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Review article: Solid dispersion currently practiced in pharmaceutical field

Sakina Sultana[1] and A H M Saifuddin[1*]

[1]Department of Pharmacy, Jahangirnagar University, Savar, Dhaka- 1342, Bangladesh
[*]Author of correspondence, E-mail= ahm.saifuddin11@gmail.com

ABSTRACT

Improvement of bioavailability of hydrophobic drugs is a great challenge. Over the years a variety of solubilization techniques have been studied and widely used, as more than 40% newly drugs are poorly water soluble in pharmaceutical field. To improve such solubility issues, solid dispersion technique is widely used. This article reviews different technologies of solid dispersion, current trends, advantages and criticisms. The remaining portion of this article is focused on various formulations which are marketed by solid dispersion technology.

Key words: Bioavailability, hydrophobic drugs, solubilization techniques, pharmaceutical field and solid dispersion.

1 INTRODUCTION

Solid dispersion method has been widely employed to improve the dissolution rate, solubility and oral absorption of poorly water soluble drugs. Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate. Since the 1960s, many solid-dispersion formulations have been developed. Solid dispersions are prepared by various methods like fusion process, solvent process, fusion solvent process and supercritical fluid process (Sekiguchi and Obi, 1961). Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature along with various hydrophilic carriers such as polyethylene glycols, polyvinylpyrrolidone, hydroxylpropyl methylcellulose, gums, sugar, mannitol and urea (Tanaka *et al.*, 2006). Chiou and Reigelman,1971 first defined solid dispersion as dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting solvent method.

2 Mechanism involved in enhanced drug solubilization by solid dispersion technique

Although mechanism is not well understood yet, the basic principle includes complete removal of drug crystallinity and molecular dispersion of the poorly soluble compound 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. Drug in soluble hydrophilic carrier improves the dissolution rate by reducing particle size and increasing the particle porosity. Remaining drug is in amorphous state and Improving wettability and hence possibility bioavailability for poorly water soluble drug. The potential advantage of this technique is enormous. Recently surfactants have been included for betterment of formulation as in many cases. Thermodynamic instability and recrystalisation of drug becomes a problem. Hence surfactants are used to avoid recrystalization and potentiating their solubility.

3 Classification

Since the 1960s, many solid dispersion formulations have been developed. Currently there are seven major types of solid dispersions together with various subtypes. These solid dispersion types are summarized in Table 1, based on their number of phases and solid-state properties.

Table 1: Solid dispersion types

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Sl No	Solid dispersion types	Phases	Drug	Carrier	Subtype
1	Solid solution	1	Molecularly dispersed	Crystalline	Continuous, Discontinuous, Interstitial, Substitutional, Amorphous
2	Glass solution	1	Molecularly dispersed	Amorphous	
3	Compound or complex formations	1	Molecularly dispersed	Amorphous or crystalline	Acid-base paired complex, inclusion complex, co-crystal co-amorphous
4	Eutectic mixture	2	Crystalline	Crystalline	
5	Solid crystal suspensions	2	Crystalline	Crystalline	
6	Amorphous precipitation	2	Amorphous	Crystalline	
7	Glass suspensions	2	Crystalline	Amorphous or crystalline	Amorphous carrier, crystalline carrier

4 Current trends in solid dispersion techniques

4.1 First generation solid dispersions

The solid dispersions, which could be designed as first generation solid dispersions were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in solid dispersions. These have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

4.2 Second generation solid dispersions

In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier (Tanaka *et al.*, 2005). These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to produce amorphous forms of the drug and carriers (Mooter *et al.*, 2006). In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile.

4.3 Third generation solid dispersions

Recently, it has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties, therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization.

5 Characterization

Several methods have been used to characterize solid dispersions, apart from classical analytical techniques (Sheen *et al.*, 1995) such as

- Differential scanning Caloriemetry (DSC) for determination of glass transition temperature,
- X-ray diffraction (XRD)
- Infrared Spectroscopy (IR)
- Hot stage and electron microscopy
- Dissolution testing
- Raman Spectroscopy
- Scanning Electron Microscope (SEM)
- Methods for determination of residual solvents (e.g. GC, Karl-Fischer, Loss on drying or non-destractive methods like NIR)

Among these, thermal and spectral methods (i.e. DSC, XRD and IR) are of special interest.

6 Advantage of solid dispersion

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages of solid dispersions are as follows:

- Particles with reduced particle size
- Particles with improved wettability
- Particles with higher porosity
- Drugs in amorphous state

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7 Criticism of solid dispersion

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited. Problems of solid dispersion involves

- Formulation of solid dispersion into dosage forms is not easy
- The physical and chemical stability of drugs and vehicles is not easy to maintain
- Drug permeability
- Drug solubility in carrier
- Dose accuracy
- Drug : carrier ratio

Yet a number of formulations are successful and commercially these products are available. These are given in Table 2.

8 Current industrial application

Solid dispersion systems can provide numerous additional benefits (Anupama *et al.,* 2011). These benefits demonstrate the current contributions and future potential of solid dispersion systems towards improving drug therapies for a variety of important medical conditions whose treatment involves poorly water soluble drug (Williams *et al.,* 2007). Commercially marketed solid dispersions are given in Table 2.

Table 2: Commercially available solid dispersions

Commercial products	**Dispersant**	**Manufacturer Company, Country**
Afeditab (Nifedipine*)	Poloxamer or Polyvinylpyrrolidone (PVP)	Élan Corp, Ireland
Cesamet (Nabilone*)	Polyvinylpyrrolidone (PVP)	Valeant Pharmaceuticals, Canada
Cesamet (Nabilone*)	Povidone	Lilly, USA
Certican (Everolimus*)	Hydroxypropylmethylcellulose (HPMC)	Novartis, Switzerland
Fenoglide (Fenofibrate*)	Poltethylene glycol (PEG)	Life Cycle Pharma, Denmark
Gris-PEG (Griseofulvin*)	Polyvinylpyrrolidone (PVP)	VIP Pharma, Denmark
Gris-PEG (Griseofulvin*)	Polyethylene glycol	Novartis, Switzerland
Intelence (Etravirine*)	Hypromellose/ Microcrystalline cellulose	Tibotec, Yardley, PA
Isoptin SRE-240 (Verapamil*)	Various	Soliqs, Germany
Ibuprofen*	Various	Soliqs, Germany
Kaletra (Lopinavir* & Ritonavir*)	Polyvinylpyrolidone(PVP) / Polyvinyl acetate	Abbott Laboratories, USA
LCP-Tacro (Tacrolimus*)	HPMC	Life Cycle Pharma, Denmark
Rezulin (Troglitazone*)[a]	PVP	Pfizer, USA
Sporanox (Itraconazole*)	Hydroxypropylmethyl cellulose (HPMC)	Janssen Pharmaceutica, Belgium
Torcetrapib[b]	HPMC acetate succinate	Pfizer, USA

*=Drug, a=Withdrawn from market, b=Halted in phase III

9 Rationale behind in using the technique in pharmaceutical industry

The main reasons to use this technique in pharmaceuticals are

- To improve drug solubility
- To improve drug stability
- To mask the bitter taste of drug
- To obtain required release profile

10 Methods of preparation of solid dispersion

Various manufacturing methods for solid dispersions have been reported in literature. These are given below in Table 3.

Table 3: Methods of preparation of solid dispersion

Sl No	**Methods of preparation of solid dispersion**

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1	Melting or Fusion method
2	Solvent evaporation method
3	Modified solvent evaporation method
4	Solvent-melting method (melt evaporation)
5	Kneading method
6	Supercritical fluid (SCF) technology
7	Co-grinding method
8	Co-precipitation method
9	Spray drying method
10	Gel entrapment technique
11	Direct capsule filling
12	Lyophilization technique
13	Electrospinning method
14	Dropping solution method

Melting or Fusion and solvent evaporation methods are the two major processes of preparing solid dispersions.

10.1 Melting or fusion method

This method involves the preparation of physical mixture of a drug and a water soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The advantage of this technique is: It is economic and solvent less process. Preparation of solid dispersions by melting or fusion method is given in Table 4.

Table 4: Preparation of solid dispersions by melting or fusion method

Drug	Carrier	Melting temperature
Carbamazepine (Zerrouk *et al.*, 2001)	PEG 6000	200^0 C
Glyburide (Betageri *et al.*, 1995)	PEG 4000, PEG 6000	120^0 C
Itraconazole (Kapsi *et al.*, 2001)	PEG 3350, 8000, 20000, glycerol, HPMC	120^0 C
Ibuprofen (Newa *et al.*, 2008)	PEG 20000	90-95^0 C
Nifedipine (Mehta *et al.*, 2002)	Pluronic F-68	100^0 C
Oxazepam (Gines *et al.*, 1996)	PEG 1500. PEG 4000, PEG 6000	100^0 C, 150^0 C
Sodium ferulate (Li *et al.*, 2006)	Compritol 888 ATO	75^0 C
Triamterene (Arias *et al.*, 1995)	D-mannitol	165^0 C

10.2 Solvent evaporation method

After complete dissolution of drug and carrier in organic solvent, the solvent is evaporated. The solid mass is ground, sieved and dried. The preparation of solid dispersion of poorly soluble drugs by solvent evaporation method given in Table 5.

Table 5: Preparation of solid dispersion of poorly soluble drugs by solvent evaporation method

Drug	Carrier	Solvent	Solvent removal
ABT-963 (Chen *et al.*, 2004)	Pluronic F-68	Ethanol	Slowly evaporate at ambient condition over one week.
Carbamazepine (Sethia *et al.*, 2004)	PVP K30, Gelucire 44/14	Methanol	Under vacuum in a rota vapor at 40^0C and 45 rpm for 24 hours.
Diflunisal	PVP	Ethanol or	Under vacuum in a rotary

(Martinez-Oharriz *et al.*, 2002)		chloroform	evaporator at 40^{0}C.
Furosemide (Lannuccelli *et al.*, 2000)	PVP	Methanol	Using rotary evaporator under reduced pressure at 70^{0}C.
Felodipine (Won *et al.*, 2005)	HPMC, Poloxamer 188, Poloxamer 407, HCO-60.	Ethanol	Using a rotary vacuum evaporator set to 45^{0}and 45 rpm for 12 hrs
Itraconazole (Chowdary *et al.*, 2000)	Lactose, MCC, Primogel, Kolidone CL, AC-Di-Sol	Dichloromethane	Evaporated at 60^{0}C for 4 hrs
Nimesulide (Chowdary *et al.*, 2000)	B-CD	Water: methanol = 1:1	Evaporated at a temperature of 45^{0}C
Naproxen (Iqbal *et al.*, 2002)	Ethyl cellulose, lactose	Ethyl ether : methanol =1:1	Constantly stirred at 40^{0}C until complete evaporation.
Nilvadipine (Hirasawa *et al.*, 2003)	L-HPC, Croscarmellose Na,Carmellose,Carmellose -Ca, Crospovidone	Ethanol	Under reduced pressure at 45^{0}C
Nifedipine (Tanno *et al.*, 2004)	Hypermellose acetate succinate, hypermellose phthalate, povidone K30, methacrylic acid ethyl acrylate copolymer	Ethanol **:** dichloromethane =1**:**1	Evaporated at 60-80^{0}C
Piroxicam (Prabhu *et al.*, 2005)	DMPC, PEG 4600.	Chloroform	Under current of N_2 gas for a period of 6 hrs
Phenytoin (Franco *et al.*, 2001)	PEG 6000, PVP K30	Ethanol	Under reduced pressure at 40^{0}C.
Pizotifen malate (Margarit et al., 2001)	PVP	Chloroform: methanol=1:1	Evaporated in oven at 40^{0}C

11 Conclusion

One of the most challenging problems in pharmaceutical field is to increase the bioavailability of orally administered poorly water soluble drug. Solid dispersion technology extremely helps in improving the dissolution property of such drugs. Various techniques described in this review are successfully used for the preparation of solid dispersions in the bench and lab scale and can be used as industrial scale also.

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