



Part 1: Oral Delivery of Poorly Soluble Drugs



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By many estimates up to 40 per cent of new chemical entities (NCEs) discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry.

Relative to highly soluble compounds, low drug solubility often manifests itself in a host of *in vivo* consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher inter-patient variability. Poorly soluble compounds also present many *in vitro* formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the *in vivo* absorption. These *in vivo* and *in vitro* characteristics and the difficulties in achieving predictable and reproducible *in vivo/in vitro* correlations are often sufficiently formidable to halt development on many newly synthesised compounds due to solubility issues.

The Biopharmaceutical Classification System (BCS) groups poorly soluble compounds as Class III and IV drugs, compounds which feature poor solubility and high permeability, and poor solubility and poor permeability, respectively. Drug substances are considered highly soluble when the largest dose of a compound is soluble in <250mL water over a range of pH from 1.0 to 7.5; highly permeable compounds are classified as those compounds that demonstrate >90 per cent absorption of the administered dose (1, 2). In contrast, compounds with solubilities below 0.1mg/mL face significant solubilisation obstacles, and often even compounds with solubilities below 10mg/mL present difficulties related to solubilisation during formulation.

A fundamental step in the solubilisation of drug compounds is the selection of an appropriate salt form, or for liquid drugs, adjustment of pH of the solution. This is an especially important selection process for polar compounds as the majority of newer solubilisation techniques such as nanosuspensions and microemulsions utilise co-solvents when applied to a polar

compound. A majority of monographs available for drugs whose solubility is greater than 10mg/mL are hydrochloride, sulphate, maleate and citrate salts of basic drugs, and potassium, calcium and sodium salts of acidic drugs (3). Due to the regulatory implications, the selection of an appropriate salt form is essentially a pre-formulation goal undertaken prior to particle engineering.

Poorly soluble drugs such as nifedipine and felodipine have motivated the development of drug delivery technologies to overcome the obstacles to their solubilisation through either chemical or mechanical modification of the environment surrounding the drug molecule, or physically altering the macromolecular characteristics of aggregated drug particles. These technologies include both traditional methods of solubility enhancement, such as particle size reduction via comminution and spray drying, addition of surfactants and inclusion in cyclodextrin-drug complexes, and the use of more novel mechanisms such as self-emulsifying systems, micronisation via nanoparticles, pH adjustment and salting-in processes.

PARTICLE SIZE REDUCTION

The bioavailability of low solubility drugs is often intrinsically related to drug particle size. By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during comminution and spray drying is also a concern when processing thermo-sensitive or unstable active compounds.

Recrystallisation of poorly soluble materials using liquid solvents and antisolvents has also been employed successfully to reduce particle size. The reliance upon organic solvents during processing often involves solvent extraction and handling procedures which may significantly increase the complexity of manufacture.

Particle size reduction through the traditional methods of comminution, such as grinding and milling, are often incapable of reducing the particle size of nearly insoluble drugs (<0.1mg/mL). Some comminution methods have been developed to specifically address the production of particles at the sub-micron level, such as so-called micro-milling; the physical and thermal stresses inherent to comminution still present difficulties related to drug stability however. Other methods have been developed to impart less physical stress upon the drug particles, such as the piston gap homogeniser used by Skyepharma to create nanoparticles through hydrodynamic cavitation. The use of disintegration processes in conjunction with colloidal suspensions (nanosuspensions) or solid-dispersions (nanocrystals, solid lipid nanoparticles) have been employed by several drug delivery companies with success, including Elan's Nanocrystals®, Skyepharma's Dissocubes and Baxter's NanoEdge technologies.

Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Through manipulation of the pressure of SCFs, the favorable characteristics of gases – high diffusivity, low viscosity and low surface tension – may be imparted upon liquids to precisely control the solubilisation of a drug with a supercritical fluid. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drug particles are solubilised within SCF, they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to sub-micron levels – current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5-2,000nm in diameter (4). Several specialty pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specialising in particle engineering via SCF technologies for particle size reduction and solubility enhancement.

The most widely employed methods of SCF processing for micronised particles are rapid expansion of supercritical solutions (RESS) and gas antisolvent recrystallisation (GAS), both of which are employed by the pharmaceutical industry using carbon dioxide as the SCF due to its favourable processing characteristics. RESS involves solubilising a drug or a drug-polymer mixture in SCF and subsequently spraying the SCF solution into a lower pressure environment via a conventional nozzle or capillary tube. The rapid expansion undergone by the solution reduces the density of the CO₂, correspondingly reducing its solvent power and supersaturating the lower-pressure solution. This supersaturation results in the recrystallisation and precipitation of pure drug or drug polymer particles of greatly reduced size, narrow size distribution and high purity. GAS processing requires the drug or drug-polymer mixture be solubilised via conventional means into a solvent that is then sprayed into an SCF; the drug should be insoluble in the SCF, while the SCF should be miscible with the organic solvent. The SCF diffuses into the spray droplets, causing expansion of the solvent present and precipitation of the drug particles (5).

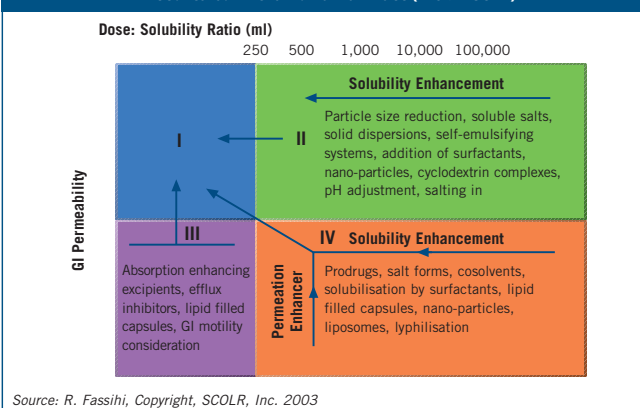
The process of efficient SCF particle size reduction is still being optimised for individual drug products. For the application of RESS to polar drug compounds, co-solvents, such as methanol, may be required for the drug to solubilise in the SCF. The use of co-solvents introduces the familiar issues of achieving sufficient solvent extraction and volatile materials handling into the manufacturing process, increasing the complexity of production. The use of high pressure CO₂ may also cause significant scale-up and operation issues to arise, such as particle aggregation upon dispersion from nozzles and capillaries. Several methods of SCF processing have been developed to address individual aspects of these shortcomings, such as precipitation with compressed antisolvents process (PCA), solution enhanced-dispersion by SCF (SEDS), supercritical antisolvents processes (SAS) and aerosol supercritical extraction system (ASES) (6).

INCLUSION COMPLEXES AND MICROEMULSIONS

Particle size reduction, whether via traditional micronisation or novel nanosizing methods, may not be applicable to all poorly soluble compounds, most notably high dose drug products and those compounds with higher melting points. In such cases, solubilisation via drug-cyclodextrin inclusion complexes may be more appropriate. In other cases, traditional comminution and micronising techniques may not be able to reduce particle size sufficiently to satisfactorily solubilise the drug, and self-emulsifying or microemulsion techniques may be applied.

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of multiple (α -1,4)-linked α -D-glucopyranose units that display the amphoteric properties of a lipophilic central cavity and a hydrophilic outer surface. Because natural cyclodextrins of 6, 7 or 8 glucopyranose units (α -, β - and γ -CDs, respectively) possess limited aqueous solubility, CD derivatives with significantly improved solubility have been synthesised, such as 2-hydroxypropyl- γ -cyclodextrin, 2-hydroxypropyl- β -cyclodextrin, sulphobutylether β -cyclodextrin, randomly methylated β -cyclodextrin and branched maltosyl- β -cyclodextrin. While the synthetic CDs improve solubility significantly, they are still limited in their drug inclusion capacity and retain disadvantageous processing characteristics for oral dosage forms; the volume of CD complexes is often much greater than the volume of drug alone, which may severely limit the types of delivery technologies that may be employed.

Figure 1: Possibilities of Shifting the Solubility-Dissolution Characteristics from a Very Poorly Soluble Drug to D:S within the Range of Values Encountered in the Human GI Tract (D:S >250ml)



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CD complexes have also been employed in conjunction with hydrophilic polymers, such as hydroxypropylmethyl cellulose, to improve the solubilising effect of the CDs. The improvement in solubilisation ability within these water-soluble polymer/drug-included CD aggregates requires less cyclodextrin to solubilise the same amount of drug, reducing the volume constraints present for non-aggregated CDs and increasing the range of delivery technologies available (7). Drug-CD complexes are commonly formed through either supersaturating a CD solution with drug and mildly agitating the solution for an extended period of time, or adding a mass of drug to a CD and solvent slurry and 'kneading' to produce a paste which is then dried and sieved. Although several delivery technologies have been developed to take advantage of drug-included CD formulations in both water-soluble polymer aggregated and non-aggregated forms, such as CAPSITOL® technology offered by CyDex and CAVAMAX® technology offered by Wacker-Chemie GmbH, relatively few oral CD-based drug products are currently on the market due to unfavorable regulatory positions in regard to toxicity and stability issues.

Microemulsions and self-emulsifying systems have emerged as potential solubility enhancing technologies, whose solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. Traditionally, long- and medium-chain triglycerides (LCTs and MCTs, respectively) have been employed with surfactants to incorporate drugs into self-emulsifying systems. The growth of self-emulsifying drug delivery systems in recent years has resulted in the optimisation of several methods of solubilising active compounds using novel, synthetic MCTs and co-solvents in addition to non-ionic surfactants. Non-ionic surfactants, such as Tweens (polysorbates) and Labrafil (polyoxyethylated oleic glycerides), with high hydrophile-lipophile balances (HLB) are often used to ensure immediate formation of oil-in-water (o/w) droplets during production (8). HLB is an expression of the balance between water-soluble and oil-soluble moieties of a surfactant: as the HLB increases, the hydrophilicity of the surfactant increases. Amphiphilic, non-ionic surfactants allow higher degrees of drug solubilisation to occur and may prevent the precipitation of drug out of the microemulsion *in vivo*.

Co-surfactants are frequently employed to increase the amount of drug capable of being dissolved into the lipid base, because the concentration of surfactant in most self-emulsifying systems is required to be in excess of 30 per cent w/w. These co-surfactants are often organic solvents suitable for oral administration, such as ethanol, propylene glycol and poly ethylene glycol. Similar to the impact of introducing organic solvents elsewhere in drug product manufacture, the use of co-solvents increases processing complexity while improving the potential drug load of the emulsion. Most self-emulsifying systems are limited to administration in lipid-filled soft or hard-shelled gelatine capsules due to the liquid nature of the product. Interaction between the capsule shell and the emulsion should be considered so as to prevent the hydroscopic contents from dehydrating or migrating into the capsule shell. One example of a stable microemulsion technology is Eurand's Nanolipispheres™: colloidal suspensions of sub-micron sized drug particles in a solid lipid matrix. This suspension is then dried to obtain physically stable drug particles in a powder form.

SOLUBILISING EXCIPIENTS

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent. Surfactants are also often used to stabilise microemulsions and suspensions into which drugs are dissolved. The presence of surfactants within a drug product formulation may result in an incompatibility with drug delivery technologies which rely upon well-regulated hydration, dissolution and erosion of a matrix or coating to achieve controlled release.

The influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals is well documented. The absorption of a drug is largely dependent upon diffusion, which varies with the pKa of the drug and the pH of the individual regions within the gastrointestinal tract, and permeability, which is not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionisation (9).

While the importance of salt selection and pH adjustment has been stressed as a critical parameter of pre-formulation, the use of pH-altering excipients within drug delivery systems is also of significant utility. Solubilised excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalising agents may increase the solubility of weakly-basic drugs.

One example of such a use of pH-inducing excipients is SCOLR Inc's self-correcting hydrogel systems. One or more electrolytes are included within the dosage form whose pKa is complementary to the drug; as the dosage form hydrates, the electrolyte is wetted simultaneously with the active compound, creating a microenvironment independent of gastrointestinal pH. Microenvironmental pH may be modulated to enhance dissolution of poorly soluble drugs via salting-in effects through the inclusion of electrolytes of varying hydrophobic character; conversely, intra-dosage form pH may induce precipitation of highly soluble drugs, thereby slowing dissolution through salting-out effects.

CONCLUSION

The growing percentage of NCEs displaying solubility issues demands that technologies for enhancing drug solubility be developed to reduce the percentage of poorly soluble drug candidates eliminated from development as a result. Drug-cyclodextrin inclusion complexes, surfactant addition and particle size reduction via comminution, spray drying and solvent recrystallisation, possess significant limitations on the extent to which they may solubilise insoluble and nearly-insoluble compounds. Novel technologies, such as supercritical fluid processing, nanosizing and pH modification, present novel methods of solubilisation that may allow for greater opportunities to deliver poorly soluble drugs. ♦

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