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Review Article

MINI REVIEW: JOURNEY OF SOLID DISPERSION TECHNIQUE FROM BENCH TO SCALE

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ABSTRACT
Solubility is one of the greatest pitfalls in the design of drug delivery systems. Poorly-soluble drugs not only increases adverse reactions and cost of therapy but also reduces the bioavailability of the drug. Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Many approaches have been discovered for the purpose, among them solid dispersion is most widely used due to marvellous potential for improving drug solubility, by improving bioavailability and dissolution rate. Although there is a great interest in solid dispersion systems from the past four decades to increase solubility of poorly soluble drugs, their commercial use has been very limited. This is due to many reasons such as difficult to incorporate into dosage forms, laborious and expensive methods of preparation, and stability of the drug and vehicle, primarily because of manufacturing difficulties and stability problems. Due to these hurdles, the solid dispersion technique has been seeing a setback. The present review focuses on these problems so that an elaborate research is carried out and the technique does not recede.
KEYWORDS: Solubility, bioavailability, dissolution, solid dispersion.

INTRODUCTION

Solubility is the phenomenon of dissolution of solid in liquid phase to give a homogenous system. It is one of the most important parameter to achieve desired concentration of drug in systemic circulation for optimum pharmacological response. The major concern in drug development is the increasing number of new chemical entities which are poorly soluble and not well-absorbed after oral administration[1,2]. Such a problem can distract from the drug's efficacy[3]. The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Currently only 8% of new drug candidates have both high solubility and permeability and 40% of the drugs are poorly soluble which leads to poor dissolution in the gastro intestinal tract (GIT)[4]. Hence, incomplete and erratic absorption ultimately limits its clinical utility. Further, poorly soluble drugs are generally administered at much higher doses than the actual dose in order to achieve necessary drug plasma levels leading to increased adverse reaction & cost of therapy. Moreover, it is responsible for inappropriate pharmacological response and poor patient compliance[5]. The formulation of poorly water-soluble drugs is one of the most challenging tasks. An enhancement in solubility and the dissolution rate can improve oral bioavailability of drugs, which will improve the therapeutic efficacy and patient compliance[6]. There are number of formulation approaches to solve these problems such as particle size reduction, modification of crystal habit, solubilisation using surfactants and complexation[7] (Table 1).

These techniques however cannot be fully exploited because of various limitations. For instance, the drugs used in micronization should not have a high dose number as it does not change the saturation solubility of the drug. Further, there are chances of chemical degradation of the active constituent due to high processing conditions. Nano-suspension is a promising method to improve the saturation solubility as well as dissolution velocity. Conversely, the use of high concentrations of surfactants makes the dosage form toxic for i.v administration[8,9]. It also produces particles with broad size distribution. Besides, the principle of particle size reduction cannot be useful for nearly insoluble drugs (<0.1mg/mL)[10]. The polymers used for modification of crystal habit in polymorphs/pseudo polymorphs have a tendency to decrease the physical stability of the drug. Micro-emulsions have attracted considerable interest due to their simplicity of preparation, clarity and ability to be filtered[11]. O/W

emulsions are more popular as they enhance the solubility of the drug in the oil phase and avoid hepatic first pass-metabolism[12]. Nevertheless, in addition to the need of high concentrations of surfactants for the formulation of emulsions, drugs which are poorly soluble in both aqueous and organic media cannot be formulated by this technique. Micro-emulsions are also sensitive to temperature and pH changes and are relatively metastable. The major drawback is again the need of high concentrations of surfactants/co-surfactants making them unsuitable for i.v administration[13,14]. Further, dilution of micro-emulsions below the critical micelle concentration of the surfactants could cause precipitation of the drug[15,16]. SMEDDS (Self micro-emulsifying drug delivery systems) were originally discovered to overcome the stability problem of microemulsions[11]. However, they too suffer from the difficulty of formulating hydrophobic drugs (log P value $\leq$ 2) into such formulations[17, 18]. SMEDDS formulations are not advisable for long-term use due to the potential of causing diarrhoea[19]. In addition, drugs with high doses pose difficulty in formulation. Above all, the various emulsified delivery systems can only be used orally because of the nature of the excipients. The concept of complexation is advantageous compared to other methods owing to the toxicity problems of surfactants. On the other hand, the regulatory and quality control issues related to presence of ligand may add complication and cost to the development process[20, 21].

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions are prepared by using several methods, such as the fusion (melt) method, hot melt extrusion and the solvent method. Solid dispersion is generally acceptable method for BCS class II drugs and has been discussed in detail by various authors[22,23]. It is becoming increasingly popular because of many potential advantages such as suitable for oral as well as i.v delivery, free from toxic constituents, simple process and reduces pre-systemic metabolism (Figure 1). Formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating for poorly water soluble drugs. Further, the concept of solid dispersion is better compared to other methods because of many potential reasons (Table 2). Regardless of numerous advantages and extensive research only a few drugs have been successfully launched in market (Table 3). This might be because of many possible problems discussed under challenges in solid dispersion approach.

CHALLENGES IN SOLID DISPERSION APPROACH

In spite of much research in the area much success has not been possible because of many prospective drawbacks such as

- problems in scale up
- cost-prohibitive nature
- stability of the drug and vehicle
- changes in crystallinity of the drug
- requirement of high percentage of carrier materials (more than 50-80% w/w)

These problems have been surmounted to some extent by some possible solutions. For instance, the problem of tackiness due to the use of water soluble (low melting point) polymers such as mannitol, poly-vinyl-pyrrolidone and poly-ethylene-glycol, have been resolved by using hydrophilic swellable polymers such as sodium carboxy methyl cellulose, sodium starch glycolate and pregelatinized starch[24]. Further, combined carriers can be used instead of using high amounts of single carrier material. This approach not only reduces the amount of carrier material required but also increases the drug dissolution[8,9]. Some other alternative strategies have been developed to commercialize solid dispersions.

Spraying on sugar beads using a fluidized bed coating system

The approach involves a fluidized bed coating system, wherein a drug-carrier solution is sprayed onto the granular surface of excipients or sugar spheres to produce either granule ready for tableting or drug-coated pellets for encapsulation in one step[25,26]. The technique is useful in solving problems related to material handling and compression. Solid dispersions are soft, waxy and possess poor compressibility and flowability. If they are encapsulated in hard gelatin capsule it delays the dissolution process of drug because the process will not start till the capsule shell has disintegrated to allow solid dispersion to come in contact with the gastric fluid and gelatin capsule shells are denaturated[27]. Solid dispersions of itraconazole using hydroxyl-propyl-methyl-cellulose (HPMC) in an organic solvent of dichloromethane and ethanol have been successfully manufactured using this approach[28].

Direct capsule filling

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. However, PEG cannot be used as a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolves more

rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevents further dissolution of the drug[29]. Therefore, surfactants such as polysorbate 80, phosphatidyl choline) must be mixed with the carrier to avoid formation of a drug-rich surface layer[30]. Changes in crystallinity have been a major problem with solid dispersion resulting in their instability. The crystallization of ritonavir from the supersaturated solution in solid dispersion system was responsible for the withdrawal of ritonavir capsule from the market. This major obstacle has been unravelled by direct capsule filling technique. Hard gelatin capsules of Triamterene have been successfully formulated using a Zanasi LZ 64 capsule filling machine (Zanasi Co., Bologna, Italy)[31].

Electrostatic spinning method

A more recent technology is the combination of solid dispersion with nanotechnology[32]. In this process, a liquid stream of a drug/polymer solution is subjected to a potential between 5 and 30 kV. When electrical forces overcome the surface tension of the drug/polymer solution at the air interface, fibers of submicron diameters are formed. As the solvent evaporates, the formed fibers can be collected on a screen to give a nonwoven fabric, or they can be collected on a spinning mandril. The fiber diameters depend on surface tension, dielectric constant, feeding rate, and electric field strength[33]. Itraconazole/ HPMC nanofibers have been prepared using this technique[34].

FUTURE PROSPECTS

Solid dispersions are one of the most attractive processes to improve drug's poor water solubility. Two trends strongly favour an increasing role for solid dispersions in pharmaceutical development: the increasing number of drug candidates which are poorly soluble and the substantial improvements in the manufacturing methods for solid dispersions that have been made in the last few years. In recent years, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited. Much research is still required for solid dispersion technique to flourish.

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Table 1: Various approaches for solubility enhancement

TECHNIQES	SUBTYPES
Particle size reduction	i) Micronization ii) Nanosuspension
Modification of the crystal habit	i) Polymorphs ii) Pseudo polymorphs
Solubilization by surfactants	i) Micro-emulsions ii) Self micro-emulsifying drug delivery systems
Complexation	i) Use of complexing agents
Drug dispersion in carriers	i) Solid solutions ii) Eutectic mixtures iii) Solid dispersions

Table 2: Comparison of solid dispersion method with other techniques for solubility enhancement

Technique	Limitations	Solution offered by Solid dispersion technique	References
Particle size reduction- Micronization Nanosuspension	Not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Chemical degradation of products due to high temperatures. Cannot be useful for nearly insoluble drugs (<0.1mg/mL) Wide size distribution and potential toxicity of non-aqueous solvents, high concentration of undesired surfactants and residual solvents. Not suitable for i.v administration	Produces particles with narrow size distribution Especially suited for poorly soluble drugs irrespective of dose Can be administered by oral as well as i.v. route Absence of extreme processing conditions	8,9,36, 37
Polymorphs/ pseudo polymorph	Most of the polymers used can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate	Problem of phase separation and crystal growth solved by alternative strategies	38,39,40
Micro-emulsions	Drugs that are poorly soluble in both aqueous and organic media cannot be formulated by this technique. High amount of surfactant/stabilizer is required	Suitable for drugs insoluble in aqueous and non-aqueous media Minimal amount of surfactants required	13,14
Self micro-emulsifying drug delivery systems (SMEDDS)	Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophillic phase. Drugs which exhibit limited solubility in water and lipids (typically with log P values of approximately 2) are most difficult to formulate Not advisable for long-term use due to the potential of causing diarrhoea	Suitable for poorly soluble drugs irrespective of dose or log P value (viz. meloxicam with a log P value of 1.5 have been formulated)	17, 18, 35
Complexation	Toxicity of complexing agent makes it difficult to administer The regulatory and quality control issues related to presence of ligand	No such complications exist	41

Table 3: Marketed solid dispersion formulations

Name of drug	Technology involved	Year of approval	Brand name	Company name	Reference
Griseofulvin	Melt Process	1975	Gris-PEG	Wander	[42]
Amprenavir	Melt process	2011	Agenerase	GlaxoSmithKline	[43]
Calcitriol	Melt granulation	2009	Rocaltrol	Roche	[43]
Cyclosporine	Spray freeze drying	2007	A/I neural	Novartis	[43]
Indomethacin	Fusion & Mold technique	2009	Indomethacin	Eisai Co	[43]
Nelfinavir mesylate	Solvent evaporation	1997	Viracept®	Agouron Pharmaceuticals	[43]
Ritonavir	Drug loading	2004	Norvir®	Abbott Laboratories	[43]
Nifedipine	Co-precipitation	2004	Adalat SL	Abbott Laboratories	[44]
Nabilone	Spray freeze drying	1977	Cesamet	Eli-Lilly	[44]

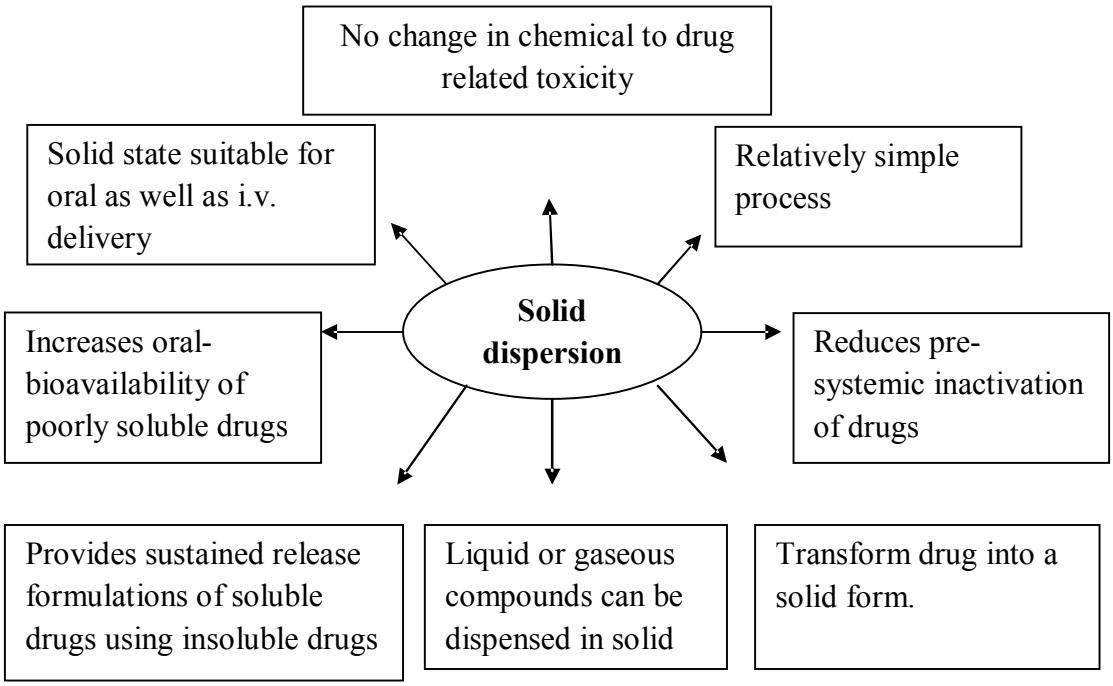

Fig 1: Benefits of solid dispersion technology