Review Article

Current trends for preparation of solid dispersion

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ABSTRACT

This review describes different types of solid dispersions and recent techniques for their preparation. The solid dispersions are mainly classified into two types such as sustained release solid dispersions and fast release solid dispersions. Further, fast release type solid dispersions are classified into simple eutectic mixtures, glass solution, solid solution, amorphous form of drug in a crystalline host and compound or complex form of solid dispersions. Solvent method , melting method , melting-solvent method, solvent wetting , spray drying, freeze drying, low temperature melting method , dropping method , super critical fluid (SCF) technology , hot melt extrusion and melt agglomeration process are usually used for preparation of solid dispersions . This review also concludes that solid dispersion methods can be used in industrial production.

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Introduction

Drugs with poor aqueous solubility is great challenge for formulation scientists for development of oral dosage for with proper bioavailability in the pharmaceutical industries[1.] Aqueous solubility of drugs is directly influence its bioavailability. Poor aqueous solubility drugs shows less absorption in the gastrointestinal track results less bioavailability. For enhancement of bioavailability of such types of drugs we need to increase its aqueous solubility .[2] The aqueous solubility of drugs is directly depends on its rate of dissolution, which is supported by the modified Noyes-Whitney equation[3, 4]. However, formulation scientists usually adopted several pharmaceutical approaches to improve the aqueous solubility of poorly soluble drugs. In recent research papers some of new methods are also reported in their research papers with justified conclusions for improvement of aqueous solubility.

Reduction of particle size to the level of nano meter is a method for improvement of solubility. [5] It is also reported anionic and cationic surfactants possesses good solubility capacity for the poorly water soluble drug gliclazide[6]. It is also reported that in case of beta- arteether anionic and cationic surfactants exhibited good solubilizing ability, but nonionic surfactants exhibit lower solubilizing capacity [7] .

However solid dispersion technique is a most reliable and widely used method for improvement of solubility of poorly water soluble drugs.

Solid Dispersions

Solid dispersion is defined as a dispersion of one or more active ingredients in an inert carrier or matrix in a solid state which is prepared by the melting (fusion), solvent or melting-solvent method[8]. Melting method of preparations of dolid dispersion was first reported by Sekiguchi and Obi in 1961, also reported that as a practical method to reduce particle size and enhance drug dissolution and absorption[9]. Another method of preparation of solid dispersion such as solvent method or solvent evaporation method was also reported by Tachibana and Nakamura in 1965[10]. In solid dispersion, drugs might be present in microcrystalline form, on exposure to aqueous media, the carrier dissolved; the drug was released as very fine, colloidal particles[11, 12].

Classification of solid dispersions

Solid dispersions are categorized into two categories such as sustained release andfast release. Sustained release soliddispersionis that in which the release of primary dose of a highly water soluble drug is prolonged by using insoluble carriers like natural gums, glyceryl monostearate, cellulose acetate phthalate, waxes, ethyl cellulose, etc. The

drug release from this type of system is due to diffusion, erosion, or leaching of the carrier material in the solvent. Sahoo et al., (2009) prepared sustained release tablets of verapamil hydrochloride by using solid dispersion technique with eudragit RLPO or Kollidon SR[13]. It concluded that drug release can be sustained for 12 h at drug-polymer ratio of 1:3 for Eudragit RLPO.

Fast release solid dispersion is that in which an insoluble or poorly soluble drug is finely dispersed in a highly soluble carrier to improve its dissolution and absorption characteristics. Again, fast release category is classified into simple eutectic mixtures, glass solution, solid solution, amorphous precipitations of drug in a crystalline carrier and compound or complex formation between the drug and the carrier.*Simple eutectic mixture*is an intimately blended physical mix of two crystalline components, which are completely miscible in the liquid state, but not in the solid state. *Glass solution*is a homogeneous glassy system, in which a solute is dissolved in a solid glassy solvent. This concept was first introduced by Chiou and Riegelman (1969), which can be used to improve dissolution and oral absorption[14]. *Solid Solution*is made up of a solid solute dissolved in a solid solvent. It can be considered as a solid solute dissolved in the solid solvent. It was reported that a solid solution of a poorly soluble drug in a rapidly dissolving carrier achieves a faster dissolution rate than a eutectic mixture, because the drug particle size is reduced to its absolute minimum as it is molecularly dispersed in the carrier in a solid solution[15 - 17]. *Amorphous precipitations of drug in a crystalline carrier* are where in, the components exist in two states such as the crystalline state and the amorphous state. The drug precipitates upon cooling or solvent removal into the crystalline state (or amorphous state) in an amorphous carrier (or crystalline carrier). The amorphous form of a pure drug shows faster dissolution and oral bioavailability than the crystalline form as it is highly energetic form compared to the crystalline state[18].

Compound or complex formation between the drug and the carrier are in which a drug forms a complex with an inert soluble carrier in the solid state. The bioavailability of the drug depends on the solubility and stability constant of the compound or complex. It is reported that the dissolution rate and oral absorption can be increased by formation of a water-soluble complex with a high dissociation constant. One of the most frequently used complex carriers are within the class of the cyclodextrines. These cyclic oligosaccharides are built up from glucopyranose units, with a capacity of

forming a cavity of which the interior is rather hydrophobic, whereas the exterior is highly hydrophilic. These characteristics enable cyclodextrines to form complexes in which guest molecules are trapped entirely or partially in the hydrophobic interior of cyclodextrin molecules, while the outer part is hydrophilic ensuring the solubility of the complex in an aqueous medium. This system is able to significantly improve the solubility of drugs [19- 22].

The dissolution and absorption of a drug from complex is shown in Figure 1.

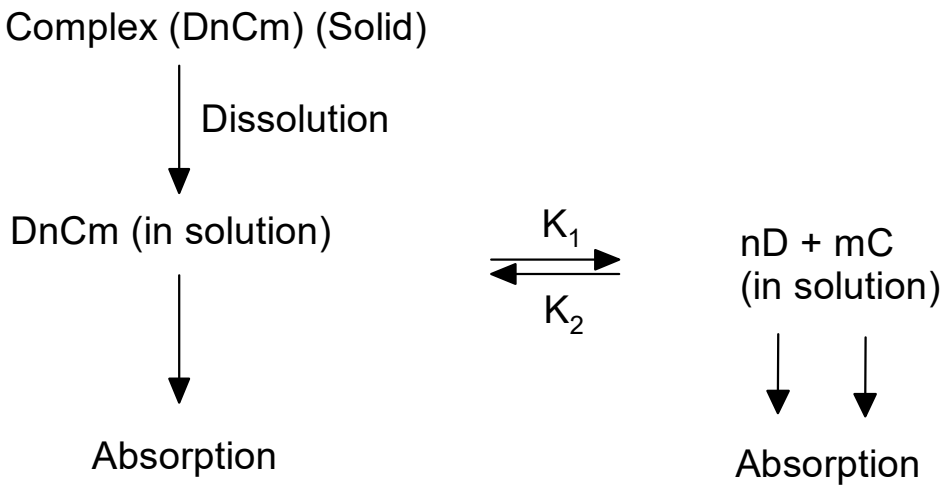

Figure 1: The dissolution and absorption of a drug from complex

Sometimes formation of insoluble complex between the drug and carrier reduce the rate of dissolution. Example of such type is formation of complex between phenobarbital and PEG 4000, 6000.

Methods of Preparation of Solid Dispersions

There are several methods are used for preparation of solid dispersions of drug and polymer for enhancement of solubility poorly water soluble drugs. The methods for preparation of solid dispersions are as given

Solvent Method: - The solvent method needs to dissolve the drug and carrier (often a polymer) simultaneously in a common solvent, followed by the removal of solvent by evaporation [14, 23, 24]. The evaporation procedure is often accomplished in a rotavapor, but the solvent can also be removed by other methods e.g., freeze-drying, spray drying or using supercritical fluids. The drug used in solid dispersions is usually hydrophobic and the carrier is hydrophilic. Mostly used solvents include, ethanol, methanol and methylene chloride. In few cases, more volumes of solvents as well

as long heating may be require to complete dissolution of both components, hence cosolvents is suggested[25].

Melting Method: The melting method needs to heat the physical mixture of drug and carrier to the liquid state followed by cooling, resulting in solidification of the melt. This melting method can be performed either by mixing drug and carrier in a beaker on an oil bath followed by cooling the mixture in an ice bath or by melting the drug/carrier mixture simultaneously, homogenizing and then extruding with a typical twin-screw extruder as used in the polymer processing field [26].

Melting-Solvent Method: The melting-solvent method is a combine approach of the aforesaid methods. It is carried out by dissolving the drug in a suitable solvent and mixing of this solution with the molten carrier followed by cooling and solidification [8, 27, 28, 23]. However, only a low drug loading is possible for this method.

Solvent Wetting: Eun-Jung Kim et al., (2006) was first used this method for preparation of solid dispersion of felodipine with PVP and HPMC. It is performed by preparing solution of drug and adding of this solution to polymeric carrier followed by removal of solvent by using vacuum.[29]

Spray Drying: Spray drying is commonly used in pharmaceutical industry and food industry to dry aqueous or organic solutions, emulsions etc. The spray drying principle involves evaporation of solvent or moisture from a mixture or an atomized feed by mixing the spray and the drying medium. The drying medium is typically air. Drying proceeds until the desired moisture content is reached in the sprayed articles and the product is then separated from the air. The particle size of the dry product is very small (ca. 10 to 500 μm) in comparison with other solvent methods. It also provides the advantage of weight and volume reduction.

Solid dispersions of lonidamine in PEG 4000 and PVP K 29/32 by the spray-drying method were prepared and evaluated, and observed for enhancement of solubility [30].

This method was used by the different researchers for preparation of solid dispersion successfully. It was used by Ram Gidwani et al., (1992) for preparation of solid dispersion of thymopentin eudragit S 100 [31].

It is also reported by the few researcher that D-α-tocopheryl polyethylene glycol 1000 (TPGS 1000) and polyvidone-vinylacetate 64 (PVPVA 64) resulted an increase in the degree of supersaturation and stability of supersaturated for itraconazole solutions, compared to a blank without excipient.[32, 33]

Freeze Drying: This technique was used as an alternative technique to solvent

evaporation.

Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.

The solid dispersions (SDs) of meloxicam (MX) in polyvinylpyrrolidone K-30 prepared by freeze-drying (FD) and solvent evaporation (SE) resulted good solubility.[34]

Low Temperature Melting Method:-Solid dispersion can be prepared at relatively low temperature by using this method. This method used a locally designed ointment formulation vessel. Drug and polymer physical mixtures at different ratios were prepared and transferred into a locally designed ointment formulation vessel[35].

Dropping method: Dropping method is a new procedure for the production of round particles from melted solid dispersions[36]. A solid dispersion of a melted drug–carrier mixture is dropped onto a cooling plate, where it solidifies into round particles. The disadvantage is that only thermostable drugs can be used, and the physical instability of solid dispersions is a further challenge [37.]

Super critical fluid (SCF) Technology: Super critical fluid Technology was introduced in the late 1980s and early 1990s, with experimental proofs of concepts. The proofs are abundant in the scientific literatures. Initially, it has been studied intensively by a number of researcher groups for the formation of biocompatible polymer and drug-loaded biopolymer micro-particles for pharmaceutical applications.

Hot melt extrusion: Hot melt extrusion approach represents the advantageous means of preparation of SD(s) by using the twin screw hot melt extruder where only thermo stable components are relevant [38]. The extruder consists of a hooper, barrel, a die, a kneading screw and heaters. The physical mixture is introduced into the hopper that is forwarded by feed screw and finally is extruded from the die [39]. The effect of screw revolution speed and water content on the preparation of SD(s) have been studied by the different researchers. In one study, it is also reported that presence of kneading paddle element of screw results in super saturation on dissolution testing while slow revolution rate of screw and addition of the suitable amount of water increased rate of dissolution although no super saturation occurred[40]. In addition, high screw speed high feed rate processes in comparison with low screw speed low feed rate processes caused an increase in extrudate radius and porosity and decrease in mechanical strength and drug release rate from the matrix attributed to the expansion promoted under certain extrusion conditions [41].

Melt agglomeration process: It has been used to prepare solid dispersions, where in the binder acts as a carrier. Solid dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer [42]. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates[43]. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration, since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate.

Conclusions:

Working experience with solid dispersions since the last 40-50 years reveals that this is a useful approach for improvement of solubility and oral bioavailability of poorly water soluble drugs.

Different types of solid dispersions are thoroughly investigated and usefulness of the same are reported. Similarly different types of methods of preparation have been used for preparation of solid dispersions; some of methods are used in pharmaceutical industries in large scale productions. Further several aspects in this area is still need to be investigated in the next years.

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