that was equipped with an excitation laser operating at 785 nm with a laser power setting of 400 mW. Data acquisition was done using an exposure time of 5s for 3 accumulations.

5.2.7. Stability studies

Stability studies were performed at 45 °C/75% RH in humidity chamber for 2 weeks by placing samples separately in aluminum bags and covering with perforated Parafilm®. Humidity condition (75%RH) was created manually using a saturated solution of sodium chloride. After two weeks, samples were characterized using XRD to observe for changes in crystallinity. Results of samples before and after 45 °C/75% RH for 2 weeks at open condition were compared.

5.3. Results and Discussion

5.3.1. X-ray diffraction (XRD)

Figure 5.1 shows no sharp peaks in the X-ray diffractograms of the films that indicate their amorphous nature of API and polymer. This is in agreement with the absence of melting point peak in DSC thermograms of the films. However, crystallinity less than 5-10% is difficult to be detected using XRD [117] but it may be based on the sensitivity of the instrument too. Therefore, techniques such as polarized microscopy can be employed to confirm the amorphous nature of the API.

5.3.2. Thermogravimetric analysis

Figure 5.2 shows the thermogravimetric profile of divalproex sodium, ethylcellulose, and 50% divalproex sodium (by dry weight of polymer) in ethylcellulose film. Divalproex sodium is a coordination complex of valproic acid and sodium valproate. Valproic acid inherently exists in a liquid form and is volatile, however, along with sodium valproate, it forms a coordination complex that melts at approximately 100 °C. It was observed that around 53% of the weight of DVS is left at 406 C i.e. at plateau phase. This is in close agreement with the theoretical weight (46% w/w) of valproic acid in DVS. The evaporation of valproic acid was observed to be in three phases. On heating to 100 °C, a saturated solution of sodium valproate in valproic acid is formed and any additional sodium valproate will precipitate out [118]. During the first phase, valproic acid evaporates at a faster rate while sodium valproate precipitates due to the decrease in the solvent (valproic acid). At the end of the first phase, approximately 15% of the total weight i.e. approximately 30% of the valproic acid is evaporated. During the second phase, the evaporation rate decreases; this can be attributed to the dissolution of sodium valproate in valproic acid as the solubility of sodium valproate might increase with temperature, which increases the viscosity of the solution, or due to the precipitation of sodium valproate that was dissolved in valproic acid, which forms a physical barrier for evaporation. During the third phase (around 290 °C), the evaporation rate of valproic acid increases since at such a high temperature, which greatly exceeds the boiling point of valproic acid (219.5°C) [101] the valproic acid molecules acquire enough energy much to overcome any physical interaction with sodium valproate. The residue at the end of the thermogravimetric analysis was observed to dissolve rapidly in water indicating the

presence of residual sodium valproate since it is readily soluble in water. The decrease in weight of ethylcellulose is due to thermal degradation at a higher temperature of around 320 °C. The aluminum crucible was found to contain charred residue that was 4 % of the initial weight. This indicates that in films, valproic acid dissociates from DVS to plasticize ethylcellulose as well as to dissolve sodium valproate. The thermogravimetric profile of 50% divalproex sodium (by dry polymer weight) in ethylcellulose can also be subdivided into three phases - the first phase is characterized by the monophasic evaporation of valproic acid. The evaporation rate of valproic acid from the film is slower than that from divalproex sodium neat API due to its hydrogen bonding interaction with ethylcellulose. At 286 °C, 16 % of the weight of the film is lost. This is in agreement with the theoretical quantity (15.48%w/w) of valproic acid in the film. In the next phase 310°C, ethylcellulose starts degrading until around 400 °C. At 422 °C, the residual weight was found to be 22 % of the initial weight. The residue is composed of sodium valproate and charred ethylcellulose. The quantity of residue of the film is in agreement with the predicted value based on the thermogravimetric analysis of divalproex sodium and ethylcellulose.

5.3.3. Polarized Microscopy

Since x-ray diffraction cannot identify crystallinity below 5%-10%, polarized microscopy provides visual qualitative identification of the presence of any crystalline material. The presence of birefringence in the polarized microscopic image (Figure 5.3) for all samples might be due to the presence of sodium valproate or divalproex sodium in crystalline form. However, since plasticization of ethylcellulose can be attributed to the presence of valproic acid as shown during DSC studies, dissociation of divalproex sodium into

valproic acid and sodium valproate should occur as indicated by TGA studies. Therefore, the birefringence can be attributed to sodium valproate crystals only. The black background is due to the amorphous monophase composed of ethylcellulose and valproic acid. Interestingly, the occurrence of sodium valproate crystals in all samples is almost similar in concentration, visually. This can be explained in this manner. At 10% divalproex sodium concentration, the valproic acid is utilized in plasticizing ethylcellulose. As the concentration of divalproex sodium increases, the plasticization of ethylcellulose increases as seen from the decrease in the glass transition temperature. However, the plasticization efficiency (decrease in glass transition temperature with plasticizer concentration) decreases at higher API concentration (40 and 50% concentration). At 50% divalproex sodium concentration with respect to the dry polymer, the overall API concentration in the film is 33.3% w/w. Nearly half the weight of the API is sodium valproate, which implies approximately 17 % of the area of the film should show birefringence due to the crystallinity of sodium valproate. However, the birefringence due to sodium valproate is much less and is scattered. This might be due to the solubility of sodium valproate in valproic acid leading to the formation of the solid solution, which is amorphous in nature. Literature shows that valproic acid can dissolve up to 50 % of sodium valproate by weight at room temperature [118]. This might explain the higher solubility of sodium valproate in valproic acid to form a solid solution.

Based on the results, the plasticization effect of divalproex sodium can be attributed to the presence of valproic acid, which is a medium chain fatty acid. The small chemical structure of valproic acid allows it to penetrate the ethylcellulose chain and plasticize it efficiently leading to decrease in glass transition temperature. Ethylcellulose is an

uncharged moiety, which does not cause flocculation with charged sodium valproate, whereas we observed that Eudragit L100-55, due to its charged nature, precipitates on the addition of divalproex sodium due to the presence of sodium valproate (unpublished data).

5.3.4. Fourier transform infrared spectroscopy analysis

FTIR spectra of DVS (Figure 5.4) shows characteristic peaks due to stretching of carbonyl group (>C=O) at 1688.39 cm^{-1}, peaks at 2956.76, and 2871.71 cm^{-1} due to methyl groups, peaks at 1555.28 and 1378.57 cm^{-1} are due, respectively, to antisymmetric and symmetric (O-C-O) stretching vibrations of the carboxyl salt, peaks at 2454.89 and 1899.26 cm^{-1} are due to –OH groups of carboxylic acid that are intramolecularly bounded. The peaks at 2932.47 and 1688.39 cm^{-1} are due to stretching of methylene groups and at 1465.48 cm^{-1} and 1378.57 cm^{-1} due to bending of C-H. Shifting of peaks towards higher wavenumber indicates intermolecular interaction. In the FTIR spectra of 50% w/w divalproex sodium in ethylcellulose, the peak due to stretching of carbonyl group was located at 1693.31 cm^{-1} in contrast to at 1688.39 cm^{-1} in the pure API. The peaks at 2454.89 and 1899.26 cm^{-1} were found to disappear indicating the extensive involvement of the hydroxyl group of carboxylic acid in the hydrogen bond formation. Considering the structure of DVS and EC and since EC has several proton donor/acceptor possibilities per monomeric unit, the shift of the carbonyl stretching frequency along with the disappearance of the stretching hydroxyl group peaks indicates the formation of strong hydrogen bond between the API and polymer. A new peak at 1980.41 cm^{-1} was found to appear. The peak at 1693.31 cm^{-1} was found to be broader, which indicates the presence of amorphous form. As per the mechanisms of plasticization, the plasticizer

interacts with the polymer by breaking polymer-polymer interaction and forming plasticizer-polymer interaction [10]. Plasticization of ethylcellulose by divalproex sodium can be explained by the formation of strong hydrogen bond as shown by the FTIR spectra. Also, strong interaction like hydrogen bonding leads to one phase system between API and polymer as indicated by single glass transition temperature. As a rule of thumb, the glass transition temperature should be 50 ° C above room temperature to avoid any phase separation. However, the formation of a strong interaction between API and polymer might help prevent any phase separation during storage.

5.3.5. Raman Spectroscopy

Figure 5.5 shows the Raman spectra of divalproex sodium, ethylcellulose and films containing divalproex sodium and ethylcellulose. Divalproex sodium shows characteristics peak at 1691 cm^{-1} due to the stretching of the carbonyl group (>C=O). This peak is absent in the Raman spectra of the films. This might be due to the involvement of carbonyl group in the formation of a strong hydrogen bond with ethylcellulose. This further strengthens the results from FTIR spectra indicating the formation of a hydrogen bond with ethylcellulose.

5.3.6. Stability studies

Phase separation of valproic acid from ethylcellulose can occur if the valproic acid interacts with sodium valproate and crystalizes as divalproex sodium. XRD diffractograms for DVS, EC and stability samples of the DVS-EC films stored at 45°C/75% RH for 2 weeks in open condition are as shown in Figure 5.6. It can be seen that there is no crystallinity in the DVS-EC films on exposure to stability conditions. This

indicates that the films are physically stable at the given storage condition similar to that of initial condition samples and there is no phase separation when exposed to stability conditions. The stability of the DVS-EC films might be due to the similar solubility parameter of DVS and EC.

5.4. Conclusion

Characterization of DVS-EC films shows valproic acid in DVS is responsible for plasticization of EC. Scattered crystals of sodium valproate were found in the films; however, since the concentration of sodium valproate was too low, it could not be detected during XRD studies. TGA study indicated that valproic acid may dissociate from the coordination complex of DVS in order to plasticize EC. FT-IR and Raman spectroscopy results proved the presence of hydrogen bonding between DVS and EC. Stability studies indicated no changes in the physical nature of DVS and EC in the films that demonstrates the compatibility of drug and polymer, which can be attributed to the hydrogen bonding attraction between and DVS and EC.

Figures

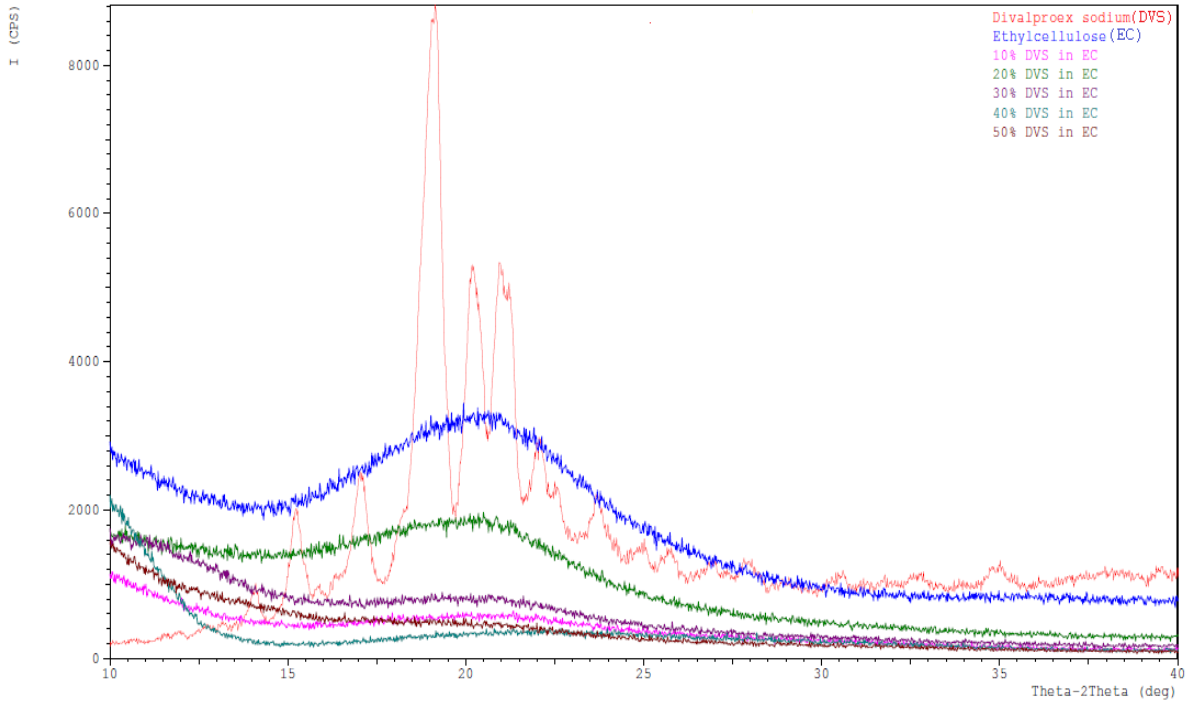


Figure 5.1 X-ray diffractograms of divalproex sodium, ethylcellulose and ethylcellulose films containing different concentration of divalproex sodium

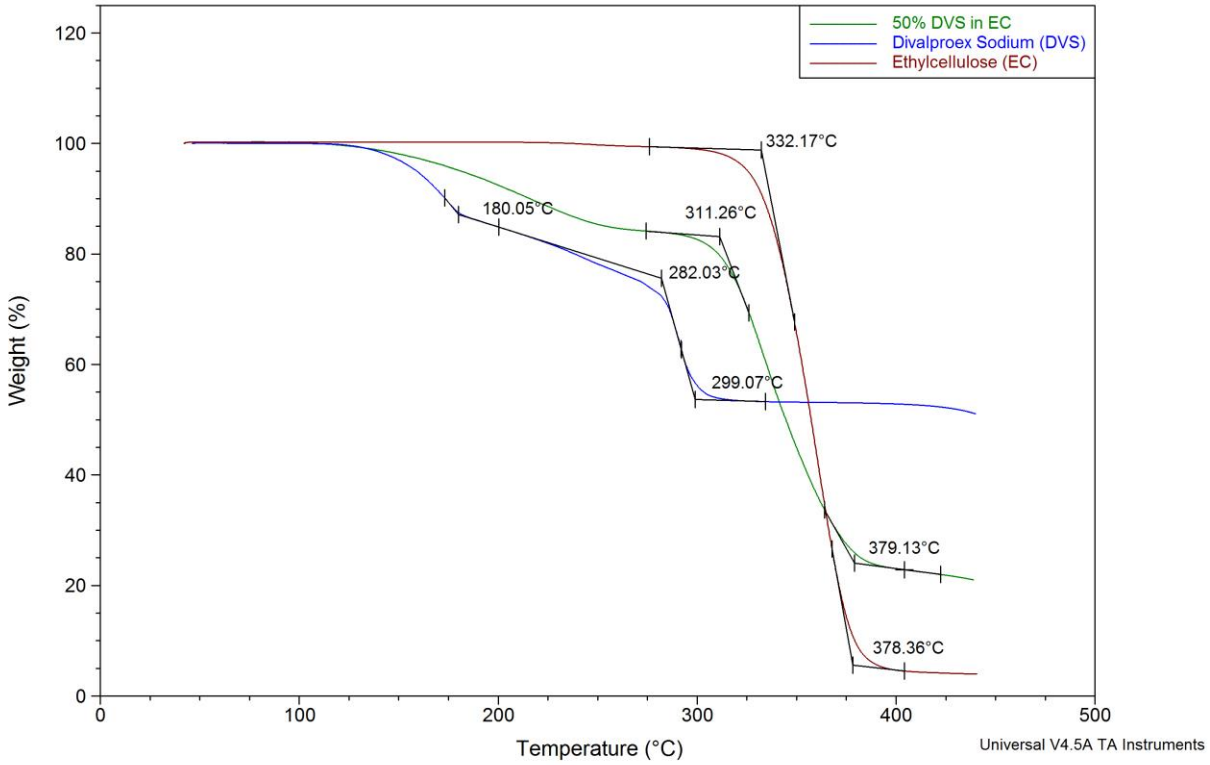
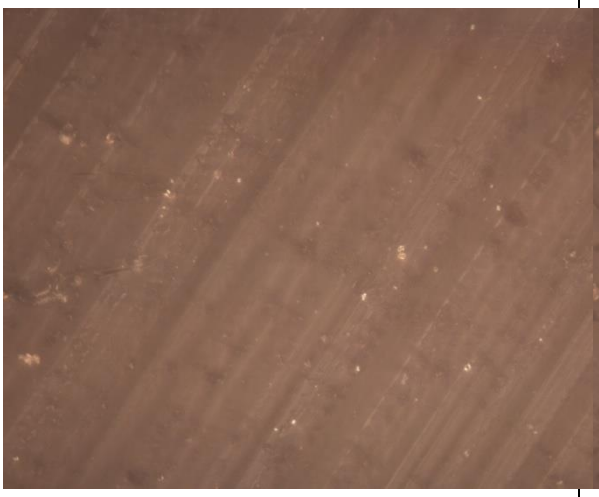
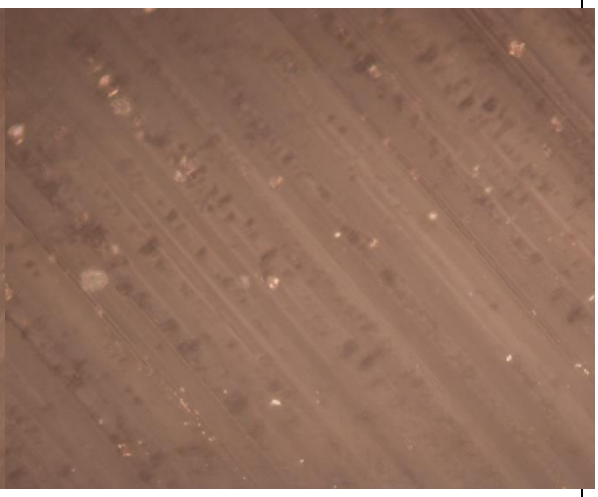
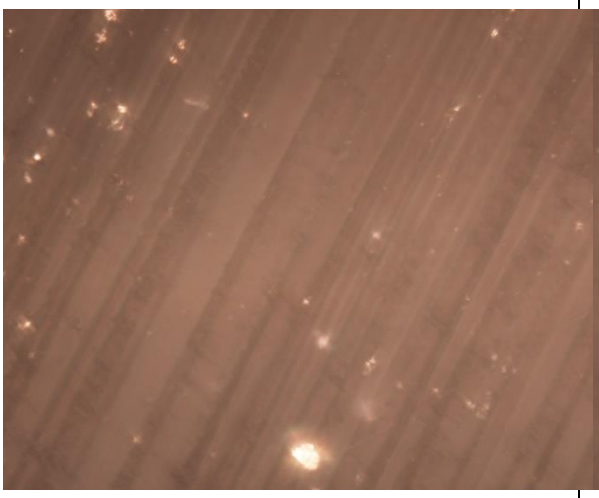
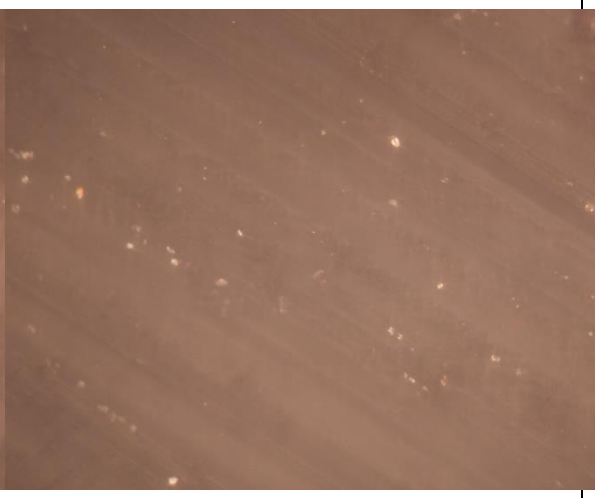
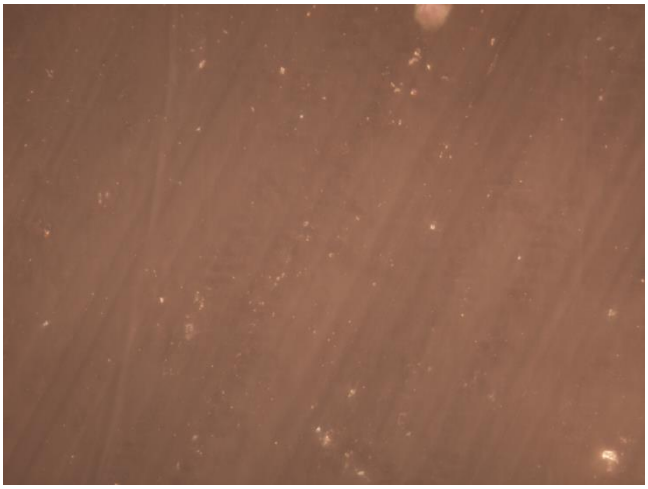


Figure 5.2 Thermogravimetric profile of Divalproex Sodium, Ethylcellulose, and 50% ethylcellulose (by dry polymer weight) in EC

	
(A)	(B)
	
(C)	(D)



(E)

Figure 5.3 Polarized microscopic image(40X) of ethylcellulose film containing (A) 10% divalproex sodium of ethylcellulose by weight, (B) 20% divalproex sodium of ethylcellulose by weight, (C) 30% divalproex sodium of ethylcellulose by weight, (D) 40% divalproex sodium of ethylcellulose by weight, (E) 50% divalproex sodium of ethylcellulose by weight

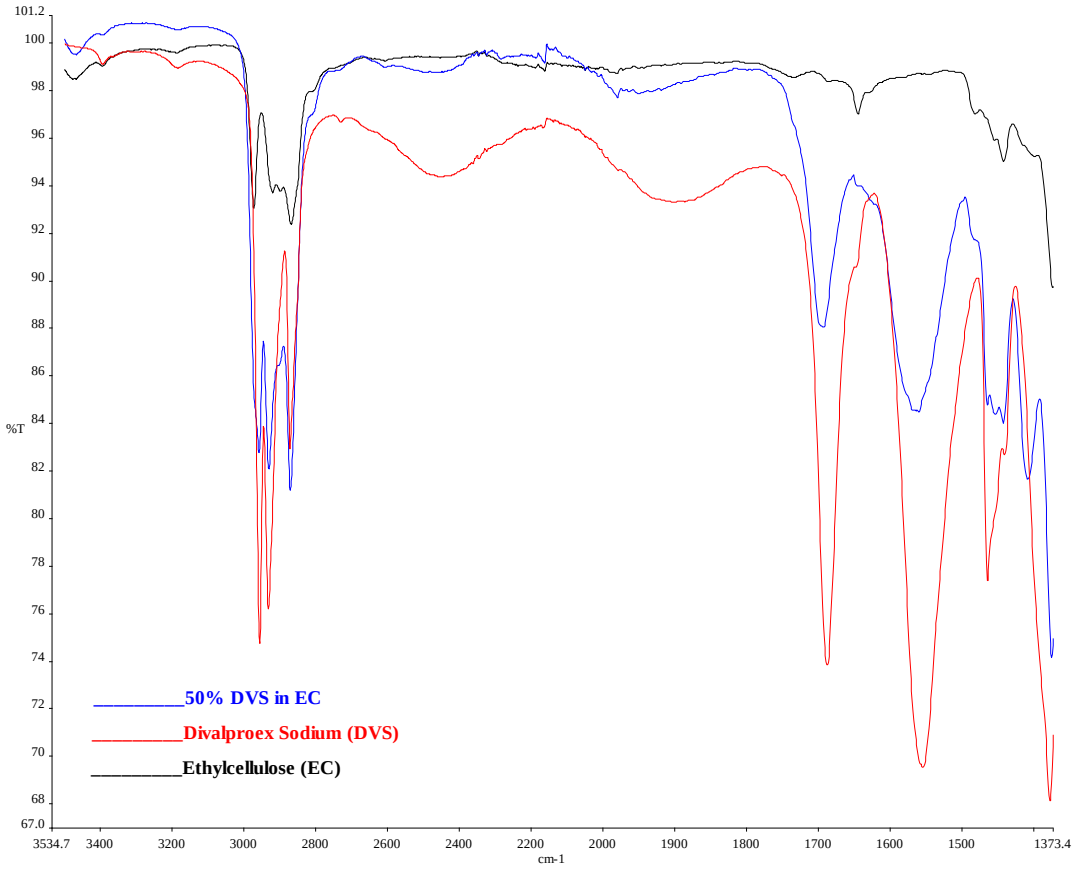


Figure 5.4 FTIR spectra of divalproex sodium, ethylcellulose and film with 50% divalproex sodium (by dry weight of polymer) in ethylcellulose

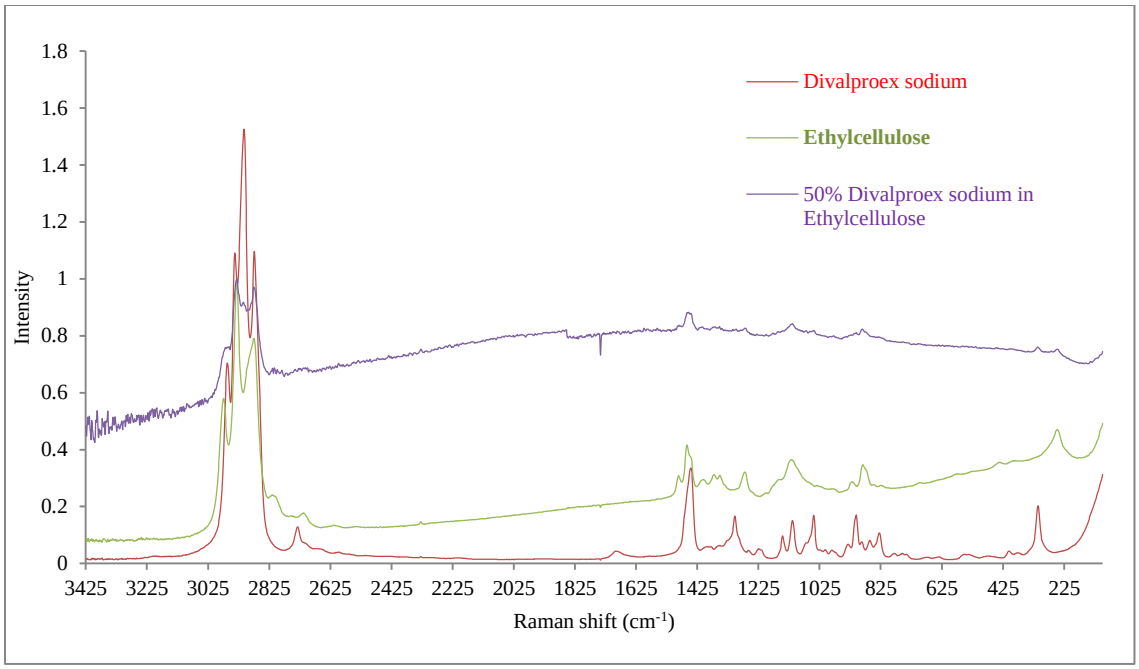


Figure 5.5 Raman spectra of divalproex sodium, ethylcellulose and film containing 50% divalproex sodium(by polymer dry weight) in ethylcellulose

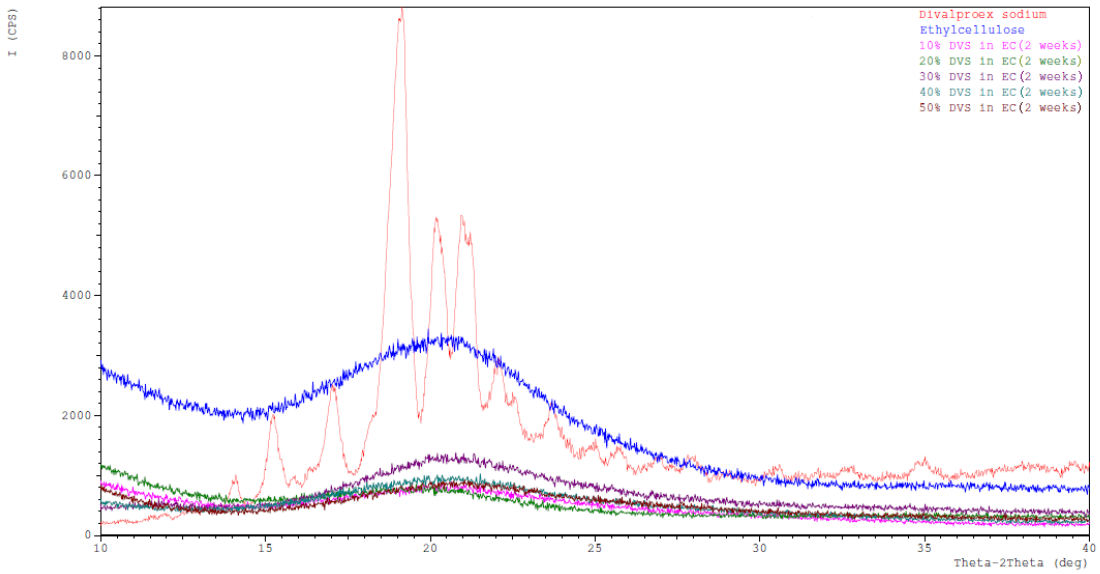


Figure 5.6 X-ray diffractograms of divalproex sodium, ethylcellulose and ethylcellulose films containing different concentration of divalproex sodium (2 weeks, 45°C/75% RH, open)

6. EVALUATION OF AFFINISOL® HPMC POLYMERS FOR DIRECT COMPRESSION PROCESS APPLICATIONS

6.1. Introduction

Direct compression is the most desirable process for tablet manufacturing in terms of time and economy. Other advantages in comparison to wet granulation include suitability to process moisture and/or heat sensitive Active Pharmaceutical Ingredients (API) and excipients for aqueous wet granulation, or improvement on the safety and environmental aspects for non-aqueous wet granulation. Since direct compression does not involve any type of granulation (wet or dry) that improves flow and compression property, the compression properties of the final blend is a function of the individual excipients and their physical mixture. Therefore, in order to produce tablets using direct compression process, it is imperative to understand the mechanical properties of the material. Tableting properties of pharmaceutical excipients comprise of compressibility and compactibility. "Compressibility" is the ability of a material to deform or decrease in volume on application of pressure, whereas "compactibility" refers to material's ability to be compressed into a compact of specified mechanical strength [119].

Hydroxypropylmethyl cellulose (HPMC) is a versatile excipient that is used as binder in wet granulation, dry binder, hydrophilic matrix polymer, maintaining supersaturation or preventing precipitation of API [120,121]. HPMC has been used to form hydrophilic matrix in tablet dosage form for extended release systems; however, higher molecular weight grades of HPMC have been shown to be harder, less plastic and require higher

pressures to deform compared to their low molecular weight counterparts [122]. Picker demonstrated the importance of the glass transition temperature(T_g) in the compaction process and proposed that there would be an improved deformation with an improved particulate bonding surface ensuing a higher strength of compact, if the T_g was exceeded reversibly during compaction (28). It was suggested that this would occur for HPMC at high compaction densities but not at low compaction densities since insufficient heat is produced during compaction at lower compaction presures[123]. Hardy et al showed the improvement in compaction properties at low compression pressure, of plasticized HPMC K4M(HPMC 2208) i.e. HPMC K4M plasticized using plasticizer like propylene glycol(29). This was attributed to the plasticization effect of propylene glycol, which caused an improved deformation and internal bonding [124].

Literature shows that K type of HPMC has better compressibility than E and F grade of HPMC [125]. However, even the Directly Compressible grade of K-type HPMC shows poor or very poor flow properties as well as low bulk density(~0.3 g/ml) [126]. Such a low bulk density may create risk of segregation, during storage or compression stage, if commonly used excipients with higher bulk density like Pregelatinized Starch, Dicalcium Phosphate or Lactose anhydrous or monohydrate are used in the formulation for direct compression process. Also, HPMC K100LV was found to have greater tendency to absorb almost 7% moisture at 60% relative humidity at 25°C [127]; this makes the K type HPMC less suitable for use in direct compression application.

Recently, new grade of low T_g HPMC (Affinisol^{TM}) was developed by Dow Chemicals to cater the needs of formulation scientist for developing melt-extrusion-based formulations. Interestingly, due to the low glass transition temperature, Affinisol^{TM}

polymers might also show better compactability, since T_g can be reversibly exceeded at relatively lower compression forces, and if they show favorable powder physical properties like bulk/tapped density and flow properties, they can be used a binder/filler for immediate release products and hydrophilic direct compression matrix former for developing sustained release drug delivery systems. Therefore, the present study was undertaken to evaluate the compaction and physical properties of Affinisol^{TM} HPMC polymers for potential use in tablet formulation. HPMC E15 was used for compaction studies for reference purposes since it had similar degree of methoxy substitution and similar viscosity as HPMC HME 15 LV. Starch 1500 was used in the lubricant sensitivity study since it is has a plastic fracture and exhibits lubricant sensitivity. We believe that this study will help to understand the compaction and flow properties of Affinisol^{TM} polymers and propose their use in future formulation development of direct compression based tablet dosage form.

6.2. Materials

Affinisol^{TM} HPMC HME 15LV and 100LV were received from Dow Chemicals (Midland, MI) and Affinisol^{TM} HPMC HME 4M LV was received from Colorcon (Westpoint, PA) as samples. HPMC E15 was purchased from Dow Chemicals (Midland, MI). Starch 1500 was purchased from Colorcon (Westpoint, PA). Magnesium Stearate was purchased from Undesa (Genova, Italy).

6.3. Methods

6.3.1. Differential Scanning Calorimetry

Differential scanning calorimetry for the polymers was carried out to determine their glass transition temperatures. DSC analysis was performed using Q200 ™ DSC differential scanning calorimeter (TA Instrument, New Castle, DE). Weighed samples (5-10 mg) were placed in T_{zero} aluminum pans and crimped with a T_{zero} lid. DSC thermograms were obtained at the heating rate of 3 ºC/min from 30 to 150 ºC comparing with the similar blank pan as a reference and continuous nitrogen flow was maintained to obtain inert atmospheres. Indium was used as a reference standard and Universal analysis software (TA Instrument, New Castle, DE) was used for the data analysis.

6.3.2. Powder physical properties

6.3.2.1. Bulk/Tapped density

Samples between 80-90 cc were poured in graduated glass cylinder, using a funnel, without disturbing the bed. The uneven powder bed was leveled carefully using a stainless steel spatula. This initial volume was recorded as bulk volume (V_b) and the bulk density (ρ_B) was calculated as per the **Equation 6-1**. The cylinders were tapped in increments of 250 taps using a Vankel Tapped Density tester. The test was discontinued when the bed volume remained unchanged from the previous reading. The final volume was recorded as Tapped Volume (V_T). The Tapped density (ρ_T) was calculated using **Equation 6-2**.

$$\rho_B = \frac{W}{V_B} \qquad \textbf{Equation 6-1}$$

$$\rho_T = \frac{W}{V_T} \qquad \textbf{Equation 6-2}$$

6.3.2.2. Powder flow

6.3.2.2.1. Angle of Repose

Powder was passed at 45° angle from a funnel until the tip of the heap of powder reaches the bottom tip of the funnel. The circumference(C) and the height of the heap (h) were noted and the angle of repose was calculated as per Equation 6-3.

$$\text{Angle of Repose} = \tan^{-1}\left(\frac{2\pi h}{C}\right) \qquad \textbf{Equation 6-3}$$

6.3.2.2.2. Compressibility Index and Hausner's ratio

Compressibility index or Carr's index and Hausner's ratio are simple fast and popular method of predicting flow characteristics. Carr's index and Hausner's ratio can be determined using Equation 6-4 and Equation 6-5, respectively [109]. Carr's index and Hausner's ratio were calculated using the bulk and tapped density results.

$$\text{Carr's Index} = \left(\frac{V_B - V_T}{V_B}\right) \times 100 \qquad \text{Equation 6-4}$$

$$\text{Hausner's ratio} = \left(\frac{\rho_T}{\rho_B}\right) \qquad \text{Equation 6-5}$$

6.3.2.3. Loss on drying (unbound moisture content)

Unbound moisture can cause drug degradation for water sensitive drugs; therefore, excipients with low unbound moisture content are preferred for direct compression. Unbound moisture content was determined using moisture analyzer. Samples of approximately 2 g were taken for analysis. The test temperature was kept at 105°C. The final moisture content was determined using the prediction mode.

6.3.3. Compactibility analysis

Two approaches are available for compactibility analysis-"out-of-die" and "in-die" approach. For "out-of-die" approach, compact dimensions are measured after ejection, while for "in-die" approach, the dimensions are estimated using apparatus like instrumented tablet press or compaction simulator. Generally, "in-die" approach is used due to generation of faster results and relative ease of data collection. However, in this study, an "out-of-die" approach was chosen to perform compactability analysis since "out-of-die" results represent only plastic deformation and not elastic deformation. Literature shows that "in-die" heckel plot analysis fails to accurately describe the compaction properties of pharmaceutical powders [106]. Powder were compressed into tablets of around 350 mg using a Hydraulic Carver Press (Carver, Menomonee Falls, WI)

with oval flat punches at different compression force of 0.45, 0.6, 1, 1.2, 1.4, 1.6 and 2 metric ton. Compression pressure which is the compression force per unit area was derived using the compression force and die surface area. The tablets were immediately ejected as soon as the desired compression pressure was achieved while increasing the pressure. Compact volume was calculated using punch design software-TabletCAD® from Natoli (Saint Charles, MO). Compact dimensions (diameter and thickness) in mm were measured with a digital thickness gauge (Mitutoya, IL) up to two decimal places. Data fitting was performed employing the Microsoft® Excel.

6.3.3.1. Axial expansion of the compact post-compression

Post-compression axial expansion provides information on the tendency of the tablet to cap or laminate on storage. Axial expansion occurs due to the need of the excipients for elastic recovery after compaction. Axial expansion causes the internal bonds to break while the tablet expands axially. Stronger inter-particle bonds prevent axial expansion post-compression. The Axial expansion was calculated from tablet thickness measured 24 h post-compression with a digital micrometer, using Equation 6-6:

$$\textbf{Axial Expansion}(\%) = \left(\frac{\mathbf{t - t_c}}{\mathbf{t_c}}\right) \times \mathbf{100} \qquad \textbf{Equation 6-6}$$

where t is the axial thickness after 24 h compression and t_c is the initial axial thickness of the tablet measured after 1 min after compaction.

6.3.3.2. Analysis using Heckel model

The equation for Heckel model for powder compressibility is given by **Equation 6-7**,

$$\mathbf{Ln\left(\frac{1}{\varepsilon}\right) = kP + A, D = \frac{\rho_a}{\rho_t}, \varepsilon = 1 - D} \qquad \textbf{Equation 6-7}$$

where D is the relative compact density (solid fraction) at compression pressure P, ρ_a is the compact density, ρ_t is the true density of the material, ε is the porosity of the compact and A the intercept. This equation represents compact formation by die-filling, particle rearrangement, and deformation and bonding of discrete particles. The slope of the linear portion of the plot(k) is inversely related to the yield pressure (P_y) or yield stress. Yield pressure indicates the plasticity of the compressed material [128].

6.3.3.3. Analysis using Kawakita equation

The Kawakita equation describes the relationship between the degree of volume reduction of the powder and the applied pressure [107]. The Kawakita equation is described by Equation 6-8.

$$\mathbf{\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}, \qquad C = 1 - \frac{\rho_b}{\rho_a}} \qquad \textbf{Equation 6-8}$$

where ρ_a, ρ_b, C, and P are the compact apparent density, powder bulk density, degree of volume reduction and compression pressure, respectively. The constant "a" and "b" represent compressibility index and resistant forces to compression, respectively [108])

6.3.4. Hardness study

Powder was compressed as shown in section 6.3.3 and tested for the hardness using a Sotax Tablet Hardness tester (Westborough, MA).

6.3.5. Friability study

Powder were compressed into tablets of around 400 mg using a Hydraulic Carver Press with round concave punches at compression force of 0.6 metric ton. The tablets were immediately ejected as soon as the desired compression pressure was achieved. Tablets (6.5 g or more) were subjected to friability test as per USP specifications.

6.3.6. Lubricant sensitivity

In order to compare lubricant sensitivity, Affinisol^{TM} HPMC polymers were compared to Starch 1500- direct-compression filler with plastic fracture. Affinisol^{TM} HPMC polymers and Starch 1500 were individually mixed with magnesium stearate (1% w/w) in a cylindrical glass vial with a cap, in a tangential circular motion at 25 rpm for 15 min. Compacts of around 0.400 g were made at 1 metric ton compression force using concave punches with a Hydraulic Carver Press (Carver, Menomonee Falls, WI). Lubricant sensitivity was expressed as a ratio according to the following relationship (Equation 6-9):

$$\textbf{Lubricant Sensitivity} = \left(\frac{\mathbf{H_0 - H_l}}{\mathbf{H_0}}\right)\mathbf{x100} \qquad \textbf{Equation 6-9}$$

Where H_0 and H_l are the hardness of tablets prepared without and with lubricant, respectively. This test was performed on a Sotax Tablet Hardness tester (Westborough, MA).

6.4. Results and Discussion

6.4.1. DSC studies

The DSC thermogram (Figure 6.1) shows the T_g of Affinisol^{TM} HPMC polymers was around 90°C which is much lower than that of HPMC E15(170-180 °C) [129]. Literature shows that increase in substitution and methoxyl/hydroxpropoxyl ratio shows lower T_g [130]. However, data presented in Table 6.1 shows that increase in substitution of cellulose leads to polymers with lower T_g. A strong correlation was observed between the degree of total substitution and T_g. Therefore, the decrease in T_g of Affinisol™ Polymers can be attributed to the increase in total substitution. The total substitution of Affinisol™ Polymers is 47.0-59.0% yielding a T_g of around 90°C; this can be correlated to the case of ethylcellulose with total substitution of 48-49.5% and T_g of around 133°C[Unpublished data]. Increase in substitution decreased the glass transition temperature due to reduction in the intermolecular hydrogen bonding and hence crystallinity of polymer, which resulted in glass transition at a lower temperature.

6.4.2. Powder physical properties

Binder/filler should have acceptable flow property and moisture content for a successful tablet formulation. Flow property of binder/filler is critical during the tablet compression, while moisture content is critical for drug stability. Table 6.2 shows the powder physical properties of Affinisol^{TM} HPMC polymers. The measured Carr's index of 19 and Hausner's ratio of 1.23 indicates that the powder flow was fair. However, angle of repose of 31° to 33° indicates the good flow. Overall, HPMC HME 15 LV showed acceptable flow property to be used as direct compression binder/filler. Binder/filler should have low moisture content, which helps in minimizing drug degradation due hydrolysis. The % loss on drying (LOD) of less than 2.5% indicates that the powder did not have excessive moisture, which can be deleterious to a drug that is sensitive to hydrolysis. Literature shows Affinisol^{TM} HPMC polymers to absorb around 3% of moisture compared to 7% moisture at 60% relative humidity at 25°C [127].

6.4.3. Compactibility analysis

6.4.3.1. Axial expansion of the compact post-compression

Figure 6.2 shows axial relaxation of Affinisol™ HPMC polymers and HPMC E15. It can be observed that the axial relaxation is maximum at low pressure. This is due to the low porosity density at lower compression pressure that causes lesser number of inter-particle bonds. At higher compression pressure (more than 50 MPa), the axial expansion did not change significantly ($p > 0.05$). Overall, the axial expansion at any pressure was less than 2.5% in 24 hours. Such a low axial expansion might be due to the plastic nature of the

polymer and formation of inter-particle bonds, due to the presence of hydroxyl group, during compaction.

6.4.3.2. Analysis using Heckel model

Heckel plot analysis shows that Affinisol™ HPMC polymers has lower yield pressure compared to HPMC E15. This can be attributed to the lower glass transition temperature of former, which leads to deformation at lower compression pressure. It should be stressed that the compaction here is solely due to plastic deformation since the tablets were allowed for elastic recovery before the measurement of the dimensions of the compacts were taken.

6.4.3.3. Analysis using Kawakita equation

It can be observed that Affinisol™ polymers showed higher compressibility index "a" than HPMC E15. This is possible due to lower T_g of Affinisol™ polymers, which is reversibly exceeded during compression at lower compression pressures. Table 6.4 shows that the values of parameter "a", which is the maximum degree of volume reduction is more for HPMC E15 than Affinisol™ HPMC polymers. This can be attributed to lower bulk density and the ability to form more inter-particle bonding due to inter molecular hydrogen bonding in HPMC E15 than in Affinisol™ HPMC polymers. This results in higher degree of volume reduction for HPMC E15 than Affinisol™ HPMC polymers. Parameter "1/b" represents cohesiveness or plasticity. Higher values of "1/b" represent more plasticity or lesser resistance to compression. It can be observed that compared to Affinisol™ HPMC polymers, HPMC E15 showed more resistance to compression due to lower plasticity. This can be attributed to the lower T_g of the former than the latter.

6.4.4. Hardness study

Figure 6.5 shows the hardness of tablets compressed at lower compression pressures (less than 88 MPa) produced stronger tablet of HPMC 15LV compared to HPMC E15. However, with the increase in compression pressure, the increase in hardness of HPMC 15LV tablets reached a plateau. This can be attributed to achieving a limiting porosity and maximum densification at pressure of 88 MPa, above which, there was no further formation of bonds. HPMC E15 tablets showed a steeper increase in hardness between 66 MPa to 110 MPa metric ton of compression pressure. This may be due to the lower degree of substitution allowing more hydroxyl groups to form hydrogen bonds. Similar trend was observed for Methocel F4M and K4M compared to E4M polymer, which showed increase in strength of tablet with increase in compression pressure [125]. Stronger tablets of HPMC E15 compared to Affinisol™ HPMC polymers at compression pressure at 88 MPa and higher can be attributed higher proportion of aromatic hydroxyl group that help in establishing inter-particle bonding once the inter-particle distance is sufficiently reduced to form during compression. Interestingly, increase in hydroxypropoxyl substitution in also introduces an aliphatic hydroxyl group capable of forming hydrogen bonds; however, aromatic hydroxyl groups tend to form stronger hydrogen bonding interaction than the aliphatic hydroxyl group due to the ability of aromatic hydroxyl group to distribute the accepted electron cloud over the aromatic ring.

Higher hardness of Affinisol™ HPMC polymers, at lower compression pressures, might be attributed to the low glass transition temperature of HPMC 15 LV, which is reversible exceeded at low compaction pressure and thereby causing greater inter-particle bonding resulting in stronger tablets. Similar observations were made for plasticized HPMC K4M

compared to unplasticized HPMC K4M, where the tensile strength was higher with plasticized HPMC K4M at lower compression pressure compared to unplasticized HPMC K4M [124]. Also, the tensile strength of plasticized HPMC K4M tablets was found to reach a plateau at higher hardness [124]. Also, literature shows that HPC SSL as a binder led to tablets with higher tensile strength compared to Kollidon® VA64 Fine (copovidone) at lower compression pressure [131]. It can be attributed to the lower glass transition temperature of -25~0°C for HPC [132] compared to 101 °C of Kollidon VA 64 [133].

6.4.5. Friability study

Table 6.5 shows at even at 0.6 metric ton compression force, the tablets of Affinisol^{TM} polymers meet the friability specifications. On the other hand, HPMC E15 yields highly friable tablets. Due to lower T_g of HPMC 15 LV, during compression, the T_g is reversibly exceeded at lower temperature, yielding stronger tablets at lower compression pressure. Similarly, tablets prepared with HPC SSL showed lower friability compared to those prepared with Kollidon Va 64 F[131]. It could also be attributed to the lower glass transition temperature of -25~0°C for HPC[132] compared to 101 °C of Kollidon VA 64 [133]. This observation shows that Affinisol^{TM} polymers have superior compression properties and can yield tablets with stronger edges, at lower compression pressures.

6.4.6. Lubricant sensitivity

Figure 6.6 shows that Affinisol^{TM} polymers are sensitive to lubricant. The lubricant sensitivity of HPMC 15 LV, HPMC 100 LV, HPMC 4M and Starch 1500 were calculated to be 0.44, 0.41, 0.32 and 0.42, respectively. This indicates that more than 30% of

compressibility was lost due to lubrication. This was attributed to the plastic nature of the Affinisol^{TM} HPMC polymers. Plastic materials like Affinisol^{TM} HPMC polymers deform under pressure but did not fracture to create new surface devoid of lubricant [134]. This led to reduced surface area for bonding and therefore tablet hardness decreases during lubrication.

6.5. Conclusion

This work has examined the potential for low T_g HPMC grade to be used as a filler/binder. Compared to higher T_g HPMC, Affinisol™ HPMC polymers yield stronger and less friable tablets at lower compression pressure. This study confirms that lowering the glass transition temperature of HPMC results in superior compaction properties at lower compression pressures. Also, Affinisol™ HPMC possesses acceptable powder flow properties, which make them suitable candidate for use as binder or controlled release matrix former in direct compression applications.

Tables

Table 6.1 Substitution and glass transition temperatures of different types of HPMC

Product Name	Ethoxyl, %[a]	Methoxyl ,%[a]	Hydroxypropoxyl[a], %	Total Substitution, %	Methoxy/Hydroxy propoxy ratio	Glass transition temperature (°C)
Cellulose	-	-	-	0	-	220[135]
Ethylcellulose	48-49.5	-	-	48-49.5	-	133[Unpublished research]
Methocel A type (Methylcellulose)	-	27.5-31.5	-	27.5-31.5	-	196 for MC A4M[24]
Methocel K type	-	19.0 - 24.0	7.0 - 12.0	26.0-36.0	2.26	196°C(HPMC K4M)[130]
METHOCEL F type	-	27.0 - 30.0	4.0 - 7.5	31.0-37.5	4.95	173°C(HPMC F4M)[130]
METHOCEL E type	-	28.0 - 30.0	7.0 - 12.0	35.0-42.0	3.05	163°C(HPMC E4M)[130]
Affinisol™	-	22.0-27.0	25.0-32.0	47.0-59.0	0.89	90°C for HPMC HME 4M

a. Dow Chemical Co. limits

Table 6.2 Powder properties of Affinisol^{TM} HPMC polymers

Parameter	**HPMC HME 15 LV**	**HPMC HME100 LV**	**HPMC HME 4M**
Bulk Density(g/cc) (n=2)	0.466	0.427	0.432
Tapped Density(g/cc) (n=2)	0.575	0.527	0.533
Angle of Repose (°) (n=2)	31	31	33
Loss on Drying (%)	1.73	2.21	1.89
Carr's Index	19	19	19
Hausner's ratio	1.23	1.23	1.23

Table 6.3 Heckel plot parameters for different grades of HPMC

Polymer	Slope 'k' (MPa^{-1})	Intercept	Yield Pressure (P_y) (MPa)	Regression coefficient of line segment used for analysis (r^2)
HPMC HME 15 LV*	0.007078	1.00	141	1.00
HPMC HME 100 LV*	0.006457	1.04	155	0.99
HPMC HME 4M*	0.006643	1.00	151	0.99
HPME E15**	0.004956	0.98	190	0.98

*Values of slope and intercept were obtained using the linearity of the compression pressures up to 110 MPa.

** Values of slope and intercept were obtained using the linearity of the compression pressures up to 133 MPa.

Table 6.4 Kawakita equation parameters for different grades of HPMC

Polymer	a	1/b	Regression coefficient (r^2)
HPMC HME15 LV	63.7	8.93	1.00
HPMC HME 100 LV	66.9	6.81	1.00
HPMC HME 4M	66.6	7.97	1.00
HPME E15	76.4	6.42	1.00

Table 6.5 Friability of HPMC 15LV and HPMC E15 tablets at 0.6 metric ton compression pressure

Polymer	Friability (%)
HPMC HME 15 LV	0.3
HPMC HME100 LV	0.6
HPMC 4M	0.1
HPME E15	2.7

Figures

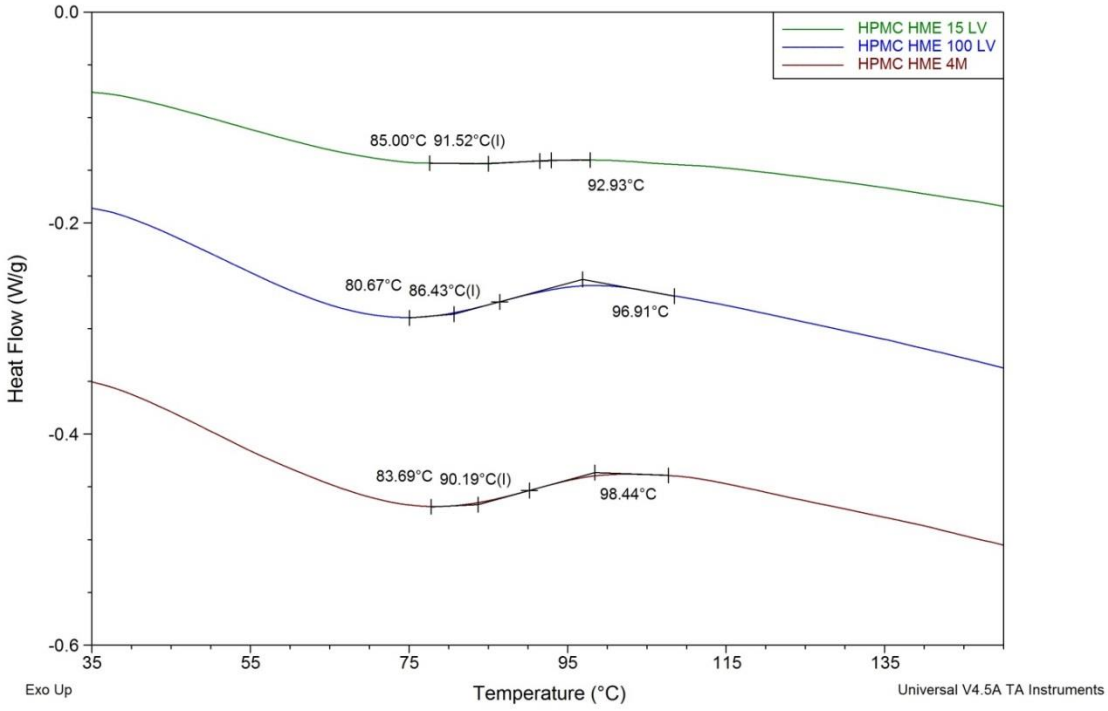


Figure 6.1 DSC thermogram of Affinisol HPMC polymers at heating rate of 3°C/min

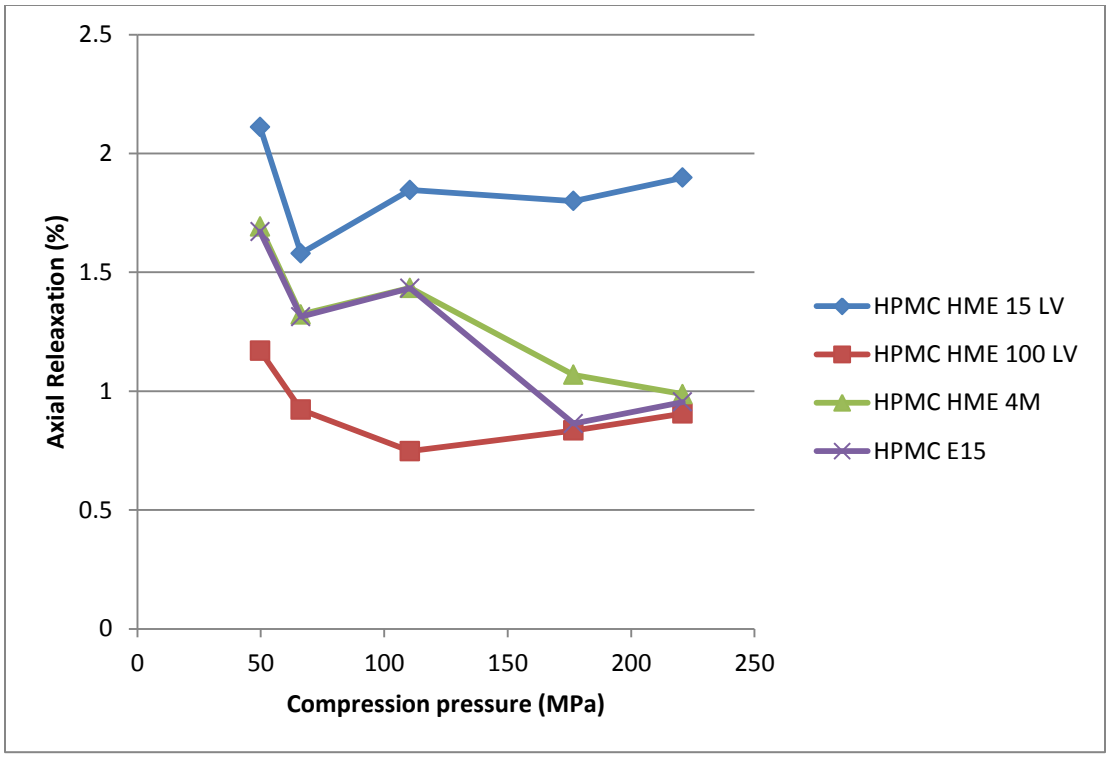


Figure 6.2 Axial relaxation of Affinisol™ HPMC and HPMC E15 compacts as a function of compression pressure at 24 h after compression. Mean values (n=3)

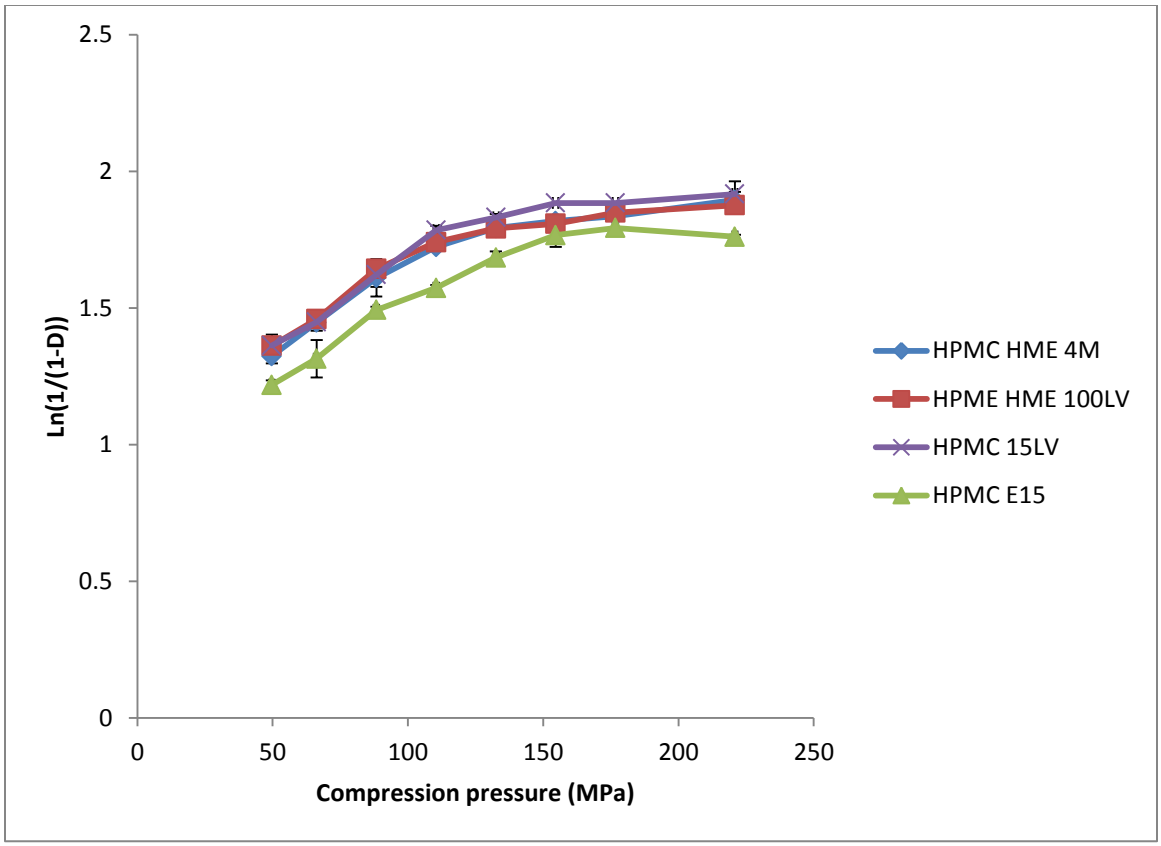


Figure 6.3 Heckel Plot for Affinisol™ HPMC and HPMC E15. Mean values (n=3)±S.D

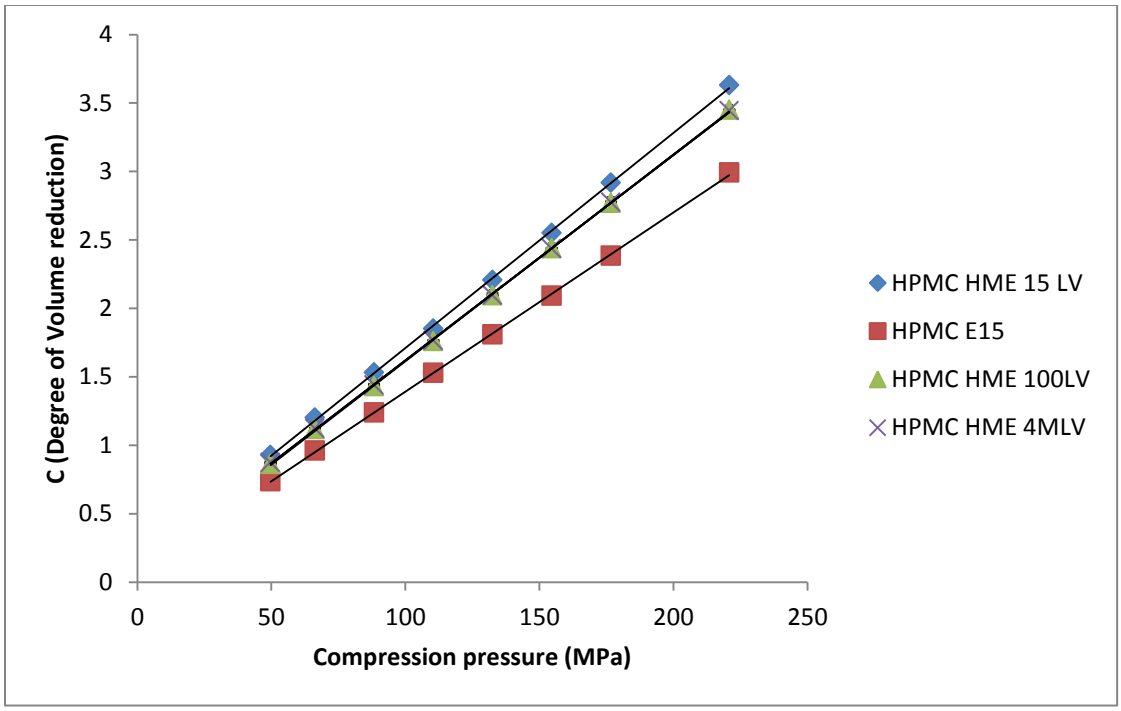


Figure 6.4 Kawakita plot for Affinisol™ HPMC polymers and HPMC E15 . Mean values (n=3) ±S.D

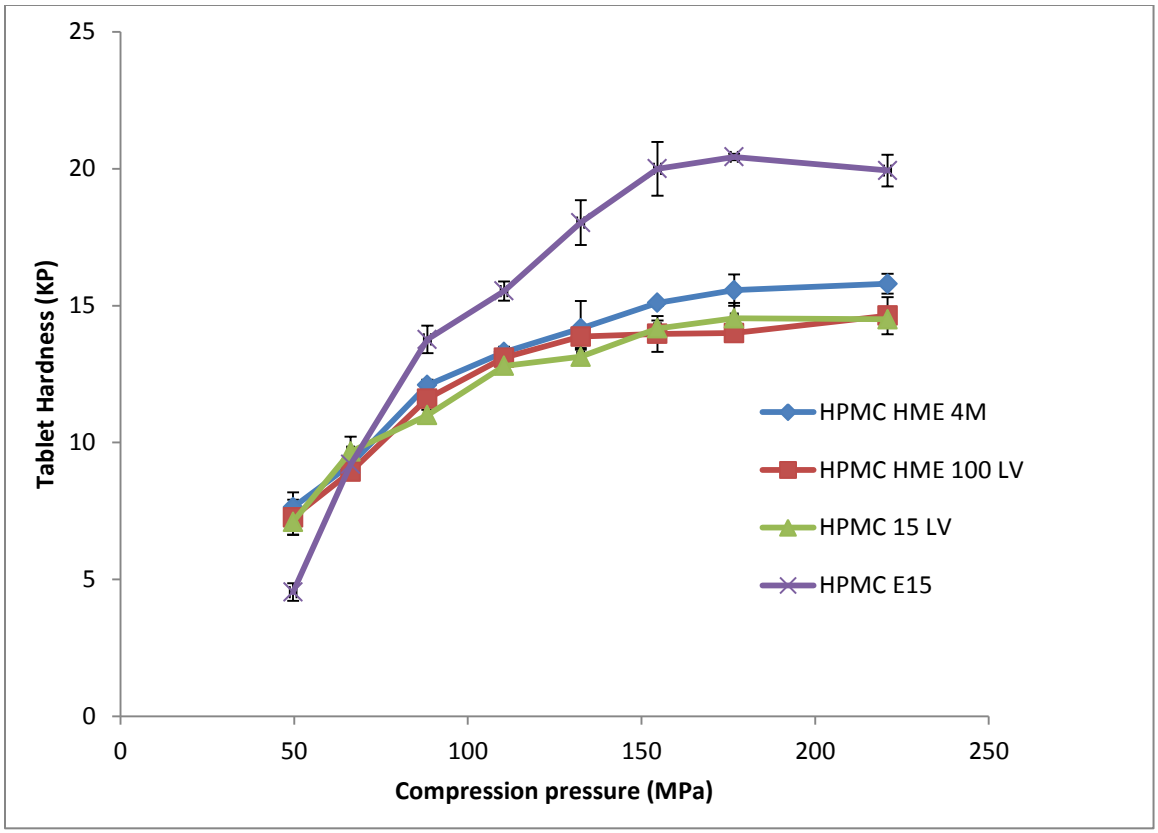


Figure 6.5 Effect of compression pressure on hardness of tablets prepared using Affinisol™ HPMC and HPMC E15. Mean values (n=3)±S.D

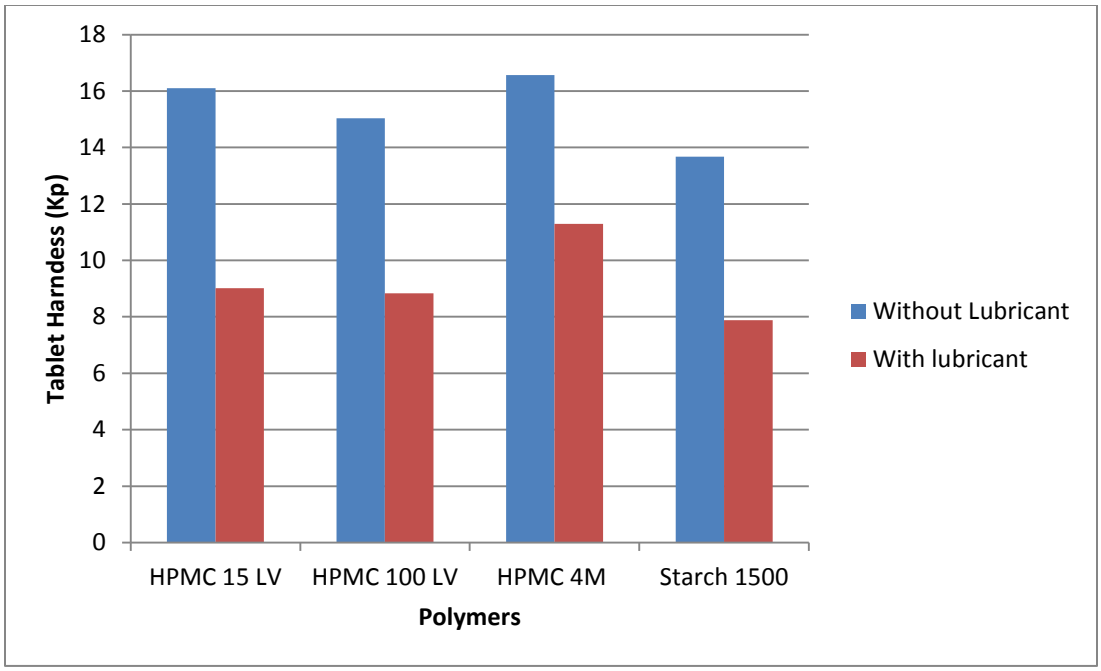


Figure 6.6 Effect of Lubricant (magnesium stearate) on tablet hardness of different polymers. Mean values (n=10)

7. Overall Conclusion

In chapter 4 and 5, the mechanical, thermal and rheological characterizations clearly demonstrated that DVS was able to plasticize EC films. The FT-IR and Raman spectroscopy results proved the presence of hydrogen bonding between DVS and EC. Along with being an API, the non-traditional role of DVS as a plasticizer makes it feasible to develop a sustained release melt extruded formulation of DVS, without the need of external plasticizer, using EC as release controlling matrix polymer since DVS can act as a processing aid to reduce the extrusion temperature owing its ability to plasticize EC.

Similarly, chapter 5 examined that Affinisol™ HPMC polymers, low T_g HPMC grade possesses, acceptable compaction and powder properties. Along with the traditional role as a polymer used for hot melt extrusion, the acceptable compaction and powder properties of Affinisol™ HPMC polymers can be harnessed for its non-traditional role as binder or controlled release matrix former in direct compression applications.

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