AN UPDATED REVIEW ON TECHNICAL ADVANCES TO ENHANCE DISSOLUTION RATE OF HYDROPHOBIC DRUGS

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Article Received on: 17/08/12 Revised on: 16/09/12 Approved for publication: 12/10/12

ABSTRACT
The dissolution behavior of drugs continues to be one of the challenging aspects in formulation development. The advent of combinatorial chemistry and high throughput screening increased the number of hydrophobic compounds significantly. The Biopharmaceutical classification scheme (BCS) takes into account three major factors: solubility, intestinal permeability, and dissolution rate and all the three govern the rate and extent of oral absorption and hence bioavailability. Especially for BCS Class II substances the bioavailability of a poorly soluble drug may be enhanced by increasing the solubility and dissolution rate of it in the gastro-intestinal fluids. Drug substances whose highest dose is soluble in less than 250 ml of water over a range of pH from 1.0 to 7.5 are considered as highly soluble. In contrast, the drug compounds with solubility below 1mg mL-1 face significant dissolution or bioavailability problems. With the introduction of advanced technologies it could be possible to overcome the problems. The article provides an overview on the theoretical definitions and technical approaches broadly covering technologies and hydrophilic carriers or excipients used. Further part of the manuscript is committed to the formulation, analytical methods for the characterization of samples, dissolution or release kinetics and model fittings.

KEY WORDS: Solubility, Dissolution rates, Bioavailability, Hydrophobic Drugs, Solid dispersion, Hydrophilic carriers

INTRODUCTION
The oral route of drug administration is the simplest, convenient, showing flexibility in designing the dosage form and has good patient compliance which makes it the most promising route of administration of drug(s)1. More than 40% of the New Chemical Entities (NCEs) which are under development are intended to be designed as oral solids due to their effective and reproducible in vivo plasma concentration after oral administration2. At times these NCEs despite their high permeability are generally absorbed in the upper small intestine that significantly reduces after the ileum resulting in a small absorption window3. Consequently if these drugs are not completely released in the gastrointestinal area they show a lower bioavailability which results in wastage of a large portion of an oral dose and adds to the cost of drug therapy3,4. Improvement of aqueous solubility in such case is a valuable goal to improve therapeutic efficacy5. When a drug is delivered orally, it must first dissolve in gastric fluids before it permeates the membranes of the GI tract to reach systemic circulation. Therefore, a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption. And their clinical efficacy would be often suboptimal and also shows few side effects due to their poor solubility6. The BCS accounts for solubility, intestinal permeability, and dissolution rates which affect the rate and extent of oral absorption from the immediate release solid oral-dosage forms7. Especially for class II substances the bioavailability of a poorly soluble drug may be enhanced by increasing its solubility and dissolution rate in the gastro-intestinal fluids8. Drug substances that are soluble in <250ml water over a range of pH from 1.0 to 7.5 are considered as highly soluble. In contrast, the drug compounds with aqueous solubility below 1mg/mL face significant solubility problems9. Thus the ability to increase aqueous solubility is an important aid to enhance the oral bioavailability for most of the hydrophobic drugs10. Solubility is an intrinsic property for a defined molecule. In order to achieve the pharmacological activity, the drug molecules need to exhibit certain solubility in the intestinal fluids. In preclinical development phase, formulation optimization is critical for drug absorption11. But for the absorption, the drug must be present in a dissolved state. The solubility or the dissolution behavior of a particular drug is primary determinant to its oral bioavailability12. The process of solubilization is the breaking of intermolecular bonds of the solute followed by the separation of the molecules of the solvent so as to provide space for the solute13,14. The solubility of a poorly soluble drug substance may be altered at two levels that include material engineering of drug substance and formulation approaches, which can be done either by improving dissolution rate or by maintaining the drug in solution state throughout its residence period in the GIT15. Dose of a drug is an important indicator for BCS class II drugs since low dosed drugs sufficiently dissolve in the gastro intestinal fluids while higher doses do not show the same solubility16. The modified Noyes-Whitney equation provides a few hints as to how the dissolution rate of poorly soluble compounds may be enhanced to diminish the limitations of oral availability (Noyes and Whitney, 1897: Nemst, 1904)17.

\[
\frac{dc}{dt} = \frac{AD (Cs - C)}{h}
\]

\[
\frac{dc}{dt} = \text{The rate of dissolution}
\]

A = Surface area available for dissolution
D = Diffusion co-efficient of compound
C_s = Solubility of drug in dissolution medium.
C = Concentration of the drug in medium at time t and h is the thickness of diffusion boundary layer adjacent to surface of dissolving compound.

Particle Size Reduction
The particle size of a drug is related to its solubility. Lesser the particle size greater will be the surface area to volume ratio. This allows a greater interaction of the drug particles with the solvent that result in increased dissolution. Conventional techniques include size reduction or...
comminution, spray drying and micronization while the principle of impact and attrition works for fluid energy milling, ball milling. All these techniques rely upon mechanical shear forces that result in deaggregation of the solid particles. Although these conventional methods have been used to increase the dissolution rate of drug, there are few practical limitations with these techniques, as the applied mechanical forces impart a significant amount of physical stress upon solid drug particles that may cause their degradation. Static charges develop on the surface of the sub micron sized drug particles during the processing which becomes a problem during handling. This leads to contamination by the fly-away powders. In order to overcome this hazard, spray drying technique could be best used as the drug would be incorporated in liquid phase which is directly sprayed into drying gas. The effect of particle size on solubility can be described by

\[
\frac{S}{S_0} = \left(\frac{2\gamma V}{2\gamma V + \pi r^2}\right)^{n}
\]

Where, \(S_0\) is the solubility of infinitely large particles, \(S\) is the solubility of fine particles, \(V\) is molar volume, \(r\) is the radius of the fine particle and \(\gamma\) is the surface tension of the solid.

Nanonization
Nanonization is novel and alternative method to the existing drug delivery technologies as it has potential to improve solubility of hydrophobic drugs. This includes study and use of materials and structures at nanoscale level which is approximately 100nm or less. It overcomes the limitations of traditional size reduction process like agglomeration of particles which reduces the exposed surface area hence decreasing solubility. Nanonization not only improves drug solubility but also diminishes possible side effects as it allows for encapsulation of pharmaceuticals permitting drug delivery to the targeted site. Nanosuspensions, nanoemulsions and polymeric micelles are different types of formulations prepared using this technique. Drugs like Estradiol, Doxorubicin, Cyclosporine and Paclitaxel are commercially prepared by nanonization technology. Methods used in nanoparticle preparation are wet milling, high pressure homogenization, super critical fluid process, and precipitation with compressed fluid antisolvent (PCA), cryogenic spray processes.

Micellar Solubilization
One of the oldest methods to enhance the solubility of hydrophobic drugs is by the use of surfactants. Reduction in surface tension causes the lipophilic drug particles to dissolve more rapidly in the aqueous medium improving their dissolution. And this surface tension can be reduced by use of surfactants which are the molecules with distinct polar and non polar region. When the concentration of the surfactants exceeds 0.05% - 0.1% i.e., Critical Micellar Concentration (CMC), micelle formation occurs entrapping the drug particles within them. These micelles are spherical in shape with the non polar region in the centre and surrounded by polar regions that come in contact with the water. This process is known as micellization. Surfactant gets adsorbed on the solid surface and modifies their hydrophobicity and surface charge. But this occurs only when the surfactant concentration is below CMC. Commonly used surfactants are polyesorbates, polyoxyethylene castor oil, polyoxyethylene glycerides, lauroyl macro glycerides, mono and di-fatty acid esters of low molecular weight polyethylene glycols. Examples of the compounds that are reported to use micellar solubilization are anti diabetic drugs, gliclazide, repaglinide, rosiglitazone, glipizide.

Inclusion Complexes
Inclusion complexes are generally the drug cyclodextrin complexes. Cyclodextrins are a group of structurally related oligosaccharides that have a hydrophilic surface externally and a hydrophobic cavity internally. The inner cavity of cyclodextrins is lined with skeletal carbons and ethereal oxygens of the glucose residues making them lipophilic or hydrophobic in nature. They act as both solubilizing and stabilizing agents in pharmaceutical dosage forms. They consist of 6, 7, and 8- D-glucopyranosyl units connected to 3-1, 4 glycosidic linkages, known as α, β, γ cyclodextrins respectively. Complexation of drug and cyclodextrins is purely a non covalent process as they undergo complexation by the physical forces such as van der Waals forces, hydrophobic interaction, electrostatic interaction, hydrogen bonding. The drug is protected from the unfavorable environment as it gets inserted within the cyclodextrin cavity depending upon structural factors, the ability of the guest molecule to displace the solvent from the host cavity, the interactions between the lipophilic groups of the guest molecule and the polar cavity of the cyclodextrins. Apart from increasing the solubility of hydrophobic compounds cyclodextrins are also used as enzyme models and has both stabilizing and destabilizing effect on chemically labile compounds. It is assumed that drug availability in cyclodextrin-containing formulations will be hindered by the slow release of drug from the cyclodextrin inner cavities. Conversely, it has been shown that the rate of formation and dissociation of drug-cyclodextrin complexes resembles the diffusion controlled limits with complexes being constantly produced and broken down. Consequently, presence of water-soluble drug/cyclodextrin complexes at the hydrated epithelial surface increases the availability of dissolved drug molecules, especially of the lipophilic drugs. But low aqueous solubility and nephrotoxicity limited the use of β-CD especially in parenteral drug delivery.

Hydrotropy
Hydrotropy is a solubilization process which designates the increase in solubility of the solute by the addition of large number of additives which are known as hydrotropic agents. The term hydrotropic agent was first introduced by Neuberg (1916). The solute consists of alkali metal salts of various organic acids. The salts that increase the solubility of a solute in a given solvent are known to “salt in” the solute and the salts that decrease the solubility are known to “salt out” the solute. “Hydrotropic salts” are those with large anions or cations that are themselves very soluble in water resulting in “salting in” of non electrolytes. Their actual mechanism is not clearly specified but it resembles to the complexation that involves a weak interaction between the hydrotropic agents and the poorly aqueous soluble drugs. The most frequently used are aromatic hydrotropes with anionic groups. Hydrotropic solutions do not show colloidal properties as they involve only a weak interaction between the hydrotropic agent and solute. The method involves only the mixing of the drug with the hydrotrope in aqueous medium. It does not require chemical modification.

Co-solvency
Non electrolytes and non polar molecules generally have poor aqueous solubility. The solubility of such substances can be increased by the addition of water miscible solvents for which they have higher solubility. These solvents which are used in combination are known as co-solvents and the
Carbon dioxide
Salt Formation
Salt formation is the most commonly used technique for increasing the solubility and dissolution rates of weakly acidic and basic drugs. The salt forms of these drugs have better solubility than their corresponding acid and base forms. Salt formation is not feasible for neutral compounds as this method is used to improve the aqueous solubility mostly for the liquid formulations (parenterals)\(^\text{45, 46}\). Apart from enhancing solubility, salt forms also prolong duration of action, mask bitter taste and avoid drug degradation in the gastro intestinal tract. The pH value functions as an indicator for the preparation of salt forms of the acidic and basic drugs. The pH−solubility inter relationships also provide the necessary data regarding the counter ions to be used for salt formation\(^\text{41}\). Generally acidic drugs form sodium salts and basic drugs form hydrochloride salts. Organic acid salts of basic drugs have higher aqueous solubility when compared to their corresponding inorganic salts. The major limitation of salt forms include high reactivity with atmospheric carbon dioxide and water that result in the precipitation of poorly soluble drugs. Some molecules like steroids and alcohols do not form salts as they do not dissociate when dissolved in water\(^\text{42}\).

Supercritical Fluid (SCF) process
It is a novel technique for producing smaller particles which are free flowing with greater surface area and the final product consist of negligible amount of residual organic solvent. Super critical fluids are those whose temperature and pressure are greater than their critical temperature (Tc) and critical pressure (Tp). This allows them to assume the properties of both a liquid and a gas. Super critical fluids are preferred because of their high compressibility and viscosity which is the intermediate between gas and liquid\(^\text{43}\). Commonly used super critical fluids include carbon dioxide, nitrous oxide, methanol, ethanol, ethane, propane, ammonia. Carbon dioxide is widely used for processing thermo sensitive products due its low critical temperature (Tc = 31.1C) and pressure (Pc = 73.8 bar) It acts both as a solvent and antisolvent. Controlled particle size can be achieved by application of this technique\(^\text{44}\). Supercritical fluids are used as solvents in rapid expansion from supercritical solution (RESS), antisolvents in gas antisolvent (GAS), precipitation with compressed antisolvent (PCA), and supercritical antisolvent (SAS) techniques\(^\text{45}\). Ease of solvent removal, high purity of the formed product and ability of the process to retain the stability of pharmaceuticals which are liable to hydrolysis make it a preferred technique for industrial use. This technique when combined with special methods like spray drying, specialized nozzles and freeze drying can be used for a variety of crystalline materials irrespective of their physical and chemical nature\(^\text{46}\).

Solid Dispersions
Among the various techniques employed to improve the rate of dissolution of hydrophobic drugs, the preparation of solid molecular dispersions is pharmaceutically acceptable as they can improve bioavailability of poorly soluble drugs which undergo dissolution rate limited gastrointestinal absorption\(^\text{47}\). Chio and Riegelman defined the term solid dispersion as “a dispersion of one or more active ingredients in an inert carrier or matrix of solid state prepared by melting (fusion), solvent or melting solvent method”\(^\text{48}\). Solid Dispersions obtained through the fusion process are often called melts and those obtained through the solvent method are referred as co precipitates or co evaporates. The drug can be molecularly dispersed, in amorphous particles (clusters) or in crystalline particles. 6 types of interactions occurring in solid dispersions include simple eutectic mixtures, solid solutions, glass solutions, glass suspensions, compound or complex formation between drug and carrier, amorphous precipitation of drug in crystalline carrier\(^\text{50, 51}\). This technique improves bioavailability when solubility and dissolution rates limit the absorption of drug. Recently it is being used to prepare sustained release forms using various carriers\(^\text{52, 53}\). Factors responsible for increase in dissolution rate of solid dispersions are found to be particle size reduction of the drug to molecular level, solubilising effect of the hydrophilic carrier on the drug, reduction of aggregation and agglomeration, possible amorphization within the dispersion and increased saturation solubility\(^\text{54-59}\).

Polyethylene Glycols (PEGs) are mixtures of condensation polymers of ethylene oxide and water\(^\text{60}\). PEGs having the molecular weights in the range of 1500 to 20,000 are generally used in solid dispersion preparation due to their higher solubility in many organic solvents. The melting points of these PEGs are usually below 65°C. Relatively low melting points of PEGs are beneficial in the manufacture of solid dispersions by melting technique\(^\text{61}\). Drugs like nimesulide, ketoprofen, nifedipine, nimodipine, tenoxicam and albendazole showed enhanced solubility when prepared as solid dispersions\(^\text{62}\). Tendency of the amorphous forms to undergo crystallization during storage, low compressibility, poor scale-up for manufacturing and high amount of carrier required to obtain desired release rate limit the usage of solid dispersions in commercial products. Few examples of solid dispersions available in market are Sporanox® (itraconazole), Intencence® (etavirine), Prograf® (tacrolimus), Crestor® (rosuvastatin), Gris-Peg® (griseofulvin), Cesamet® (nabilone)\(^\text{63, 64}\).

Simple eutectic mixtures
A simple eutectic mixture can be described as an intimately blended physical mix of two crystalline components A and B which are miscible completely in liquid state but almost immiscible in solid state but when mixture of both these compounds in a particular composition (E) is cooled, they simultaneously crystal out. But when the other compositions are cooled, one of them crystallizes earlier than the other. Figure 1 shows two components: a hydrophobic drug and hydrophilic carrier forming a mixture with composition E\(^\text{65}\).

Characterization of Solid Dispersions
Solid dispersions can be characterized by various techniques like dissolution testing, thermo analytical methods like differential scanning calorimetry (DSC), X-ray powder diffractometry (XRPD), spectroscopic methods like Fourier transform infrared spectroscopy (FTIR), microscopic methods including scanning electron microscopy (SEM) and polarization microscopy. In addition to characterization of
solid dispersions, these methods can also be used to distinguish solid dispersions in which drugs are molecularly dispersed (solid solutions), in which they are partly molecularly dispersed and physical mixtures of drug and polymers. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.\(^6\)\(^6\) Dissolution Data Analysis

Dissolution studies of the pure drug in its powder form, solid dispersions of drug and carrier can be carried out using dissolution apparatus. Thus obtained dissolution profiles can be compared by analysis of variance (ANOVA) based, model-independent and model dependent approaches.\(^7\) ANOVA methods detect statistically significant differences between dissolution profiles.\(^7\)\(^1\) Model-independent approaches are based on the ratio of area under the dissolution curve (dissolution efficiency) or on mean dissolution time. Relative performance of different concentrations of carriers in solid dispersions can be found by computing percent Dissolution Efficiency (%DE) and mean dissolution time (MDT).

\[
y(t) = \frac{\int_{0}^{t} F(t) \, dt}{\int_{0}^{\infty} F(t) \, dt}
\]

Where, \(y(t)\) is the drug percent dissolved at time \(t\)

\[
MDT = \frac{\sum_{j=1}^{n} y_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j}
\]

Where \(j\) is the sample number, \(n\) is the number of dissolution sample times, \(t_j\) is the time at midpoint between \(t_{j-1}\) and \(t_{j+1}\) and \(\Delta M_j\) is the additional amount of drug dissolved between \(t_j\) and \(t_{j+1}\). In model-dependant approaches, release data can be fitted to different kinetic models.\(^7\)\(^2\)\(^-\)\(^7\)\(^5\) (Given in Table).

<table>
<thead>
<tr>
<th>Solubility definition</th>
<th>Parts of solvent required for one part of solute</th>
<th>Solubility range (mg/mL)</th>
<th>Solubility assigned (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very soluble</td>
<td>&lt;1</td>
<td>&gt;1000</td>
<td>1000</td>
</tr>
<tr>
<td>Freely soluble</td>
<td>From 1x10</td>
<td>100-1000</td>
<td>100</td>
</tr>
<tr>
<td>Soluble</td>
<td>From 10 to 30</td>
<td>33-100</td>
<td>33</td>
</tr>
<tr>
<td>Sparingly soluble</td>
<td>From 30 to 100</td>
<td>10-33</td>
<td>10</td>
</tr>
<tr>
<td>Slightly soluble</td>
<td>From 100 to 1000</td>
<td>1-10</td>
<td>1</td>
</tr>
<tr>
<td>Very slightly soluble</td>
<td>From 1000 to 10000</td>
<td>0.1-1</td>
<td>0.1</td>
</tr>
<tr>
<td>Practically insoluble</td>
<td>&gt;10000</td>
<td>&lt;0.1</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Table 2: Carriers used in solid dispersion preparations**

<table>
<thead>
<tr>
<th>Type Of Carrier</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrophilic carriers</td>
<td>polyethylene glycols (PEG molecular weight 1500-20000), polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), plasdone S630, poloxamer (188, 407), hydroxy propyl methyl cellulose (HPMC), mannitol, (\beta)-cyclodextrin</td>
</tr>
<tr>
<td>surface-active or self-emulsifying agents</td>
<td>bile salts, lecithin, lipid mixtures, Gelucire 44/14 and poloxamer (188, 407)</td>
</tr>
<tr>
<td>enteric polymers</td>
<td>hydroxypropyl methylcellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), Eudragit L100 and S100 and Eudragit E</td>
</tr>
</tbody>
</table>

**Table 3: Kinetic models used for fitting dissolution data**

<table>
<thead>
<tr>
<th>Model</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero order</td>
<td>(F = kt)</td>
</tr>
<tr>
<td>Baker-Lonsdale Peppas</td>
<td>(F = k t^n)</td>
</tr>
<tr>
<td>Peppas</td>
<td>(1 - (1 - F)^{1/n} = k t)</td>
</tr>
<tr>
<td>Higuchi</td>
<td>(F = k t^{1/2})</td>
</tr>
<tr>
<td>First order</td>
<td>(F = 1 - e^{-kt})</td>
</tr>
<tr>
<td>Weibull</td>
<td>(F = 1 - e^{-\left(\frac{t}{\tau}\right)^\beta})</td>
</tr>
</tbody>
</table>

\(F=\) Cumulative fraction dissolved of drug. In the corresponding equation the \(t_0\) is the time-lag, \(\tau\) is the scale parameter, and \(\beta\) is the shape parameter.
SUMMARY AND FUTURE OUTLOOK

Increase in the understanding of solid state properties of drug molecules, their evaluation and modification towards more stable and better dissolution characteristics have created a series of new technologies in the past years. Dissolution is the rate limiting step in the process of absorption from gastrointestinal tract and hence affects the bioavailability of oral solids. This is more significant in case of hydrophobic drugs. The techniques described above alone or in combination may be used to overcome this limitation. Appropriate selection of technique and carrier can improve the oral bioavailability, reduce dose frequency, and show better subject compliance, with a low cost of formulation and therapy. Experience with solid dispersions is a very fruitful approach in improving the release rate and bioavailability. Problems related to large scale production, physical stability,
high drug to carrier ratio in formulation have become the cause for this limited success. Formulation of high dosed drugs to an appropriate sized tablet or capsule that can be easily swallowed is a problem if the carrier to drug ratio is more. The application of hot melt extrusion is an important breakthrough for scale-up of solid dispersion manufacture. After applying techniques to improve its solubility, the other aspect that must be considered for hydrophobic drugs is the correlation between in vitro and in vivo results. The continuous scientific evolution also makes us aware of the complexity in identifying and developing innovative therapies for unmet medical needs. Neither medicinal chemistry or pharmacology nor pharmaceutical sciences alone will solve the challenges for developing safe and effective therapies for the unmet needs, it is a multidisciplinary approach. Solubility enhancement approaches have been developed and will continue to evolve.

ACKNOWLEDGEMENT
We thank Dr. Sudarsan Biswal (Drugs control Department, Govt. of Orissa) for his discussions on some aspects of the manuscript.

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