Enhancing Therapeutic Potential of Poorly Soluble Drugs

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The pharmacological potential of many pharmaceutical drugs is limited by their low aqueous solubility. The solubility parameter cannot be compromised therefore different approaches are used to enhance their solubility and bioavailability. Pharmaceutical active molecules with low solubility are at higher risk of failure for drug innovation and development as solubility directly impacts pharmacokinetics and pharmacodynamics as well as other *in-vivo* parameters, such as drug absorption, distribution and protein binding. Among all pharmaceutical dosage forms, more than 50% of dosage forms are available for oral delivery. Figure 1 demonstrates the ratio of drugs on market and in pipeline as per BCS classification. Currently marketed drugs represent a somewhat uniform distribution between the BCS classifications, with Class I compounds expectedly ranking the highest. However, 90% of pipeline drug candidates are either Class 2 or Class 4 molecules creating a need to enhance drug solubility. This can be achieved using a variety of techniques.

Dr Neetika Taneja is an experienced formulation scientist with a PhD in Pharmaceutical Technology and more than eight years of academic and industrial experience in formulation and development of solid oral and parenteral dosage forms.

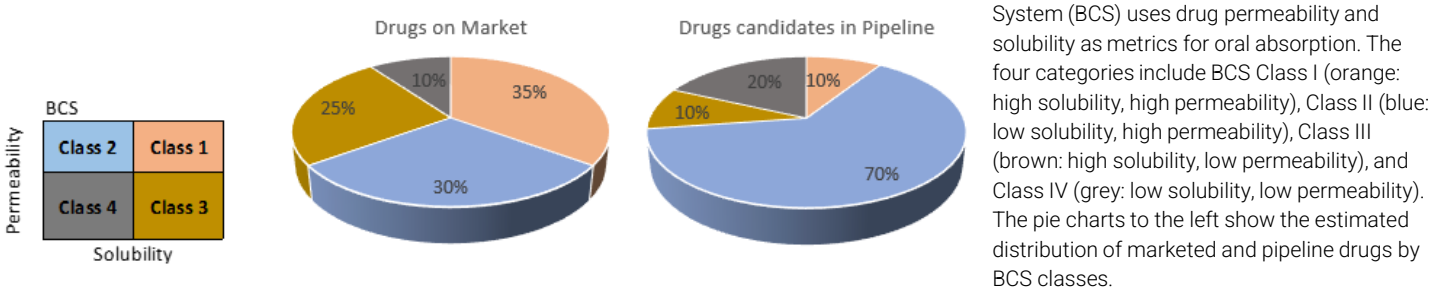

Figure 1: The Biopharmaceutics Classification System (BCS) uses drug permeability and solubility as metrics for oral absorption. The four categories include BCS Class I (orange: high solubility, high permeability), Class II (blue: low solubility, high permeability), Class III (brown: high solubility, low permeability), and Class IV (grey: low solubility, low permeability). The pie charts to the left show the estimated distribution of marketed and pipeline drugs by BCS classes.

Techniques to enhance bioavailibility

Solid Dispersion:

Solid dispersion is a promising technique for enhancing the absorption and therapeutic efficacy of drugs in dosage forms. It generates and sustains a supersaturated state where the drug possesses high energy that causes its rapid dissolution and helps to generate intraluminal concentrations of the drug above its saturation solubility. The basic principle incudes complete removal of drug crystalline structure and its molecular dispersion in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves, and the drug releases as fine colloidal particles. This increases surface area of dissolution rate and hence bioavailability of poorly water-soluble drugs. It is suitable for drugs with poor aqueous solubility and high permeability (Class II drugs of the BCS classification).

Advantages	Disadvantages
× Easier to produce and more applicable × Increase in the exposed surface area × Have higher degree of wettability & porosity × stabilise the unstable drug against hydrolysis and oxidation × Mask unpleasant taste and smell of drugs	✓ Sometimes, conversion of amorphous drug into less soluble crystalline form can occur due to exposure to moisture during storage and lead to phase separation and instability. ✓ Incorporating solid dispersion into some dosage form is challenging ✓ Less reproducible ✓ Expensive ✓ Poor Scale-up

Other techniques used along with amorphous solid dispersion to improve the stability includes co-amorphous drug delivery system, pH modulated solid dispersion, surfactant based solid dispersion and sustained release solid dispersion. The solid dispersion is prepared using amorphous carrier, surfactant carrier or a mixture of amorphous polymer and surfactant carrier where the drug is molecularly dispersed into polymeric carrier. A wide variety of polymers are available for solid dispersion such as Polyethylene glycol, Polyvinylpyrrolidone, and cellulose derivatives. The most relevant methods used for solid dispersion preparation are spray drying and hot melt extrusion.

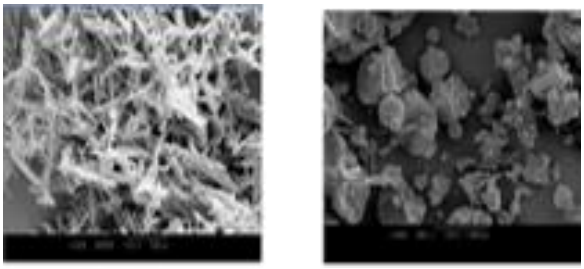

Figure 2: Scanning Electron Micrographs of Crystalline and Amorphous Itraconazole

Spray Drying:

Spray drying is a solvent-based process in which a drug and the required amount of carrier polymer is dissolved into suitable solvent. In the spray drier, spray solution is passed through an atomizer forcing the solution to break up into small droplets within the chamber. The formed droplets are then exposed to a hot drying gas that rapidly evaporates the solvent from the droplets, leaving isolated amorphous solid dispersion particles behind. This produces a powder with controlled particle size, density, and flow. The powder is further subjected to a secondary drying process to remove any residual solvent.

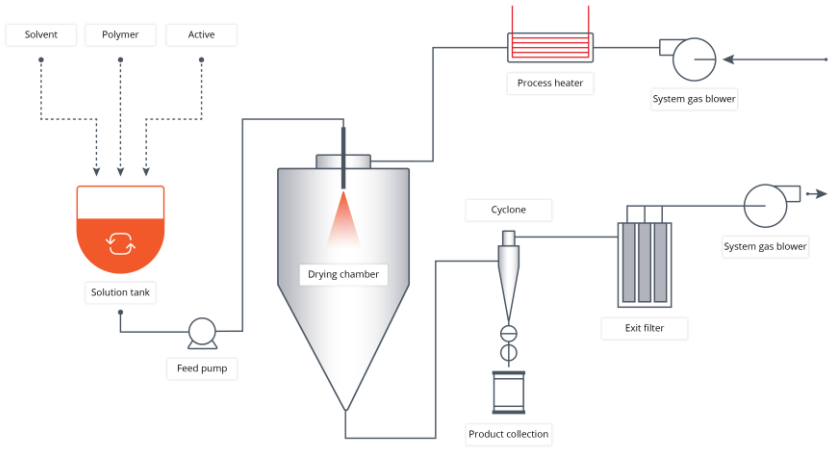

Figure 3: Schematic representation of spray dryer instrumentation configuration.[13]

A few process variables are taken into consideration during spray drying including the total concentration of solid in the spray solution, process conditions such as spraying solution viscosity, nozzle diameter, inlet and outlet temperature and drying gas flow rate. These parameters determine the particle characteristics of the dispersion including particle size, density and morphology that impact the physical and chemical stability of the formulation.
A few examples of marketed formulations using spray drying includes Itraconazole, Nilvadipine, and Tacrolimus.

Hot Melt Extrusion:

Hot melt extrusion is a thermal-driven process in which drug, polymer and surfactant are fed through an extruder at processing temperatures causing the drug to either dissolve into the polymer matrix (processing temperature < drug melting temperature) or melt into the polymer matrix (when the processing temperature > drug melting temperature). This produce an extrudate with drug molecularly dispersed within the polymer matrix that can be milled into solid particles.
The process is not suitable for heat sensitive drugs. A key consideration for solid dispersion produced via hot melt extrusion is ensuring that processing temperatures do not degrade the polymer or drug.

Developmental Considerations in Solid Dispersion techniques:

- ❑ Understanding of key attributes affecting manufacturing and product stability.
- ❑ Spray drying leads to smaller and more porous particles, whereas hot melt extrusion tends to produce extrudate that have higher bulk and tapped densities with superior flow.
- ❑ Spray dried powder can be dry blended with excipients for filling into capsules. Hot melt extrudate requires milling prior to filling into capsules.
- ❑ Spray dried particles may require dry granulation before being compressed into tablets, hot melt extrude requires milling before tablet compression.

Lipid Based Formulation

Lipid based formulations are used for the oral administration of drugs with poor aqueous solubility (BCS Class 2 and Class 4). These formulations represent 3 % of total drug products available in the market. Lipid-based formulations are an attractive approach for oral application owing to their inherent biocompatibility, particle size versatility, scaling-up ability, and cost-effectiveness. Based on the composition, size and chemical characteristics, lipid-based systems can be classified into lipid solution, lipid suspensions, emulsions, self-micro-emulsifying systems, solid lipid nanoparticles, solid lipid dispersions, niosomes, and liposomes. In order to achieve better physiochemical stability and ease of commercialization, these formulations are transformed into solid dosage forms. Liquid lipid formulations can be converted into solid intermediates using spray congealing, spray drying, adsorption into solid carriers and melt granulation. Selection of solidification process is vital to ensure sufficient desorption of drug and lipid excipients from the solid carrier.

These lipid formulations can be administered as liquid-filled hard capsules or tablets as well as oral liquids in the form of solutions or suspensions. They can also be administered as conventional solid oral formulations when adsorbed onto solid carriers or granulated or utilized for sustained release formulations. A lipid -based carrier is effective for the oral delivery of hydrophobic drugs as it enhances solubility and dissolution rate in the GI tract. The digestive enzyme lipase along with its co-lipase facilitates the breakdown of glycerides into diglycerides, monoglycerides and fatty acids.

Advantages	Disadvantages
✓Non-immunogenic and Bio-compatible ✓Particle size versatility ✓Scaling -up ability ✓Cost effective ✓Phospholipids and cholesterol in the formulation form vesicles and micelles that facilitate the drug absorption	× Physical and chemical stability issues during long term

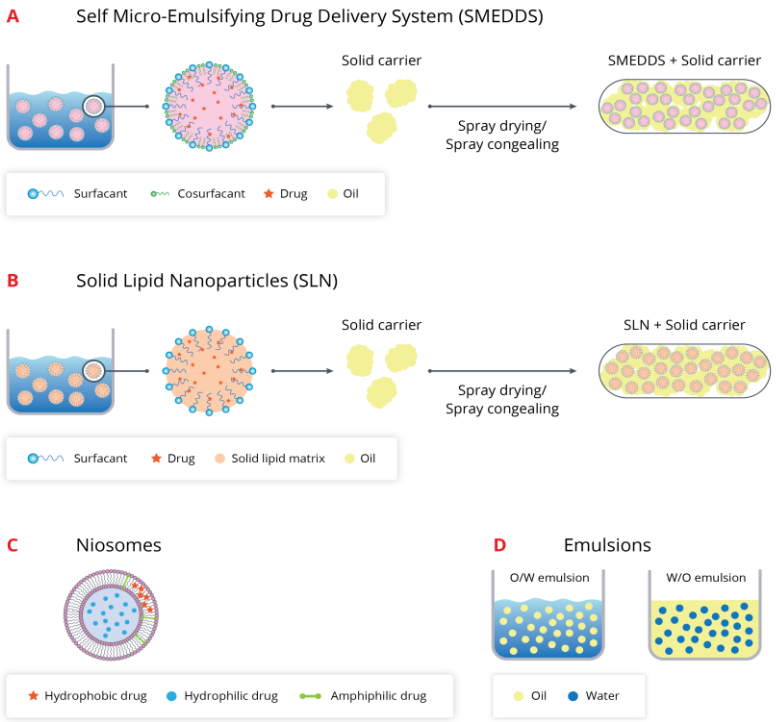

Figure 4: Emulsion-based system including lipids and polymers

Development Considerations:

The following factors should be considered when evaluating the best approach towards enhancing solubility and bioavailability:

- ❑ For API with low bio-availability solution lipid-based formulations are preferred
- ❑ For API with dose loading issues, suspension lipid-based formulations are suggested
- ❑ Compatibility of API with excipients
- ❑ Prototype formulation should be evaluated for dispersibility in gastric fluid, digestibility using lipolysis and kinetic solubility.
- ❑ Performance of lipid based formulations rely on the dispersion of the formulation and degree of digestibility.
- ❑ Adequate formulation stability is required to assure formulation performance (potency, dispersion and/or digestibility) over the expected duration of study.

Factors affecting the choice of excipients for lipid-based formulations include solubility dispersion, digestion, and absorption.

The lipid formulation classification system is considered the best way to understand and identify the most appropriate type of formulation for a specific drug and interpret the performance of the lipid-based formulation *in-vivo*. Briefly, the lipid formulation classification system can be differentiated into 4 types according to dispersibility in water and digestibility.

Formulation type	Material	Characteristics	Advantages	Disadvantages
Type I	Oil without surfactant	Poor aqueous dispersion but rapid digestion	It has GRAS status (Generally Recognized As Safe); Good compatibility with capsules	Poor solvent capacity unless drug is highly lipophilic
Type II	Oil and water insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion Likely to digest	Turbid o/w dispersion (particle size 0.25–2 µm)
Type III	Oil, surfactants (water soluble and insoluble), and cosolvents	SEDDS/SMEDDS formed with water-soluble components	Clear or almost clear dispersion, drug absorption without digestion	Loss of solvent capacity on dispersion, less easily digested
Type IV	Water-soluble surfactants and cosolvents	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Chances of loss of solvent capacity on dispersion May not be digestible

Table: 1 The lipid formulation classification system

Conclusions

The evolution of small molecule medicinal chemistry has resulted in the development of new chemical entities with increasing hydrophobicity. In order for this generation of molecules to have the best opportunity to achieve their desired pharmacological objective it is advantageous to improve their aqueous solubility.

The technologies discussed in this white paper enable various options towards the desired increase in aqueous solubility, each best suited to the drug molecule and the final dose form.

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