Optimising excipients to improve bioavailability

Ingredients

Abstract

Guy Tiene, Director of Strategic Content, That's Nice LLC/Nice Insight, discusses excipient market trends, the use of excipients to improve the poor aqueous solubility of increasingly complex drug candidates and how drug developers choose excipient suppliers

New trends in drug discovery, design and development have led to an increasing number of drug candidates that are poorly water soluble, which can lead to poor or erratic bioavailability. In fact, about 40% of drugs with market approval – and nearly 90% of molecules in the discovery pipeline – are poorly water soluble, falling into Biopharmaceutical Classification System (BCS) categories II and IV. As a result, the demand for solubility enhancing excipients has been on the rise, especially for oral solid dosage form applications.

Developers of both small- and large-molecule therapeutics urgently need to overcome drug formulation and delivery challenges to improve solubility, bio-availability and therapeutic performance. A 2016 Nice Insight research study shows that 66% of companies today focus on large molecule drugs and half on biosimilars as new biological entities (NBEs) for current and future product pipelines. Small molecule products for new chemical entities (NCEs) are the focus of 57% of companies, while 53% focus on small molecule generics.

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The growing concentration on large molecule products, traditionally requiring parenteral administration, has spurred efforts to develop oral delivery routes. Other challenges include the growing number of highly potent compounds in the pipeline and a focus on specialised areas, such as orphan drugs and combination products. Many of these challenges can be resolved with the optimal choice of excipients, as well as newer insoluble-drug delivery technologies.

The global pharma excipient market has grown significantly in recent years, as excipients are increasingly viewed as aiding APIs to achieve better functionality, overcoming issues and providing a means to give products a competitive advantage. Valued at US$6.1bn in 2014, the market is projected to reach $8.4bn by 2019.
at a CAGR of 6.7% from 2014 to 2019 as estimated by Markets and Markets.\(^3\)

The barrier to the absorption of low soluble, highly permeable drugs is dissolution based on the solubility of the 
API. Many strategies have been developed to improve the solubility of these drugs, including co-crystallisation 
with soluble carriers, nanosizing of APIs, and hot-melt extrusion (HME) with soluble carriers. API solubility 
can also be improved through the careful selection of formulation excipients. The choice of excipients for a 
formulation is typically driven by functionality requirements and compatibility with the API. The major types of 
solubility improving excipients are lipid-based, polymer-based, and surfactant-based excipients.

**Lipid-based excipients**

Lipid-based formulations have unique abilities to enable the oral absorption of difficult molecules, primarily 
lipophilic drugs, and concurrently address physical, chemical and biopharmaceutical challenges. Lipid 
excipients enhance the bioavailability of a poorly soluble drug by keeping it in a liquid form, such as a liquid-
filled capsule or solution, until it reaches the site of absorption. These excipients can also influence *in vivo* 
processes, absorption barriers, and even the route of absorption. Pre-dissolving drugs in lipids, surfactants, or 
mixtures of lipids and surfactants omits the dissolving/dissolution step, which is a potential rate-limiting factor 
for oral absorption of poorly water-soluble drugs.

Lipids not only vary in structures and physio-chemical properties, but also in their digestibility and absorption 
pathway

Formulations with lipids are effective delivery systems for poorly water-soluble chemical entities when 
designed with careful selection of excipients. Lipids not only vary in structures and physio-chemical properties, 
but also in their digestibility and absorption pathway. As a result, the selection of lipid excipients and dosage 
form has a pronounced effect on the biopharmaceutical aspects of drug absorption and distribution both *in vitro* 
and *in vivo*. A wide range of novel lipid excipients with acceptable regulatory and safety profiles is available for 
screening as carriers for delivering hydrophobic drugs with low bioavailability, and for optimal solubilisation of 
the drug. Drug absorption depends on factors such as particle size, degree of emulsification, rate of dispersion 
and precipitation of the drug upon dispersion.\(^4\)

Since the bioavailability of BCS class II molecules is limited by low solubility in aqueous fluids, a significant 
advantage of lipid-based formulations is that they can deliver the drug directly as a solution in the 
gastrointestinal tract. Most lipid systems are liquid or semi-solid, and are predominantly encapsulated with soft 
or hard gelatin capsules.

**Polymer-based excipients**

Polymer-based solubility-enhancing excipients are expected to witness rapid growth compared with other types 
because of high adoption by drug formulators. TechNavio analysts forecast the global polymer-based solubility 
enhancement excipients market for oral solid dosage forms to grow at a CAGR of 16.8% over the period 2014– 
2019.\(^5\)

Polymeric excipients stabilise the amorphous API in a solid state and then maintain its super-saturation in 
aqueous media. Excipients can also be used to control the release when the API is solubilised.

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A growing body of pharmacokinetic literature points to drug-polymer solid solutions/dispersions to enhance 
bioavailability. The terms solid solution and solid dispersion define related compositions in which at least one 
active ingredient is dispersed in an inert matrix. In solid dispersions, separate regions of drug and polymer exist 
throughout the matrix, and the drug can be crystalline or be rendered in its amorphous state. A special subset of 
solid dispersions, solid solution refers to the case in which drug-polymer miscibility is attained at the molecular 
level, and the drug exists in its amorphous form.
Pharmaceutically acceptable polymers are ideal to create this matrix, due to the wide range in functionalities attained with polymer chemistries and molecular weights. Polymer selection is based on many factors, including physicochemical (e.g. drug-polymer miscibility and stability) and pharmacokinetic (e.g. rate of absorption) constraints.

**Surfactant-based excipients**

Drugs with high lipophilicity can have poor wetting properties, and surfactants can facilitate their solubilisation. Further, surfactants can solubilise poorly soluble drug molecules by micelle formation or by acting as cosolvents. Non-ionic surfactants are widely used. Polyglycol glycerides, for example, are useful in preparing lipid-based formulations that can significantly enhance solubility and therefore oral bioavailability using various self-emulsifying systems. Micro-emulsions, which are thermodynamically clear dispersions, can also be used to solubilise hydrophobic APIs.

According to a 2015 Nice Insight survey of 412 pharma excipient buyers and 189 sellers/manufacturers, 28% spend $1m–$10m annually for excipients and more than one third spend $10m–$100m (see Table). It also showed that when researching to select excipient suppliers, buyers rely primarily on their already approved supplier list, followed by supplier databases, known suppliers outside their approved supplier list, and contacts at industry events. Meeting product specifications and regulatory compliance are top of mind when they are selecting a new excipient supplier.

In addition, the survey showed that to acquire new customers, excipient manufacturers primarily promote brand credibility, and to retain existing customers, they tend to focus on price.

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The top quality attribute sought by manufacturers is quality assurance. The next highest ranking attribute is reliability of supply, followed by product specifications that exceed the buyer’s expectations and competitive prices for common excipients. Excipient sellers tend to focus on brand credibility and price to secure new contracts.

When assessing the manufacture and supply of excipients, the EU provides the following characteristics to look for:

- Potential presence of transmissible spongiform encephalopathy (TSE)
- Potential for viral contamination
- Potential for microbiological or endotoxin contamination
- Potential for the presence of impurities
- Supply chain complexity and security
- Excipient stability
- Tamper-evident packaging

These characteristics can be used to evaluate excipient suppliers, and are in addition to manufacturing excipients in conformance to excipient GMP. Other considerations for choosing a supplier are detailed in the American National Standard for Pharmaceutical Excipients (ANSI) excipient GMP standard, which highlights
the following criteria to assess for risk to protect an excipient from contamination:

- Hygienic practices: excipient contamination due to personnel hygiene, illness, attire, unauthorised access, food, medication, tobacco, etc.
- Infrastructure, building: excipient contamination, cross-contamination, mix-ups
- Infrastructure, equipment: excipient contamination due to material of construction, utilities, water, process materials, and work environment (air handling, cleaning/sanitation, pest control and drainage).

References


2. 2016 Nice Insight Contract Development & Manufacturing Survey


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