PharmTech.com
ADVANCING DEVELOPMENT AND MANUFACTURING

Taking On Mission Insoluble with Polymers

Industry experts explain why polymer structures and functionalities are important considerations in formulation development.

Jul 02, 2016
By Adeline Siew, PhD [1]
Pharmaceutical Technology
Volume 40, Issue 7, pg 18-23


Hiroshi Watanabe/Getty ImagesPoor solubility is one of the major problems hindering a molecule from progressing through the drug development pipeline. Approximately 70% of new chemical entities (NCEs) have been reported to be poorly soluble (1), which is not surprising given that modern drug-discovery techniques select compounds based on their binding affinities to target receptors. The most promising candidates are often highly lipophilic, hence, leading to solubility and bioavailability issues. Even for marketed drugs, it is estimated that 40% consists of APIs that fall into class II (low solubility, high permeability) or class IV (low solubility, low permeability) categories of the biopharmaceutics classification system (BCS) (2). Of 45 NCEs approved in 2016, 32 were small molecules and a significantly large number of them were poorly soluble (3).

Various approaches have been used to tackle solubility challenges from particle size reduction, salt formation, and the use of cosolvents or cyclodextrins to formulation into solid dispersions or lipid-based drug-delivery systems among others. Of all the solubility enhancement strategies available, a study conducted by Patheon analyzing the drug products approved by FDA between 1970 and 2013 revealed that lipid systems were the most widely used solubilization platform, followed by solid dispersions (4). Both of these approaches involve the use of polymers.

Over the years, polymers have played a key role as solubilizing excipients in many types of formulations, including liquid, semisolid, and solid-dosage forms. Typically, formulations that contain BCS class II and IV compounds will require the use of solubilizing polymers, observes William W. Porter III, research scientist at Dow Pharma Solutions.

The choice of polymers used will depend on the drug properties and route of administration, according to Ian Barker, principal scientist at Juniper Pharma Services. “For oral formulations, such as self-emulsifying and self-microemulsifying drug delivery systems (SEDDS and SMEDDS) and amorphous solid dispersions, solubilizing polymers have found widespread applications, have proven effective in increasing the solubility and consequently, the bioavailability of poorly soluble drugs,” he says. Robert Harris, chief technical officer at Juniper Pharma Services continues, “For topical products, polyethoxylated surfactants and co-block polymers such as poloxamers (e.g., Kolliphor P188 and P407) are often incorporated to achieve drug solubility in the vehicle.”

Polymer structures and functionalities

The industry has begun to pay closer attention to the polymers’ structures and functionalities in recognition that the physicochemical properties of polymers aid in the selection of appropriate excipients for the desired formulation, notes Andreas Gryczke, global technical marketing manager, Solubilization, BASF Pharma Solutions. Solubilizing polymers are amphiphilic in nature. “The hydrophilic and hydrophobic characteristics are crucial because they provide sites for intermolecular interactions (e.g., hydrophobic van der Waal’s and hydrogen bonding) with the lipophilic drug,” Gryczke explains. “Non-amphiphilic polymers are often used in combination with a surfactant to maintain the drug in supersaturated solution after its being released from the dosage form.”

“A good solubilizing excipient will depend upon the affinity of the drug with the polymer,” Harris points out. “In particular, hydrogen-bonding between drug and polymer plays a key role in maintaining the drug in a dissolved state and promoting miscibility and stability of the formulation.”

Gryczke adds that when using polymer-surfactant combinations, attributes such as

wettability, surface active properties, and hydrophilic lipophilic balance (HLB) are also important in drug solubilization to ensure that the molecule remains encapsulated in the polymeric assemblies as nanoparticles, micelles, or emulsion/microemulsion. Polymer chain length and molecular weight can also have an effect on the dosage form's performances by leveraging the stronger drug-polymer entanglements, which are crucial for stability of the solubilized drug and for maintaining supersaturation of drug without precipitation or nucleation, says Gryczke.

According to Barker, generally when reference is made to use of polymers to aid drug solubility, it is usually associated with amorphous solid dispersions. The most commonly used excipients in solid dispersions are cellulose-based polymers (e.g., hydroxypropyl methylcellulose [HPMC], hydroxypropyl methylcellulose acetate succinate [HPMCAS]), vinyl pyrrolidones and their co-polymers (e.g., Kollidon VA64), and methacrylates (e.g., Eudragit, Kollicoat MAE). "Within each of these classes, there are multiple polymer chemistries that are used in this application space," adds Kevin P. O'Donnell, research scientist at Dow Pharma Solutions. "Some of the useful properties of these polymers include having a molecular weight significantly higher than that of the drug, sufficiently high glass transition temperature to promote amorphous physical stability, and the ability to have hydrogen bonding interactions with the drug in the solid-state and in solution."

"Polymers enhance solubility of the poorly soluble drug by increasing the degree of API distribution or by even changing the crystalline structure of the active to an amorphous higher energy state," explains Firouz Asgarzadeh, Evonik's director of technical service for North America. According to Asgarzadeh, maintaining the solubility enhancement effect requires the long-term stabilization of the amorphous structure via molecular interactions (i.e., ionic and/or hydrogen bonding) and by minimizing the molecular mobility below the glass transition temperature of the polymer. He further points out that the selection of polymers through a systematic approach of estimating miscibility levels based on the structures of polymers and actives can significantly accelerate the formulation development. In the following roundtable discussion, industry experts provide insight on the factors that influence polymer selection and the importance of screening studies in formulation development.

Physicochemical properties

PharmTech: How do the physicochemical properties of the polymer and API affect performance of the formulation?

Asgarzadeh (Evonik): According to the organic/polymer chemistry's rule of thumb 'like dissolves like,' the miscibility of polymer and API will influence the processing conditions and stabilization of the resulting amorphous solid solutions and dispersions. Polymers and APIs with similar solubility parameters and potential for hydrogen bonding and ionic interactions are expected to be more stable and easier to process. Such interactions may allow for the formation of amorphous solid dispersions at temperatures well below the melt temperature of the API. When the intermolecular bonding forces of the polymer and drug in amorphous solid dispersions are stronger than the intramolecular forces, combined with the glassy state of the polymer, recrystallization is inhibited, which can improve storage stability.

Gryczke (BASF): The fact that polymers can be used to formulate drugs into a dosage form has to do with the polymer's physicochemical properties, physics, and chemical constitution. In respect to physical properties, we have to take into consideration the polymer's melting point and glass transition temperature, melt and/or solution viscosity, and the overall rheological behavior as these properties also determine a polymer's suitability when being used, say for example, as a binder in melt or wet granulation process.

In terms of formulation development for poorly soluble drugs, the different features of polymers have proven useful. For example, polymers are often used to serve as a matrix for a drug to be (molecularly) dispersed in it. In this case, the drug's crystal lattice energy is overcome already, meaning that the drug has been dissolved and the polymer controls its release later. The drug release rate is not just determined by the chemical composition but also the molecular weight of the polymer.

Polymers can consist of different monomers with different chemical functionalities. Nowadays, we have available a variety of polymers with different functional groups such as carbonyl, hydroxyl, and amino- moieties; hence, for many drug molecules, a suitable polymer that stabilizes the drug in its dispersed state can be found.

In respect to the manufacturing process of a drug product, polymers play a decisive role in term of compressibility, elasticity, rheology, and many other parameters. The glass transition temperature is a good example as this parameter is considered when making a decision on the manufacturing of a solid dispersion. Overall, the polymer's physicochemical properties have to match the requirements for the drug molecule and the available processing technology.

Barker and Harris (Juniper Pharma Services): The physiochemical properties of the drug and polymer are critical when assessing the most appropriate formulation route. Generally, both drug and polymer have to be stable to processing. In addition, the polymer has to sustain long-term stability of the drug with regards to properties such as recrystallization. An example is hot-melt extrusion (HME) where high heat and shear can cause degradation of not only the API, but the polymer as well. Advances are being made in producing polymeric materials for HME applications, with notable examples being the tri-block co-polymers and cellulosic materials with wider HME processing windows.

Porter and O'Donnell (Dow): The physiochemical properties of the API will direct polymer selection. The polymer will be selected to improve critical API attributes and allow for downstream processing of the amorphous solid dispersion. For example, an API with a low glass transition temperature will require a polymer with a suitably high glass transition temperature to allow for physical stability of the dispersion. Similarly, if the dispersion is manufactured using a solvent-based process, the polymer must dissolve in a solvent that is also compatible with the API. In addition, if the dispersion is manufactured via a thermal process, the polymer and API must be thermally stable at reasonable processing temperatures. Finally, the API and polymer interactions need to be sufficient to promote both solid-state stability of the dispersion as well as sustained supersaturation upon dissolution.

Excipient selection

PharmTech: How do you decide which polymers to use? What are the key considerations in excipient selection?

Barker and Harris (Juniper Pharma Services): In solid amorphous molecular dispersions, polymer choice is often dictated by pre-formulation screening work, which aims to match an excipient to the API being formulated. It is, therefore, critical that polymers amenable to industrially viable processing techniques (e.g., HME or spray drying) are used from the outset. Typically, such polymers have a high amount of polar groups capable of hydrogen bonding, are stable to heat, soluble in a wide range of solvents including water and are widely available from numerous pharmaceutical excipient suppliers.

Porter and O'Donnell (Dow): Polymers for solid dispersions are typically selected based on the physiochemical properties of the API. A key consideration is the intended method of production because HME and spray drying will have different critical quality attributes for the polymer. For example, spray drying requires a polymer that is soluble in organic solutions while maintaining a low solution viscosity for atomization. Alternatively, HME requires a polymer with a moderate softening temperature and adequate melt viscosity over a broad processing window.

Gryczke (BASF): To begin with, there are several aspects that need to be considered, such as the drug release site, the desired release rate, the desired dosage form, the required dose per dosage form, and the available manufacturing technologies. All these factors will influence the decision on which polymer can be used in solid dispersions.

There are many polymers available on the market, for example, polymers that release the drug independent of pH such as Kollidon VA64, and polymers that serve as both a matrix polymer as well as a solubilizer such as Soluplus. There are also polymers proven to have good properties in inhibiting drug precipitation after being released such as povidone K30 (Kollidon 30) and HPMC.

Polymers are selected based on their parameters such as melting point (if there is one), glass transition temperature, melt viscosity, hygroscopicity, chemical nature, available in-house process technology, and the available experience and know-how, all to match the requirements of a drug molecule.

Asgarzadeh (Evonik): When selecting polymers for the development of pharmaceutical formulations with enhanced solubility, one of the most important criteria is the regulatory compliance of the polymer (compendial status) and established use in existing oral drug products.

The quality attributes will depend on the process that is used to manufacture the solid dispersion. For polymers used in a melt process (e.g., HME), the selection criteria typically includes a glass transition temperature that is moderately higher than the desired storage temperature while possessing conditions with sufficient thermal stability. A glass transition temperature or melt temperature that is too high may require HME process temperatures that could accelerate drug and/or polymer degradation. On the contrary, a glass transition temperature or melt temperature that is too low may cause product instability and premature recrystallization.

For a spray-drying dispersion process, polymers with high solubility in organic solvents are necessary to minimize solution preparation and spray times. Actives with stability problems at higher temperatures are more suitable for spray drying than HME techniques. In both spray drying and HME processes, the miscibility of the active and polymer is necessary. The presence of appropriate hydrogen-bond donor or acceptor groups, and in the case of ionic actives, the presence of appropriate counter-ions on the polymer and active will ease the formation of solid solutions and the inhibition of crystal growth.

Screening studies

PharmTech: Can you tell us more about the importance of screening studies when developing a formulation for a poorly soluble drug? What screening tools are typically used to reduce trial and error?

Porter and O'Donnell (Dow): Screening studies are necessary to guide formulation toward the optimal polymer. High throughput supersaturation screening and thermal screening tools are frequently used to identify the best polymer candidates and starting drug loads. A secondary screening can be performed by small-scale spray drying or HME to verify the initial screening and provide processing guidance for scale up. Combined, these methods reduce trial and error and minimize the amount of API needed for early formulation development work.

Asgarzadeh (Evonik): The rational selection of formulation ingredients for solid solution formation leads to a significant reduction in the number of experiments and hence speeds up formulation development. A first screening study using solubility parameters of the polymer and active is essential when investigating the solubility issues with a systematic approach rather than a random mixing and matching empirical approach. A tool developed by Evonik is MemFis (Melt Extrusion Modeling and Formulation and Information System). We have stories of clients who had already started an empirical development approach with no acceptable results and MemFis proved useful in identifying polymer-drug combinations that were overlooked in the original screening studies. Once appropriate combinations with potential miscibility are identified, a quick evaluation using film casting, spray drying, or HME at a very small scale can further confirm the formation of stable solid solutions with enhanced solubility. The application of MemFis not only enhances formulation development but also saves drug substance, which may be expensive and/or limited in supply, especially at the early stages of development.

Gryczke (BASF): The screening we recommend involves several phases, aimed to achieve the decision for a lead formulation in a fast manner. It begins with the in-situ phase where the chemical requirements of the drugs are matched with polymers, which is based on computer simulations and miscibility estimations to reduce the set of polymers in the next phase of conduction experiment. Following that, small-scale screening tests are conducted to verify the computer simulation. This type of testing can be done manually or by high-throughput screening systems. BASF uses a combination of these approaches to understand the following three things:

- How to best bring the drug into supersaturated solution over an extended period (>4 hours)
- How to maintain the drug in supersaturated solution (depending on the

surrounding medium), and how to inhibit drug precipitation to a level where sufficient absorption is expected
How to stabilize the drug in the formulation until it is released.

The use of design of experiments is important because it allows us to generate data to find a comprehensive solution with reasonable effort.

Barker and Harris (Juniper Pharma Services): With more than 80% of new chemical entities exhibiting poor solubility, screening studies form an important part of early development. Preclinical toxicology studies often require enhanced formulations to ensure suitable exposure is achieved. Screens focus on drug/polymer miscibility and stability and can be achieved using miniaturized techniques (e.g., film casting) where mg quantities of the drug and test polymer are used. The physicochemical analysis that accompanies these tests, such Raman spectroscopy, x-ray powder diffraction, differential scanning calorimetry, and optical microscopy provide crucial data to inform appropriate drug in polymer formulation routes. The process can be rapid and can include initial pharmacokinetics animal data.

References

1. S. Basavaraj and G.V. Betageri, *Acta Pharm Sin B*, 4 (1) 3-17 (2014).
2. T. Loftsson and B.E. Brewster, *J Pharm Pharmacol*, 62 (11) 1607-1621 (2010).
3. L. M. Jarvis, *Chemical & Engineering News*, 95 (5) 12 (2016).
4. A. Siew, *Pharm Tech*, 39 (7) 20-27 (2015).

Article Details

Pharmaceutical Technology
Vol. 40, No. 7
Pages: 18–23

Citation

When referring to this article, please cite it as A. Siew, "Taking On Mission Insoluble with Polymers," *Pharmaceutical Technology* 40 (7) 2016.