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Review Article

SOLUBILITY ENHANCEMENT BY SOLVENT DEPOSITION TECHNIQUE: AN OVERVIEW

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ABSTRACT

Most of the drugs being discovered with potential therapeutic effect are water insoluble in nature due to which they are poorly absorbed from the site of administration. With number of solubility enhancement techniques known, solid dispersion is mostly used in oral formulations. However, delivery of solid dispersion into tablet and capsule dosage form is a challenging task due to physiochemical, stability and manufacturing problems. Solvent deposition technique can overcome the problems faced by solid dispersion up to a great extent. Excipients used in tablet formulation having high surface area can be used as carrier or adsorbent. Solvent deposition technique when applied with superdisintegrants provided fastest release of drug. Thus, a combination of drug adsorption in minuscular form on carrier and disintegrant action gives good results.

Keywords: Water insoluble drugs, Solid dispersion, Solvent deposition system, Carrier, Superdisintegrants.

INTRODUCTION

Solubility is defined as the concentration of the solute in a solution when equilibrium exists between the pure solute phase and the solution phase. At low concentrations, solubility is difficult to measure analytically, and at high concentrations, solubility is not an issue in the discovery process.[1] To ensure a rapid and efficient formulation development, a solubility classification for the selection of an appropriate formulation system for highly active compounds with good permeability (P_{eff}> 10^{-6} cm/s) was introduced. This formulation system suggests that standard formulations can be applied for the compounds with the solubility greater than 100µg/ml and only minimum effort is required. For the compounds with solubility greater than 10µg/ml and less than 100µg/ml, enabling formulation may be needed depending on dose. If the solubility is less than 10µg/ml, enabling formulations are considered mandatory. [2]

It was in August 2000, the U.S. FDA issued Guidance for Industry covering the Biopharmaceutical Classification System (BCS). The BCS is a scientific framework for classifying a drug substance on the basis of its equilibrium aqueous solubility and intestinal permeability. [3] When combined with the *in vitro* dissolution characteristics of a drug product, the BCS takes into account three major factors: solubility, intestinal permeability and dissolution rate. These three factors govern the rate and extent of oral drug absorption for immediate release solid oral dosage forms. [4] The BCS defines four classes of drug substances on the basis of their solubility and permeability characteristics. [5]

	High Solubility	Low Solubility
High permeability	Class I	Class II
Low permeability	Class III	Class IV

Class Boundaries Used In BCS:

- A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml water over a pH range 1 to 7.5.
- A drug is considered highly permeable when the extent of absorption in humans is determined to be 90% of an administered dose, based on the mass balance or in comparison to an intravenous dose (drug and metabolite).
- A drug product is considered to dissolve rapidly when 85% of the labeled amount of substance dissolves within 30 minutes, using USP apparatus I or II in a volume of 900 ml buffer solution. [6]

WATER INSOLUBLE DRUG CANDIDATES

With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly water-soluble drugs are being identified as potential therapeutic agents. It is commonly recognized in the pharmaceutical industry that on average more than 40% of newly discovered drug candidates are poorly water soluble. Poor "drug like" properties of lead compounds led to ineffective absorption from the site of administration, which has been designated as an important part of the high clinical failure due to poor pharmacokinetics. [7]

Drugs with very low aqueous solubility usually have sizeable inter- and/or intra-subject variability in their pharmacokinetics, [8] which makes the study design and conduct of Phase I studies very challenging, makes the assessment of dose–response and exposure response relationships more difficult, and makes the dose recommendation and optimization less feasible for NDA and product labeling. Water insoluble drugs usually have high propensity for drug interactions at absorption level, such as food interaction, [9] interactions with GI prokinetic agents, [10] especially if these drugs also have narrow therapeutic windows. Such hurdles and risks should be taken into consideration when a clinical drug development plan is put together.

SOLUBILITY ENHANCEMENT TECHNIQUES

Some drugs classified as low solubility drugs on the basis of *in vitro* measures of aqueous solubility may have acceptable *in vivo* solubility because of either pH dependence or solubility in GI fluids. If these drugs with acceptable *in vivo* solubility are BCS Class II, they would then be expected to have acceptable oral bioavailability from standard solid oral dosage forms. [3] For BCS Class II drugs that are shown to have low bioavailability owing to their poor solubility and inability to dissolve rapidly, the selection of formulation is often of great importance in developing a successful product for oral administration of Class II drugs. The bioavailability of these drugs can be improved by several formulation approaches (Figure 1).

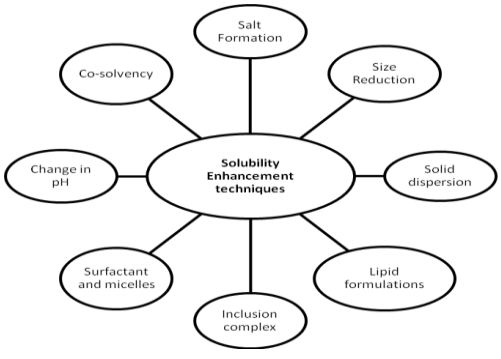

Figure 1: Methods of solubility enhancement for poorly soluble drugs

SOLID DISPERSION

As early as in 1961, the concept of solid dispersion to enhance absorption of poorly water-soluble drugs was developed. It involved formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. [11, 12] Later, it was demonstrated that a certain fraction of the drug may also be molecularly dispersed in the matrix, forming solid solutions, while other investigators reported that the drug may be embedded in the matrix as amorphous materials. [13, 14] On the basis of these considerations, Chiou and Riegelman defined solid dispersion as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states. [15]

Challenges in development of solid dispersion

Among various approaches, preparing solid dispersions has successfully improved dissolution rates for water insoluble drugs. Despite its importance and potential advantage in the development of poorly water-soluble drugs, solid dispersion had limited application in pharmaceutical dosage form development for commercial use. [16] Solid dispersions were typically prepared by either of two main techniques: a fusion or solvent method. Considerable difficulties lie in manufacturing this solid dispersion and with physical instability on storage.

- For example, potential problems associated with the fusion method include drug degradation and drug/carrier immiscibility in the molten state. [17]
- Besides that solid dispersion prepared by melting method can be difficult to pulverize as well as involves problem in preparation of dosage form due to soft and tacky nature and possesses poor flow characteristics. [18]
- When employing the solvent method, it is often difficult to find a common solvent for a hydrophobic drug and a hydrophilic carrier. Large volumes of organic solvents as well as heating are usually required to achieve initial solubilization, causing possible risks and could be prohibitively expensive. [17]

By reviewing the literature on solid dispersion, Serajuddin in 1999 had reported that only two solid dispersion products were introduced in the market during the first four decades of the availability of this technology (Gris-PEG, Novartis; Cesamet, Lilly). [19] Various issues that impeded the commercial development of solid dispersions include:

(a) Inability to scale bench-top formulations to manufacturing-sized batches.

(b) Difficulty to control physicochemical properties.

(c) Difficulty in delivering solid dispersion formulations as tablet or capsule dosage form.

(d) Physical and chemical instability of the drug and/or the formulation itself. In addition, a fundamental knowledge of solid dispersion principles that could lead to successful products was also inadequate. [16]

SOLVENT DEPOSITION TECHNIQUE

Reduction of particle size remains the accepted method for increasing dissolution rates. However, upon micronization, hydrophobic drugs have a tendency to clump when exposed to the dissolution medium. [20] Sekiguchi and Obi proposed that the incorporation of a microcrystalline or molecular dispersion of a poorly soluble drug in a solid matrix of water-soluble carrier would increase the dissolution rate and absorption of the drug. [11] Since then, modifications of the technique have been suggested under a variety of names, including solid solutions, eutectics, co-precipitates, and fast-release solid dispersions. [21]

This new method was investigated for increasing the dissolution rate of drug by depositing drug in "minuscular form" on the surface of an adsorbent. This technique was termed as solvent deposition. The term "minuscular form" implies that the drug has undergone molecular micronization when it is dispersed on the extensive surface of the micro particulate adsorbents. It is an approach used for increasing the dissolution rates of relatively insoluble powders. [22]

Mechanism of drug release

During dissolution, since carriers are insoluble, the minuscular drug system releases only free, absorbable drug into solution. Hydrogen bonding and van der Waals' forces are accounted for desorption of the drug from the adsorbent surface. The minuscular drug delivery system can be regarded as drug in a micro-particulate form molecularly dispersed on the very extensive surface of carrier. The resulting decrease in particle size and the concomitant increase in surface area serve to increase the thermodynamic activity of the drug in the dispersed state which, in turn, greatly enhances the rate of solution of the drug. [22]

The solvent deposition system is a solid preparation in which a drug is deposited from a solvent on the surface of a matrix. This step is usually done by simple evaporation of the solvent used for distribution of the drug onto the matrix. This is accomplished by equilibration of the drug in an organic solvent on water-insoluble excipients with an extensive surface e.g., fumed silicon dioxide. [22, 23] Till now a wide variety of drug have been employed in making solvent deposited solid dispersion with different types of water insoluble carriers as mentioned in Table 1.

Advantages associated with solvent deposition system over other solid dispersion

- This method is readily adaptable for thermolabile drugs and carriers.
- Many polymers with high melting temperatures that cannot be utilized in melt solid dispersion processes could be carriers for solvent deposited drug formulations.
- Tackiness and stickiness associated with melt or fusion method can be avoided.
- A common solvent having solubility for both hydrophobic drug and a hydrophilic carrier is not necessary. [17]

General method of preparation for solvent deposition system

Fine powders of the drug and different water-insoluble adsorbents or carriers are accurately weighed in certain ratios (Figure 2). Drug is added to organic solvent in a beaker sufficient enough to dissolve the drug. Then required quantity of adsorbent is added to above drug solution. This slurry or gel are stirred by a magnetic stirrer and evaporated by a stream of filtered air or water bath. Temperature maintained for evaporation is generally a little higher than the boiling point of solvent to allow organic solvent to evaporate. The samples are then placed in a heated vacuum desiccator or vaccum oven to facilitate the drying process. The solid masses are then pulverized in a mortar and passed through sieve. These powders are remixed by tumbling end over end for few minutes. Then solvent deposited system is stored in desiccators for future use. [21, 22, 24-27]

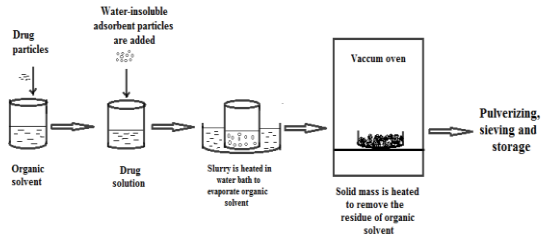

Figure 2: Schematic diagram of method of preparation

SOLVENT DEPOSITION SYSTEM USING SUPERDISINTEGRANTS

Disintegrants are commonly used in tablets to assist disintegration. The disintegration action of swelling, wicking and deformation during hydration resulting in deaggregation and wetting of the drug

particles may provide a high surface area for dissolution. An attempt was made to employ tablet disintegrants for drug deposition to investigate their influence on drug dissolution. It was suggested that the dissolution rate of the drug can be improved by combination of the disintegration effect with the solvent deposition effect. [28]

It was attributed that increase in the dissolution rate from solvent depositon system is due to the micronization of drug particles on the large surface of the excipient when the solvent is evaporated during the preparation of the dispersions. [21] In addition to the micronization, conversion of drug to an amorphous form during the preparation might have also contributed to the increased dissolution rates observed with the solid dispersions. Since the amorphous form is the highest energy form of a pure compound, it produces faster dissolution rates. The higher dissolution rates observed with the dispersions in superdisintegrants when compared to other excipients may be due to their easy and rapid dispersibility in the aqueous dissolution fluids. [29] Solvent deposition systems prepared with different drugs and superdisintegrant are mentioned in Table 2.

Table 1: Solvent deposition system prepared with different drugs and carrier

Investigators	Water insoluble drug	Solvent Used	Carrier used
Monkhouse *et al.*[21]	Indomethacin, Aspirin, Sulfaethidole, Griseofulvin, Reserpine, Probucol, Chloramphenicol, Oxolinic acid, hydrochlorothiazide	Acetone, Chloroform, Dichloromethane	Fumed silicon dioxide, silicic acid
Johansen *et al.*[22]	Phenylbutazone, Norethindrone, Digoxin	-Acetone -Chloroform -Chloroform-MeOH (1:1)	Lactose, starch, silicon dioxide
Liao *et al.* [23]	Corticoids (Prednisone, Prednisolone, and Hydrocortisone)	N,N-dimethylacetamide-polyethylene glycol 400 (7:3 v/v)	Nonporous and porous amorphous silicas
Alsaidan *et al.* [24]	Indomethacin	Alcohol solution	Kaolin and microcrystalline cellulose (Avicel PH 101)
Dastmalchi *et al.* [25]	Glibenclamide	Chloroform	Microcrystalline cellulose (Avicel PH-102 and RC591)
Barzegar-Jalali *et al.* [26]	Piroxicam	Dichloromethane	Microcrystalline cellulose (Avicel PH 101)
Cui *et al.* [27]	Nitrendipine	Ethanol and dichloromethane (1/2 v/v)	Microcrystalline cellulose, light anhydrous silicic acid, lactose and low substituted hydroxypropyl cellulose
Kakkar *et al.*[35]	Chlordiazepoxide	Dichloromethane	Starch-lactose granules

Table 2: Solvent deposition system prepared with different drugs and superdisintegrant

Investigators	Water insoluble drug	Solvent Used	Carrier and superdisintegrant used
Law *et al.*[28]	Griseofulvin	Acetone	Primojel (modified Starch or sodium starch glycolate), Mobile Starch (unmodified wheat starch) and Nymcel (modified cellulose)
Chowdary *et al.*[29]	Itraconazole	Dichloromethane	lactose, microcrystalline cellulose, Primogel, Kollidon CL, and Ac-Di-Sol
Yen *et al.* [30]	Nifedipine	Chloromethane	lactose, Explotab (sodium starch glycolate), Ac-Di-Sol (Croscarmellose sodium), or Kollidon CL (Crospovidone)
Williams *et al.*[17]	Ibuprofen	Ethanol	Microcrystalline cellulose and cross-linked polyvinylpyrrolidone
Chaulang *et al.*[31]	Furosemide	Water-ethanol (1:1 ratio)	Sodium starch glycolate

CHARACTERIZATION OF SOLVENT DEPOSITION SYSTEM

1) Differential Scanning Calorimetry (DSC)

The drug has a characteristic peak, absence of this peak in DSC thermogram indicates that the drug is in amorphous form in formulation and it is molecularly dispersed within the system. [17, 27, 29-31]

2) Fourier transform infrared (FTIR) spectroscopy

FTIR studies are performed to determine the chemical interaction between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates there is no chemical interaction. [25, 26, 31]

3) X-ray diffraction (XRD) studies

The XRD pattern of pure drug exhibits sharp, highly intense and less diffused peaks indicating the crystalline nature of drug. The XRD patterns of the physical mixture are simply a superimposition of each component with respect to the peaks of drug. The lack of sharp peaks in the diffractograms of solid dispersions indicates that the drug is in the amorphous form in these dispersions. [21, 25, 26, 31]

4) Dissolution rate studies

Dissolution studies are performed using USP dissolution apparatus, generally paddle apparatus in dissolution medium which may be, distilled water [28] or 0.1 N HCl with or without surfactant [26] or Simulated Gastric Fluid pH1.2 [31] or Phosphate buffer. [25] Then dissolution rate is estimated.

5) Scanning Electron Microscopy (SEM)

The SEM studies are performed to indicate crystallization processes with crystals and aggregates of sizes that increase with an increasing drug content. [28] The disappearance of large crystals of drug indicates decrease in crystallinity or conversion to amorphous form. [22]

6) *In vivo* evaluation

The solvent deposition technique has been proved to be an efficient approach for the enhancement of drug release of poorly soluble drugs. The absorption of glibenclamide drug was observed in white male healthy albino rabbits by measuring drug serum concentration. The pure drug release was compared with physical mixture of drug and Avicel PH102 (1:19) and its solid dispersion (1:19) administered in an aqueous suspension form. Glibenclamide serum

concentrations for solid dispersion at times 2-6 hr were significantly higher than those for pure drug and the physical mixture. Serum glucose concentration was also measured in male rabbits based by the standard glucose oxidase method using a commercial kit according to the supplied instruction. Serum glucose concentrations for solid dispersion at times 1 and 2 hr were found to be significantly lower than those for pure drug and the physical mixture. [25]

Different solvent deposition systems and simple physical mixtures of piroxicam and carrier were prepared and assessed for their dissolution characteristics and *in vivo* anti-inflammatory effects. Anti-inflammatory effects were detected in the carrageenan paw oedema assay in female wistar rats. Piroxicam delivered in form of solvent deposition systems showed significantly more anti-inflammatory effects and suppressed the total oedema to 51%. This pronounced anti-inflammatory effect of solvent deposition systems (1:9 - drug: Avicel PH101ratio) was attributed to the increased availability due to enhanced gastrointestinal absorption of the drug as a result of its improved dissolution rate. [26]

APPLICATION

1) **Solubility enhancement for drugs in Capsule and Tablet dosage form**

   The solvent deposition system of griseofulvin using disintegrants Primojel, Mobile Starch and Nymcel were punched to form tablet containing 125 mg griseofulvin. The tablets of the Primojel system demonstrated the highest dissolution rate. This was resulted from the fast disintegration time of the tablets and the small particle size of the griseofulvin. [28]

   Solid dispersions involving superdisintegrants could be formulated into tablets. The itraconazole solid dispersion tablet was prepared with superdisintegrants (Primogel, Kollidon CL, and Ac-Di-Sol). These tablets, apart from fulfilling all official and other specifications, exhibited higher rates of dissolution and dissolution efficiency (DE) values. [29]

   The dissolution of nifedipine from the solvent deposition system in capsule was compared to that in the tablet dosage forms prepared using superdisintegrants Ac-Di-Sol, Kollidon CL, and Explotab. [27] The capsule dosage form showed less dissolution than tablets because the loose content, without compression, possesses large void space inside the capsule, and that the void space allows the swelling of superdisintegrants. This makes superdisintegrants relatively ineffective in enhancing disintegration and dissolution of the capsule dosage form.[32]

   Tablet containing an equivalent of 40 mg furosemide solid dispersion was prepared by solvent deposition method with sodium starch glycolate. When compared with commercial tablets of furosemide, solid dispersion tablets were significantly better ($P < 0.05$) than Lasix® (2.34-fold) and Sanilex® (3.44-fold). [31]

2) **To increase flow property**

   In one of the study two nonporous and three porous amorphous silicas were used as dispersion media to convert corticoid solutions into free-flowing powders. The corticoids (prednisone, prednisolone, and hydrocortisone) were dissolved in N, N-dimethylacetamide-polyethylene glycol 400 (7:3 v/v) and their 10% (w/v) solutions were mixed with the silicas (1:3 v/w). Simple admixture of the corticoid solutions with amorphous, porous, or nonporous silicas converted them to free-flowing powders. The corticoids in such powdered solutions are thus in a molecular state of subdivision. Dissolution rates of such water-insoluble, neutral compounds were found to increase due to localized dilution with simulated GI media which does not cause their precipitation. [23]

3) **Sustained release microspheres containing solid dispersion structure**

Sustained release microspheres having solid dispersion structure were prepared for nitrendipine, which is a water insoluble drug. In this investigation, the quasi-emulsion solvent diffusion method for preparation of microspheres and the solvent deposition method were combined in one step. The solvent deposition method was used as one of the solid dispersion techniques. The Aerosil, an inert solid dispersing carrier was introduced in this formulation to improve the dissolution rate of water insoluble drug and the Eudragit RS was employed as the controlled release polymer to bind the inert solid dispersion carrier into microspheres and control the drug release rate. The combining of both the method into one simplified the traditional manufacturing processes for sustained-release preparation of poorly water-soluble drug, which usually consists of the preparation of solid dispersion, crushing, sieving, and mixing with other excipients, being granulated for compacting into tablet and being coated with suitable coating materials if necessary. And it was indicated that this method could also be used to improve the micromeritics properties of solid dispersion system with simple preparation process. [33, 34]

CONCLUSION

From the studies performed by investigators, it is quite evident that the use of adsorbents can facilitate the dissolution process of relatively insoluble powders. Excipient used for preparing tablet with high surface area can be a good candidate for use as carrier in solvent deposition system. Employing superdisintegrants for preparing solvent deposition system have shown best results in comparison to other excipients. The significant enhancement in aqueous solubility and dissolution of various drugs achieved by solvent deposition technique opens up the possibility of development of solid dispersion system with newer water-insoluble and inert excipients.

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