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Review Article

Solid dispersion as a formulation strategy: A mini review

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Abstract: Oral route has been the most preferred route for administration of drug. However, in recent years majority of new drug candidates exhibit poor aqueous solubility for oral administration and hence pose a challenge for the formulation scientist [1]. Dissolution and/or permeation across the gastrointestinal membrane are the rate limiting step for oral absorption of drugs. Majority of the drugs belong to Class II of Biopharmaceutical Classification System (BCS). For these drugs, dissolution is the sole rate limiting step in oral absorption [2]. The current review lightens the advantages of the solid dispersion and discusses the production techniques, types of solid dispersion, and methods to choose a suitable carrier. Also, the common characterization techniques are explained. This mini review would help the readers understand the overall concept of solid dispersion as a drug delivery system.

Keywords: solid dispersion, solubility, drug delivery systems, amorphous, crystalline, review

Introduction

Despite the advancement in drug discovery and high throughput screening, majority of new molecules are lipophilic having poor aqueous solubility and hence poor oral bioavailability. To develop a dosage form with the improved oral bioavailability of such poorly soluble drugs yet remains a challenge and hence less drugs have been launched in the market lately [3]. Based upon the solubility and membrane permeability of the drug molecules, Biopharmaceutical Classification System has defined 4 classes. Various drug delivery systems including but not limited to polymeric nanoparticles, lipid nanoparticles, liposomes, solid dispersions etc. have been developed to resolve the problems associated with poorly aqueous soluble drugs [3–6]. The common aim for all of the drug delivery system was to increase the drug solubility. According to the Noyes–Whitney's equation to increase the dissolution rate one or more of the factors such as increase in drug solubility, increase in surface area, and increase in diffusion coefficient of the drug or decrease in the thickness of diffusion layer can be employed. In this review, we will focus on solid dispersion.

Noyes–Whitney equation provides some insight on dissolution rate enhancement of even very poorly soluble compounds. It is given by equation 1.

$$\frac{dC}{dt} = \frac{AD(C_s - C)}{h} \quad \text{..... Equation 1}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, C_s is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound [7]. As per this equation, increase in drug solubility, surface area for dissolution, diffusion coefficient of the compound or decrease in the thickness of diffusion layer can improve the dissolution rate.

Strategies commonly employed for improving the dissolution rate, and thereby oral absorption, of poorly soluble drugs include salt formation, solubilization, and particle size reduction. However, there are some practical limitations of these techniques. It is not feasible to form salts for neutral compounds and often the synthesis of appropriate salt forms of weakly acidic or weakly basic drug may not be accomplished. Even if salts can be prepared, increased dissolution in the gastrointestinal tract may not be guaranteed in many cases due to the reconversion of the salts into aggregates of respective poorly soluble acidic or basic forms. Solubilization of drugs using organic solvents, surfactants or co-solvents lead to liquid formulation that are usually undesirable from the viewpoints of patient compliance and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by commonly used methods such as controlled crystallization, grinding, etc. [8]. Moreover, in some cases, the micronized powder tends to agglomerate, thereby at least partially negating the significance of the milling procedure.

Other techniques to improve the solubility and hence dissolution include use of the polymorph, amorphous form of the drug and complexation. Of the formulation approaches, solid dispersion has shown great promise for improving dissolution. Solid dispersions prevent aggregation/agglomeration of the individual drug

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particles, lowers solid-liquid surface tension, and create a microenvironment, in which, the apparent drug solubility is very high [7].

The term 'solid dispersion' has been used to refer a family of dosage forms, in which the drug is dispersed in a biologically inert matrix, more often with a view to enhancing oral bioavailability [9]. In 1971, Chiou and Riegelman have described it as dispersion of one or more active ingredients are present with an inert carrier or matrix at solid state by method of melting, solvent or melt-solvent method [10]. Traditionally, solid dispersions have been used to improve the dissolution rate of drug utilizing water soluble carriers like polyethylene glycols but the definition of solid dispersion encompasses the use of water insoluble carriers like Eudragits in order to produce a sustained release dosage form [9].

Advantages of solid dispersion

Reduced particle size: When solid dispersion containing hydrophilic carrier comes in contact with the aqueous medium, the hydrophilic carrier rapidly dissolves leaving the drug particles in a microfine state having tremendously increased surface area and subsequently increased dissolution rate [7,11].

Improved wettability: A major contribution to enhancement in drug solubility by the hydrophilic carrier is related to the drug wettability improvement verified in solid dispersions. Generally, carriers showing surfactant activity like cholic acids improve wettability. However, carriers like urea that are devoid of any surfactant properties were shown to improve drug wettability.

Higher porosity of particles: Particles in solid dispersions have been shown to have a higher degree of porosity. Carrier properties also influence the porosity, for example, solid dispersion containing linear polymers produce larger and more porous particles than those containing reticular polymers and, hence, result in a higher dissolution rate. Increased porosity allows better penetration of the dissolution fluid as well as increased surface area of contact between the solid dispersion and dissolution medium that improves drug dissolution.

Drugs in amorphous state: Drugs in amorphous state are known to have greater aqueous solubility than their crystalline counter parts. This is due to the randomly ordered state of the amorphous drug that requires less energy to dissolve compared to highly ordered crystalline drug particles that require additional energy to overcome the crystal lattice.

In solid dispersions, drugs are present as amorphous form and hence produce a supersaturated solution after dissolution. In case the drug precipitates, it will be in a metastable polymorphic form with higher solubility or will be in a finely particulate state that exhibits enormous dissolution rate [12].

Types of solid dispersions

Choiu and Riegelman have classified solid dispersion into six groups on the basis of the interaction between drug and carrier, namely, simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitations of a drug in a crystalline carrier, compound or complex formations between the drug and the carrier and any combinations of these. Table 1 summarizes the different types of solid dispersion.

Table 1. Types of solid dispersion. Summarized from [7,10,26]

	Type of solid dispersion	Matrix	Drug	Number of phases
I	Eutectics	C	C	2
II	Amorphous precipitation in crystalline matrix	C	A	2
III	Solid solutions			
A	Continuous solid solutions	C	M	1
B	Discontinuous solid solutions	C	M	2
C	Substitutional solid solutions	C	M	1 or 2
D	Interstitial solid solutions	C	M	2
IV	Glass suspensions	A	C/A	2
V	Glass solutions	A	M	1

A= Amorphous; C=Crystalline; M=Molecular dispersion

Simple eutectic mixtures

Two components showing miscibility in the liquid state but negligible solid-solid solubility are termed as simple eutectic mixtures. In terms of thermodynamics, such system is regarded as an intimately mixed physical mixture of two crystalline components. Dissolution improvement in case of eutectics may be due to the dispersion of drug as fine particles with enormous surface area, better wetting, solubilization in some cases as well as deaggregation of drug particles [10]. Reduction in particle size to submicron size may also increase the drug solubility of poorly soluble drugs that in turn can increase the dissolution rate [13].

Solid solution

Solid solution is one phase system of the components incorporated in to it, irrespective of their number. The particle size of the drug reduces up to molecular level, which results in significant increase in the dissolution rate. Compared to eutectic mixtures, solid solutions increase the

dissolution rate to several magnitudes higher than eutectic mixtures due to greater size reduction, lack of crystal lattice structure of drug in the solid solution, solubilizing, wetting and precipitation inhibiting capability of carrier. Solid solutions can be further classified by the method used. Based on the basis of their miscibility or distribution of solute in the solid solvent, they are classified into continuous and discontinuous solid solutions as well as into substitutional and interstitial solid solutions.

Continuous and discontinuous solid solutions

In a continuous solid solution, the incorporated components are miscible in all ratios. This may be due to the stronger bonding strength between the molecules of two different components than between the molecules of same components. If the solubility of one component into other is limited, i.e. solubility below or above a certain ratio, then it is termed as discontinuous solid solution. For practical consideration, the term solid solution should be used only if the mutual solubility is more than 5% [7].

Substitutional and interstitial solid solutions

When solute (i.e., drug) molecules are substituted for solvent (i.e., carrier) molecules in the crystal lattice, it is termed as the substitutional solid solution. The substitution is possible only when the solute molecule size differs by less than 15% from the size of solvent molecule. The dissolved solute molecules are arranged interstitially between the solvent molecules and form interstitial solid solution. In order to form interstitial solid solution, the solute molecule should have a molecular diameter of less than 59% to that of the solvent molecule and the molecular volume of the solute less than 20% that of the solvent. In amorphous solid solutions, the solute molecules are dispersed molecularly but in an irregular way within the amorphous solvent. Polymeric carriers like PVP are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature and hence improving stability of solid dispersion.

Amorphous precipitation in crystalline carrier

The crystalline drug may precipitate out in an amorphous form and gets deposited within the crystalline carrier matrix. Amorphous forms possess higher solubility due to lowest degree of intermolecular bonding and high energy state among all polymorphs, which leads to improvement in dissolution. During melting or solvent evaporation method, the drug may precipitate out in an amorphous form in the crystalline carrier like citric acid or urea. Since the amorphous form has a highest free energy than any form of the neat drug, it should produce faster dissolution and absorption rates than the crystalline form irrespective of them being dispersed in the carrier or not. Presence of carrier may retard the crystallization of the amorphous form in solid state or during dissolution in dissolution media or gastrointestinal fluids. PVP was found to inhibit crystallization of furosemide at 40% RH at 6 ° to 45 °C [14]. HPMC was found to retard the crystallization of the amorphous form of felodipine as well as restrict the crystallization of drug during dissolution [15].

Glass solution/Glass suspension

When the amorphous carrier is used, solid solution is termed as the glass solution because of the glass forming property of amorphous carriers on cooling. If the drug is present as particulate dispersion within the amorphous polymer, it is termed as the glass suspension [10].

Methods of preparation of solid dispersions

Fusion/melting method: In this method, physical mixture of drug and carrier are completely melted and the molten mixture is cooled rapidly. The resultant solid dispersion is then pulverized and sieved. Supersaturation is produced while cooling but due to solidification of the carrier matrix, the dispersed drug becomes trapped within the carrier matrix. If the drug is suspended in the molten carrier, it is termed as the fusion method that reduces process temperature and hence advantageous for the thermolabile drugs [12]. The disadvantage of this method is high viscosity of the melt that results in incomplete miscibility between the drug and carrier [16].

Solvent method: In this method, the drug and the carrier are dissolved into a common solvent, separately or as a physical mixture, and solvent is removed using spray drying, freeze drying or rotary evaporator. Except in freeze drying, solvent is evaporated at a temperature range 23-65 ºC, with or without the application of vacuum as organic solvents have low boiling points. This method is particularly advantageous for thermolabile materials, for formulating products with better flowability and with high melting carriers like PVP [17].

The prerequisite to use the solvent method is sufficient solubility of the drug and carrier in a common solvent. Organic solvents such as ethanol, chloroform and acetone have been widely used solvents as most pharmaceutical compounds are soluble in these solvents. However, finding a common solvent, which can dissolve both hydrophobic drug and hydrophilic carrier, is difficult due to the difference in polarity between drug and the carrier. The mixture of organic solvents can also be used when a common solvent is not available. Implications of residual solvent, ecological hazards and economic considerations

limit its use on an industrial scale [8]. However, some of the marketed products use spray drying for preparation of solid dispersion.

Melt-solvent method: This method involves dissolution of drug in the suitable solvent and incorporation of this solution directly into the molten carrier. This is advantageous when a common solvent is not obtained for the drug and carrier and/or the drug is thermolabile. However, it is limited to the drugs with low therapeutic dose due to practical implications [10].

Electrostatic spinning: In electrostatic spinning method, high voltages are used to induce surface charges that are adequate to overcome the surface tension in a pendant polymer droplet, and hence trigger the formation of a jet that solidifies as a fine fiber. This method has been used to prepare solid dispersions with polymeric carriers [17].

Supercritical fluid processing: In supercritical fluid processing (SCP), super critical fluid is used as an anti-solvent to the solvent dissolving the drug and carrier. It has emerged as an alternative to solvent-evaporation method for formulating coprecipitates of smaller particle size, lower residual organic solvent and better flowability. A supercritical fluid exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is currently the most commonly used supercritical fluid due owing to its properties of being non-toxic, non-flammable, inexpensive and low critical temperature, carbon dioxide makes it attractive for processing thermolabile pharmaceuticals [18].

Hot-melt extrusion: Hot-melt extrusion is modified form of the conventional melting method. In this process raw materials are pumped with a rotating screw under elevated temperature through a die into a product of uniform shape.

This method has gained impetus in recent years due to its advantages that bypass the requirement of solvent thereby reducing the number of processing steps and eliminating time-consuming drying steps. Moreover, the intense mixing and agitation due to the rotating screw cause deaggregation of suspended particles in the molten polymer producing a more uniform dispersion [19].

Mechanism of release of drug from solid dispersion

Many theories have been put forth to explain the mechanism of release of drug from solid dispersion. Overall, there appears to be consensus on two set of observations regarding the mechanism of drug release that are as follows.

Carrier-controlled release: In this case, the drug release is controlled by the carrier used to prepare the solid dispersion. Initially, a polymer rich diffusion layer is formed at the drug dissolving surface (at least at low drug loading). Drug within the solid dispersion has to pass through this layer to enter the bulk medium. While passing, the particles dissolve into the polymer-rich diffusion layer at a considerably fast rate and therefore the drug exists as drug molecules in this diffusion layer rather than drug particles. These drug molecules now have to diffuse out through the layer to enter the bulk. Drug diffusion through this layer can be estimated by the Stokes-Einstein equation. (Equation 2) As the viscosity of the diffusion layer is sufficiently high, the diffusion rate is assumed to be very slow.

$$D = \frac{KT}{6\pi\eta r} \quad \text{.....Equation 2}$$

where, *K* is Boltzmann's constant, T is the absolute temperature, η is the viscosity and *r* is the radius of the diffusing molecule. It can be inferred from the above discussion that the rate limiting step in this process is the dissolution of carrier itself in forming the diffusion layer. In case of water soluble carrier, the process is however complicated by the dissolution of the carrier in the medium. Nevertheless, this approach is still applicable to understand the drug release pattern.

Drug-controlled release: Here, the release is independent of the carrier incorporated. In this approach, the drug dissolution in the polymer-rich layer is comparatively slow that results in the release of drug particles rather than drug molecules into the bulk. Therefore, the drug release in this case will be determined by the drug properties, like particle size, physical form, etc.

From the above discussion, it is apparent that the drug dissolution in the polymer-rich layer is of prime importance for a carrier-controlled dissolution. As per Noyes Whitney equation, dissolution rate is directly proportional to solubility [9]. Therefore, phase solubility studies of drug with carriers can indicate the impact of solubility increase on the dissolution rate enhancement.

Selection of suitable carriers: The purpose of incorporation of carriers in solid dispersion is to aid in improving the dissolution rate of the drug through various mechanisms like improving wetting, solubilizing, and capability to stabilize amorphous drug against water-induced crystallization [9,20]. Inhibiting crystallization of amorphous drug in the solid dispersion. Various mechanisms attributed to the inhibitory effects of polymers against crystallization include antiplasticization by the polymers, interactions between the API and polymers in solid dispersions, reduction in local molecular mobility due to coupling between the polymer and API motions, and an increase in the activation energy for nucleation [21]. Carriers that are commonly

incorporated in solid dispersion have been discussed in Table 2.

Table 2. Types of carriers used in immediate release solid dispersion formulation. Adapted and modified from [7,12,26]

Carriers	Examples
Sugars, polyols and their polymers	Mannitol, Sorbitol, Chitosan
Small molecules	Urea
Emulsifiers	Tween 80, Sodium lauryl sulfate, Sodium dodecyl sulfate, Bile salts
Organic acids and derivatives	Succinic acid, Citric acid, Nicotinamide
Fully synthetic polymers	Polyethylene glycol, Polyvinylpyrrolidone, Polyvinylalcohol Polyacrylates and Polymethacrylates (Eudragit® E, Eudragit® L)
Natural product based polymers	Hydroxypropylmethylcellulose, Hydroxypropylcellulose, Carboxymethylethylcellulose Cyclodextrins
Surface active carriers	Vitamin E TPGS Poloxamer-188, Poloxamer-407 Gelucire 44/14 Phospholipids, Inutec SP1, Compritol, Precirol

Selection of carrier using solubility parameters

Though solid dispersion technique is an attractive choice to improve the dissolution, it suffers from the major drawback of physical instability on storage and problems of drug/carrier miscibility. Physical instability during storage is associated with the incompatibility between the drug and carrier. Efforts to improve the physical stability include formation of specific interaction like hydrogen bonding, incorporation of a crystallization inhibitor and carrier with high glass transition temperature (T_g). A suitable carrier can be selected using a solubility parameter technique [22].

Drug/carrier ratio

The drug/carrier ratio in a solid dispersion has a major influence on the performance of a solid dispersion. High drug load will lead to the formation of small crystals within the dispersion rather than remaining molecularly dispersed. Low drug loading can result in a complete absence of crystallinity of the drug and thereby enormous increases in the solubility and release rate of the drug [7]. Lin and Cham have shown that solid dispersions of naproxen in PEG 6000 released drug faster when a 5 or 10% naproxen loading was used rather than when a 20, 30 or 50% loading was used. It was explained on the basis of X-ray diffraction results that dispersions with low loading levels of naproxen were amorphous whereas those with high loadings were partly crystalline [23]. However, the upper limit to the percentage carrier that can be employed is governed by the ability to subsequently formulate the solid dispersion into a dosage form of administrable size. Large percentage of low melting carriers like PEG 6000 and PLX 188 may pose a challenge during scale up due to their waxy nature [24]

Method of physical characterization of solid dispersions

Differential scanning calorimetry (DSC): DSC enables the quantitative detection of all processes in which energy is required or produced. The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC [7,11].

X-Ray diffraction (XRD): XRD is based on the principle that when an X-ray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Characteristic fingerprint region in the diffraction pattern is the evidence of crystallinity in the sample. Due to the specificity of the fingerprint, crystallinity in the drug can be easily separated from the crystallinity in the carrier. As a result, it is possible to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinities of under 5–10% cannot generally be detected with XRD [7]. It can also be used to detect change in the polymorph

during formulation as different polymorphs exhibit different and characteristic diffraction pattern.

Fourier Transform Infrared Spectroscopy (FTIR): Infrared spectroscopy is based on the principle of bond strength. It allows study of intermolecular interactions, involving one or more chemical species that alters the dipole as a result of unassociated or differently associated chemical conformation. FTIR spectra of crystalline and amorphous forms showed discernable changes with the latter exhibiting generalized broadening and diffusion of bands that can be attributed to the differences in hydrogen-bonding patterns between the two solid-state forms. In amorphous form, the relative disorder of the molecules results in a broader distribution of bond lengths and energies with respect to the crystalline counterparts.

FT-IR spectra of neat materials show characteristic peaks at particular wavenumber owing to specific group present in the chemical structure. The bond strength between drug and carrier molecule changes due to the hydrogen bonding which is expressed as the shift of peak to the lower wavenumbers (red shift). Such a red shift is proportional to strength of the hydrogen bonding caused by lengthening of the X-H bond on interaction [25].

Future Direction

Solid dispersions have been in the development since almost 5 decades now. However, only few products have successfully survived in the market. Ritonavir capsule (Norvir, Abbott) and troglitazone in PVP (Rezulin, Parke-Davis) were withdrawn from the market due to issues like crystallization and toxicity, respectively. Industrial Scale application of solid dispersion has been limited due to problems associated with the method of preparation, reproducibility of physicochemical properties, formulation into dosage forms, scale up during manufacturing processes, and the physical and chemical stability of drug and vehicle [8,24].

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