Review Article

A Review on Solid Dispersion

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Abstract

The new drug entity is mostly poorly water-soluble; their oral bioavailability and solubility remain the major criteria for pharmaceutical formulations. Solid dispersion techniques have attracted much interest in improving the dissolution rate of highly lipophilic drugs. It improves their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. Use of one or more carrier for solid dispersion. The formulation of solid dispersion uses hydrophilic carriers. The poorly water-soluble drug comes in contact with a solid carrier or its solution. These types of drugs face challenges in tablets and capsules formulation. Solid dispersion involved several techniques. This review provides an overview on BCS classification system; several approaches for enhancement of drug dissolution/bioavailability of poorly soluble drug; classification of solid dispersion based on carrier involved, component involved and chemical nature; it also emphasis on the choice of the solvent; preparation of solid dispersion by various methods like kneading method, solvent evaporation method, fusion method or melting method, melting solvent method, melt agglomeration method, hot melt extrusion method, spray drying method, electrospinning method, co-grinding method, and co-precipitation; characteristics (FTIR, DSC[Differential Scanning Calorimetry], SEM[Scanning Electron Microscopy], In-vitro dissolution studies and Powder X-ray diffraction) and provides a list of solid dispersion available in the market.

Keywords: Bioavailability, carriers, solid dispersion, solubility, biopharmaceutical classification system.

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INTRODUCTION

Nearly about 40% of drugs suffer from poor aqueous solubility [1] because of which high doses requires to meet the therapeutic level [2]. After oral administration drug reaches to the systemic circulation, because of poor solubility the drug is not completely dissolved in GIT resulting in poor bioavailability and high intracellular and intercellular pharmacokinetic variability [3]. According to BCS (**Biopharmaceutical Classification System**) categories drug under four classes, based on their solubility and permeation [4]. Mostly, the drug has poor oral bioavailability, which is because of its low solubility in aqueous medium, and they belong to the BCS Class II. In the BCS Class II and IV, the rate-limiting steps are solubility and drug release. BCS Classification System is shown below in (**Fig. 1**).

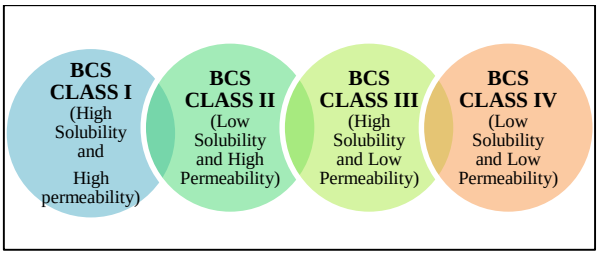

Figure 1: Showing BCS Classification system

Noyes Whitney Equation:

The rate of dissolution can be expressed by using this equation. It provides parameters for improving the solubility and dissolution rate [5- 9].

$Dc/Dt = A. D (Cs-C) /h$

Where,

Dc/Dt = Rate of dissolution,

A = Area available for dissolution

D = Diffusion coefficient,

Cs=solubility of the component in dissolution medium,
C = concentration of a component at time t,
H = Thickness.

As the Surface area increases the particle size reduces, and from the equation as the area increases the rate of dissolution decreases [10].

Solid Dispersion

A solid dispersion is the technique used to enhance the solubility of a poorly soluble drug. Sulphathiazole [11] was the first drug used in solid dispersion. The solid dispersion contains two components one is the hydrophilic carrier, and other is hydrophobic drug. According to Chiou and Riegelman (1971) the process of dispersion of drug in an inert carrier is known as SOLID DISPERSION [12]. This technique is also used to convert the component from crystalline form to amorphous form [13, 14].

Importance

Particle size reduction: As in solid dispersion the small form of particle size, provides a large surface area for absorption of the drug as a result it enhances the bioavailability and solubility of the drug [15].

- ❖ Wettability: It is the ability of liquid to remains in contact with the solid. The carriers play an important role in increasing the wettability, as the amount of carrier increases the solubility also increases [16].
- ❖ Amorphous state: If the drug is in crystalline form than its solubility is decreases but if it is converted into amorphous form, then its solubility and state of drug releases will be at the higher rate, because of there is no need of energy for breaking the lattice.
- ❖ Masking the unpleasant taste.

Approaches of Solid Dispersion:

1. Enhancing solubility and dissolution rate of poorly water-soluble drugs.
2. Enhancing permeability of poorly permeable drugs.

Table 1: Showing different approaches for enhancement of drug dissolution / bioavaila--bility of poorly soluble drugs

PHYSICAL MODIFICATION	CHEMICAL MODIFICATION	OTHERS
Micronization	Salt formation	Supercritical fluid method
Nano suspensions		Spray freezing
Polymorphs		Solvent evaporation method
Pseudo polymorphs		Hot melt extrusion
Use of surfactants		High -Pressure Homogenization
Use of Cyclodextrin		Inclusion Complexes
Dispersion of Drug in a carrier		Polymeric Alteration
Solid dispersion		Lyophilisation

Classification of Solid Dispersion:

I. Solid Dispersion Based on Number of Components Used:

Solid dispersion was classified in two types on the basis of components being used during preparation.

i. Binary solid dispersion: Two components are involves in the preparation of solid dispersion i.e. drug and a hydrophilic carrier.
   Drug + Carrier (PVP) = Binary Solid Dispersion
ii. Ternary solid dispersion: Three components (drug, hydrophilic carrier and surfactant or any other agent which enhances solubility) are involves in the preparation of solid dispersion [17].
iii. Drug + Carrier (PVP) + Surfactant (SLS) = Ternary Solid Dispersion.

II. Based on Structure:

i. Eutectic mixtures

It comprises two components, those are freely soluble in liquid state but shows less solubility or miscibility in solid state. At the

specific point E the temperature decreases, both components become crystallized. When exposed in GIT or water the carrier dissolves rapidly and drug was released in the form of fine crystals, hence solubility improved [18].

ii. Solid solutions

Two types of solid solution are available one is continuous solid solutions (CSS) and second one discontinuous solid solutions.

a) Continuous solid solutions: The components are miscible in all portions. In this type, the bonding between the components is stronger than the bonding between individual components.
b) Discontinuous solid solutions: Components are not soluble with other components; they show different solubility profiles [20].

iii. Amorphous solid solutions

These are same as the eutectic mixtures, but only difference is that the drug is precipitated out from the solution [20].

iv. Glass solid solutions

It is a homogeneous solution in which the drug is dissolves a carrier in glassy form. Glass suspension is those in which the drug is precipitated in glass solvent [18].

v. Interstitial solid solutions

Dissolved components occupy the interfacial space between the lattice and solvent molecule [17].

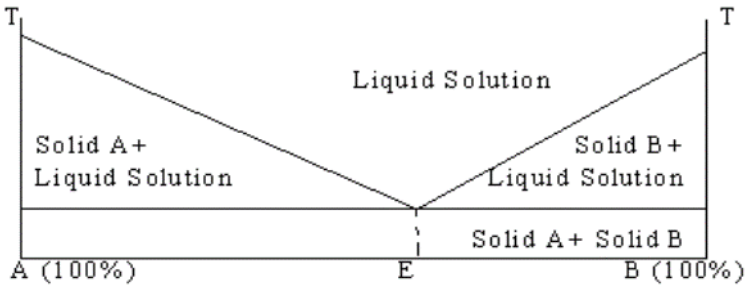

Figure 2: Phase diagram for eutectic mixture [19]

Table 2: Showing Carriers involved in different types of solid dispersion.

Types of Solid dispersion	Carriers involved
First generation Solid dispersion	Mannitol, sugar and urea
Second generation Solid dispersion	Natural polymers are HPMC(Hydroxy Propyl Methyl Cellulose), Cyclodextrin, Syntheticpolymers PVP and PEG
Third generation Solid dispersion	Poloxamer 407, Insulin
Fourth generation Solid dispersion	HPMC

Selection of Solvents:

- ❖ Solvents play an important role in the formulation of solid dispersion.
- ❖ The solvent must be able to dissolve the drug and carrier.
- ❖ Solvents must be compatible with drug and other agents like surfactants [18].
- ❖ Toxic solvent must be avoided.
- ❖ Water based systems are preferred.
- ❖ Commonly used solvents are given in (**Table 3**).

Carrier:

The carrier has an important role in the formulation of solid dispersion. Choice of the carrier plays an important role for release of drug, as hydrophilic carrier enhances the rate of drug release while the hydrophobic carrier slow down the drug release.

Carriers Involved in Solid Dispersion:

A. Polymeric carriers
B.Cellulose carriers
C. Other carriers

A. Polymeric Carriers:

PVP (polyvinylpyrrolidone)
PEG (polyethylene glycol)

PVP (polyvinylpyrrolidone):

PVP is a hydrophilic carrier, and it is formed by the polymerization of vinyl pyrrolidine.

The molecular weight of PVP was ranging from 2.5 to 3000 Kilo Dalton. It is further classified into different grades on the basis of their K values that represent their viscosity.

It is soluble in ethanol, IPA (Isopropyl Alcohol), dichloromethane and chloroform. As molecular weight enhances, the viscosity increases as a result of dissolution decreases. So low molecular weight PVP are use in solid dispersion as they have low swelling time, and they enhance the dissolution [22].

PEG (Polyethylene glycols):

These are polymers of ethylene oxide; polymerization of ethylene oxide leads to Polyethylene glycols. The molecular weight ranges from 200 to 300000. As the molecular weight rises the viscosity increases which decrease dissolution rate. So for the formulation of solid dispersion, low molecular weight PEG is uses, mostly ranging from 1500 to 20000.

PEG is fluid at the molecular weight of 600, 800-1500 is Vaseline like form, and about 2000-6000 they are in waxy form, while MW above 6000 is in solid form. The advantage of solid dispersion is that it has good solubility in organic solvents.

Table 3: Showing solvents used in solid dispersion: [19, 21]

Solvent	Melting Point (°C)	Boiling Point (°C)	Vapor pressure at 25 °C (pka)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic Acid	17	118	1.64

B. Cellulose Polymer:

Hydroxy propyl methyl cellulose (HPMC)

Hydroxy propyl cellulose (HPC)

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These are the mixed ethers of cellulose which contains 16.5% -30% methylated hydroxyl group and 4 - 23% hydroxyl group. Molecular weight of HPMC was ranging from 10000 to1500000. HPMC is soluble in water and in a mixture of ethanol and DCM (dichloromethane) and in methanol and DCM. Weak acidic drugs show faster release from solid dispersion [12, 18].

Hydroxy propyl cellulose (HPC)

HPC is non-ionic water soluble cellulose ether. It has good solubility range including ethanol, methanol, chloroform, and water. Molecular weight of HPC lie between 4000 - 1150000. On the basis of their viscosity it has seven different grades E, EL, L, H, J, G, and M. As the ratio of HPC increases the drugrelease increases only low molecular weight HPC are used for solid dispersion [18].

C. Other Carriers:

Urea increases bioavailability of a poorly soluble drug. It has good solubility with many organic solvents [20].

Sugar containing components is highly water-soluble but few shows toxicity if any sugar component shows toxicity then it is not used as a carrier in the formulation. It shows poor solubility in organic solvents [20].

Cyclodextrin

These are the cyclic oligosaccharides comprising glucopyranose units liked together by glucose units. It provides chemical protection, enhances the solubility and masks the taste of unpleasant drug.

D. Surfactant:

Surfactants are surface active agents which decrease the interfacial tension between drug and medium, which promotes wetting, solubility and release profile of drug. Surfactants used are SLS (sodiumlaurylsulphate), SDS (sodium

dodecylsulphate), and DTA (dodecyl trimethylammonium).

Techniques of Solid Dispersion [23-25]:
1. Kneading method
2.Solvent evaporation method
3.Fusion/melting method
4.Melting solvent method
5.Melt agglomeration method.
6.Hot melt extrusion method
7.Spray drying method
8.Electrospinning method
9.Co-grinding method
10.Co-precipitation method

1. Kneading Method:
Drug and Carrier transfers in mortar pestle and water is added to make proper dough (mass) and the kneaded mixture dried and passed through a sieve.

2. Solvent Evaporation Method:
Dissolving the mixture of drug and carrier in a same solvent. The mixture is prepared in different ratios of drug to carrier like 1:0.5, 1:1, 1:2, 1:3 and so on. Solvent evaporates at low temperature with vigorous stirring on magnetic stirrer. Solvents involved are ethanol, chloroform, acetone, dichloromethane [12, 26].
Main challenge is to dissolve both the components in same solvent.
Advantage:
Thermal decomposition of the carrier and drug is prevented because of evaporation of the solvent under low temperature.

3. Fusion or Melting Method:
This method invented by Obi and Sekiguchi in 1961.
Procedure
I: Preparation of physical mixture (drug and hydrophilic carrier).
II: Melting of mixture.
III: After that the mixture rapidly cooled with vigorous stirring on an ice bath.
IV: Resultant mass is crushes and passes through the sieve [27].

4. Melting Solvent Method:
Combination of solvent evaporation method and the fusion or melting method. The steps involved in this method are:
STEP I: Drug dissolves in a suitable solvent.
STEP II: Hydrophilic carrier melts under suitable temperature.
STEP III: Dissolving the drug mixture in melted carrier.
STEP IV: Solvent evaporated at low temperature.
STEP V: The resultant mixture solidifies rapidly and passes with a sieve.

5. MELT Agglomeration Method:
Heating of a binder and drug at a temperature above the melting point of the binder. Drug dispersion sprays on molten binds by shearing.
The rotary processor is an alternative of this procedure as it regulates the temperature easily. This method is used for the preparation of Diazepam solid dispersion [28].

6. HME (Hot Melt Extrusion Method):
HME is a process in which heat, and pressure is used to melt the polymer. It is a medical device used for proper mixing of drug with the polymer for enhancing the bioavailability of drug. It contains an extruder which comprises two or more rotating screws that helps in transportation of material towards downward. Mainly there are two types of extruder, one with the single screw, and another is with twin-screw extruders. It has four parts:
Feed entry: it contains the hopper which is fills with material to be extruded.
Process section: it transports the material for mixing.
An orifice: used for shaping the material.
Downstream equipment for cooling, cutting and collection of solid dispersion [29].

7. Spray Drying:
It is most commonly used technique for preparing solid dispersion. It converts material from liquid state to solid state in a single step.
Procedure: Dissolving the drug and carrier into a suitable solvent and sometime surfactant is also used, the continuous spraying of the solution in a heating chamber where solvent is completely evaporated and converts into powder form [30].

8. Electrospinning Method:
In this method the melted polymer or polymeric solution passes through a nozzle of mm size as the solvent evaporates, the solid fiber forms and these particles were collected. It involves the electrostatic forces.

It is a mixture of solid dispersion technique and nanotechnology [28].

9. Co-Grinding Method:

Grinding of drug and carried out in vibrational chamber containing balls. As, the force increases, the activation energy decreases which leads to the formation of crystal lattice. Vibrational balls enhance the solubility and bioavailability of drug.

10. Co-Precipitation Method:

Drug dissolves in the organic solvent, and the carrier dissolves in water. Mixing of the aqueous solution and organic solution of drug and then solvent evaporates, the mixture passed through a sieved and dried [30].

Characterization:

Several techniques are used for investigating an arrangement of molecules present in solid dispersion.

- FTIR (Fourier Transform Infrared Spectroscopy).
- DSC (Differential Scanning Calorimetry).
- SEM (Scanning Electron Microscopy).
- In - vitro dissolution studies.
- Solubility studies.
- Powder X - ray diffraction.

SUMMARY

- Solid dispersion of Sulindac was prepared in 2014 by hot melt mixing method [31].
- Solid dispersion of Lopinavir was prepared in 2015 by physical mixture, solvent evaporation method, solvent kneading method [32].
- Solid dispersion of Itraconazole was prepared in 2015 by co–evaporation method [33].
- Solid dispersion of Artemether was prepared in 2015 by Freeze - Dried Method [34].
- Solid dispersion of Efavirenz was prepared in 2016 by solvent evaporation method and freeze drying method [35].
- Solid dispersion of Lansoprazole was prepared in 2016 by solvent evaporation method [36].
- Solid dispersion of Cefixime (Antibiotics), Ibuprofen (NSAIDS), and Valsartan (angiotensin receptor blockers) was prepared in 2016 by physical mixing and kneading method [37].
- Solid dispersion of Tacrolimus was prepared in 2016 by solvent evaporation method [38].
- Solid dispersion of Spironolactone was prepared in 2016 by fusion method [39].
- Solid dispersion of Telmisartan was prepared in 2016 by Melt extrusion technique, Spray drying technique [40].
- Solid dispersion of Azilsartan was prepared in 2017 by combining Wet milling and Spray drying techniques [41].
- Amorphous solid dispersion of Ciprofloxacin (Antibiotics) was prepared in 2017 [42].
- Solid dispersion of Epigallocatechin Gallate was prepared in 2017 by Lyophilization technique [43].
- Solid dispersion of Ginger Extract - Loaded was prepared in 2017 by freeze drying technique [44].
- Solid dispersion of Ginkgolide B was prepared in 2018 by solvent evaporation method [45].
- Solid dispersion of Fenofibrate was prepared in 2018 by solvent evaporation and fusion method [46].
- Solid dispersion of Tamoxifen with Resveratrol was prepared in 2018 by hot melt Extrusion method [47].
- Solid dispersion of Lacidipine was prepared in 2018 by HME method [48].
- Solid dispersion of Kaempferol was prepared in 2019 by solvent evaporation method [49].
- Solid dispersion of Telmisartan was prepared in 2019 by fusion and solvent evaporation method [50].
- Solid dispersion of Famotidine was prepared in 2019 by kneading method [51].
- Solid dispersion of Gliclazide was prepared in 2019 by solvent method [52].
- Solid dispersion of Voriconazole was prepared in 2019 by solvent evaporation method and melting method [53].
- Solid dispersion of Atorvastatin was prepared in 2019 by kneading, rotary evaporation and Spray drying [54].

CONCLUSION

This review concludes that the dissolution is the rate limiting step for absorption of poorly water soluble drugs. Solid dispersion is one of the effective techniques used for

enhancing the solubility of this drug. Research shows that hydrophilic carriers increase the solubility and oral bioavailability of this drug. This review contains Noyes witney equation which is useful for enhancing the dissolution rate of this drug, approaches involved for increasing the dissolution rate. It provides information about different carriers involved in the preparation of solid dispersion and various methods for formulation and it also contains a list of marketed formulation of solid dispersion and contains an overview on research done in last few years. Solid dispersion has a lot of future scope.

Marketed Preparations of Solid Dispersion [55]:

Table 3: Showing list of marketed solid dispersion [55]:

Sr.No.	Product	API	Excipients	Dosage Form
1	Afeditab	Nifedipine	Poloxamer/PVP	Tablet
2	Afinitor	Everolimus	HPMC	Tablet
3	Certican	Everolimus	HPMC	Tablet
4	Cesamet	Nabilone	PVP	Tablet
5	Crestor	Rosuvastatin	HPMC	Tablet
6	Gris-PEG	Griseofulvin	PEG-6000	Tablet
7	Intelence	Etravirin	HPMC	Tablet
8	Isoptin	Verapamil	HPC/HPMC	Tablet
9	Kaletra	Lopinavir	PVP	Capsule
10	Nivadil	Nivaldipine	HPMC	Tablet
11	Novir	Ritonavir	PVP	Tablet
12	Onmel	Itraconazole	HPMC	Tablet
13	Prograf	Tacrolimus	HPMC	Capsule
14	Shuilinjia	Silibinin	Lecithin	Capsule
15	Sporanox	Itraconazole	HPMC	Capsule
16	Votubia	Everolimus	HPMC	Tablet
17	Zortess	Everolimus	HPMC	Tablet

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