In the lifecycle management of pharmaceutical products, novel drug delivery technologies that offer positive differentiation over first-generation products provide an important means for staying competitive in today’s business environment.

Many existing active pharmaceutical ingredients (APIs) and new chemical entities (NCEs) are poorly water soluble and subsequently have low oral bioavailability if formulated in their unmodified forms. Traditional approaches to overcoming this include:

- Improvement of water miscibility by employing self-emulsification, lipid-based techniques, solubilisation into micellar cores, or alternatively complexation with cyclodextrins.
- Reduction of particle size to nano-scale via mechanical milling or high-shear processing accompanied by particle stabilisation.
- Impacting crystal lattice energy using polymorphs or co-crystals, or through the creation of solid dispersions of drug in inert carriers or matrices.

Increasingly, solid dispersions are being looked at as a viable solution to this pervasive issue. Although only a few solid dispersions are currently marketed, the approach has some inherent advantages over other approaches. Presence of an active compound as a molecular or nanoparticle dispersion combines the benefits of decreasing crystal lattice energy and maximising surface area, thus facilitating better contact with dissolution media. Fortuitously, many of the carriers that can be employed for the production of solid dispersions are generally recognised as safe (GRAS) and are already extensively used as excipients in marketed products, easing the regulatory burden.

In this article, Mark Mitchnick, MD, Chief Executive Officer, and Robert Lee, PhD, Vice-President, Pharmaceutical Development, both of Particle Sciences, and Amir Zalcenstein, PhD, Chief Executive Officer, SoluBest, introduce Particle Sciences’ formulaic DOSE™ system for dosage form development and drug delivery technology selection, and discuss one such technology, SoluBest’s Solumer™, a scalable solid dispersion approach based on spray drying that is suitable for BCS Class II APIs and NCEs.

In the case of many poorly soluble drugs, solid dispersions can be developed to improve dissolution and bioavailability. This methodical iterative approach allows one to rapidly narrow in on the formulation approaches most likely to yield the desired results.
are screened for their impact on solubility and permeability. This methodical iterative approach allows one to rapidly narrow in on the formulation approaches most likely to yield the desired results.

THE CHALLENGE

An increasing number of compounds coming out of discovery are poorly soluble. By some estimates 40-70% of new lead compounds in development fall into this category. Additionally many new compounds also exhibit poor permeability. In 1993, the Biopharmaceutical Classification System (BCS) was proposed as a way to facilitate the marketing of generic drugs. The system classifies a given compound by its aqueous solubility and gut permeability.

Beyond its regulatory use, the BCS provides a very useful framework in which to evaluate APIs and chart a logical course to achieve the desired pharmacokinetics (PK), including greater bioavailability. For BCS II and IV molecules, where solubility is the main or largely contributing limiting property, there are a number of approaches including increasing surface area through particle size reduction, surface morphology modification and solid solutions.

ONE POSSIBLE SOLUTION: SOLUMER™ TECHNOLOGY

Generating human data as quickly as possible is a goal of every drug developer and there are several philosophies as to how best to achieve first in human (FIH) dosing. It has been estimated that 3-6 formulation changes occur from FIH to commercialisation. At Particle Sciences, we believe that FIH experience should be in a formulation that will provide useful developmental data. For a BCS Class I molecule, the prototypical formulation could be a simple powder-filled capsule. For a poorly water-soluble molecule, BCS Class II or IV, such a simple system is unlikely to provide any commercially helpful data, speed development or bring to light clinically relevant findings. Therefore, a FIH formulation designed to deliver the drug in a commercially viable way is, in our view, important. For drugs with limited aqueous solubility, one such approach is Solumer™, a patented dual polymer system utilising GRAS excipients and traditional processing techniques. In this approach, the API is solubilised in an organic solvent, usually ethanol. An amphiphilic polymer is separately mixed in water. The drug and polymer solutions are then mixed and spray dried. The exact compositions of the feed stocks are determined in an extensive, yet efficient, preformulation phase utilising Design of Experiment (DoE) methodology, when appropriate. Key drivers include the APIs solubility in various organic solvents, the APIs molecular weight, the solubilities of the polymeric excipients, and the compatibility of the API and polymeric excipients in the spray drying solution.

Solumer FINGERPRINTS

Formulating lipophilic crystalline drugs results in a self-assembled drug-polymer complex. This provides two features that are required for improved bioavailability:

- Depression of melting temperature and energy
- Formation of colloidal dispersions upon contact with aqueous media

<table>
<thead>
<tr>
<th>API</th>
<th>Formation</th>
<th>Tm (ºC)</th>
<th>ΔHm (J/g)</th>
<th>Tm (ºC)</th>
<th>ΔHm (J/g)</th>
<th>Particle size (nm)</th>
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<td>Resveratrol</td>
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<td>253.6</td>
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<td>14.0</td>
<td>1224</td>
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<tr>
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<td>166.2</td>
<td>1190</td>
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<td>1310</td>
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<tr>
<td>Nifedipine</td>
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<td>113.4</td>
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<td>8.4</td>
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<tr>
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<td>74.3</td>
<td>64.4</td>
<td>9.3</td>
<td>669</td>
<td></td>
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<tr>
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<td>60.5</td>
<td>118.0</td>
<td>52.0</td>
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<tr>
<td>Clarithromycin</td>
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<td>70.2</td>
<td>207.9</td>
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<td>Albendazole</td>
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<td>209.7</td>
<td>161.4</td>
<td>31.2</td>
<td>555</td>
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<tr>
<td>Fenbendazole</td>
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<td>166.3</td>
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<td>84.4</td>
<td>155.6</td>
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<td>910</td>
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Figure 1: Comparative Thermodynamic Characteristics (Melting Temperatures and Melting Energies) of Various Unformulated APIs and their Corresponding Solumer™ Formulations.

Figure 2: Comparison of X-ray Diffraction Patterns of Naproxen API (Naproxen) and Naproxen processed using the Solumer™ Technology (Solu-Naproxen).

Figure 3: Differential Scanning Calorimetry of Naproxen API (Raw Naproxen) and Naproxen processed using the Solumer™ Technology (SoluNaproxen 294-153).
itted to polyethylene oxides (PEO, also commonly referred to as polyethylene glycol or PEG), PEO derivatives, PEO copolymers such as PEO/polypropylene glycol (PPG) copolymers, PEG-modified starches, poloxamers, poloxamines, polyvinylpyrrolidones, hydroxypropyl cellulose, hypromellose and esters thereof, vinyl acetate/vinylpyrrolidone random copolymers, polyacrylic acid, and polyacrylates. Hydrophilic polymers are defined as those soluble in water or in a mixture of organic solvent and water, but not soluble in organic solvent alone. Examples of hydrophilic polymers include but are not limited to starch, sodium carboxymethylcellulose, hydroxyethylcellulose, polyvinyl alcohol, sodium alginate, chitosan, and carrageenan. Notably, Solumer formulations utilise only FDA-approved polymers.

The use of hydrophilic polymers that ionise at different pH allows for the design of formulations targeted either to the stomach or the intestine. For example, chitosan, which is ionised at low pH, promotes drug release in the stomach, while sodium carboxymethylcellulose and sodium alginate, ionised at neutral conditions, facilitate release in the small intestine.

The resulting powder is free flowing and will contain 25% or more API. Characteristics of the drug product include:

- Solubilised drug homogeneously interwoven into a polymer matrix
- Formation of crystalline drug within the polymer matrix
- Modified thermal behavior demonstrating depressed melting temperature and enthalpy of melting of the drug (see Figure 1)
- Spontaneous formation of nanocolloidal dispersions upon contact with aqueous media
- Enhanced dissolution rate/solubility of the drug in aqueous media as well as prolonged supersaturation in relevant biological fluids, and GI site-targeted release of the drug.

**CHARACTERISATION**

Comparing X-Ray diffraction patterns of a model API, naproxen, with its corresponding Solumer™ formulation, shows that in the Solumer™ formulation, the drug (naproxen) is present in its crystalline form (see Figure 2). In contrast to some systems dependent on amorphous forms, this technology results in very stable constructs since the drug is present in its most thermodynamically favoured state.

Several commercial compounds have been thoroughly evaluated using this technology. In Figure 3, the impact of the technology on melting temperature and enthalpy of melting is clearly demonstrated. It is believed that these thermal property alterations are responsible for the drastic increase in solubility provided by the technology.

Figure 4 shows the dissolution profiles and porcine pharmacokinetic data for fenofibrate. (A: dissolution profiles of raw API, commercial product, and Solumer™ fenofibrate (Solumer-Fenofibrate); and B: porcine PK data for commercial product versus Solu-Fenofibrate).

Figure 5 shows the dissolution profiles and porcine pharmacokinetic data for albendazole (A: dissolution profiles of raw API and Solu-Albendazole in 0.05 M SLS; B: dissolution profiles of raw API and Solu-Albendazole in fasted simulated intestinal fluid; C: porcine PK data for commercial product versus Solu-Albendazole; and D: efficacy in porcine model of commercial product versus Solu-Albendazole).

**CONCLUSION**

Drug product formulation development will become increasingly sophisticated over time. Whether reformulating an existing compound or working with an NCE, the ability to understand and manipulate those factors within our control that dictate PK behavior is key. For compounds with low solubility, we have presented one approach to oral dosage form development. Using GRAS ingredients and a readily scaled, patented process, Solumer™ technology results in stable crystalline constructs that increase bioavailability by increasing the solubility of the API. To date the technology has been demonstrated in more than a dozen compounds and is currently being scaled for Phase III commercialisation.

**REFERENCES**


**Figure 5: Dissolution Profiles and Porcine Pharmacokinetic Data for Albendazole.**

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