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REVIEW ARTICLE

PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSION: A REVIEW

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ABSTRACT

Solid dispersions in water-soluble carriers have attracted considerable interest as a means of improving the dissolution rate, and hence possibly bioavailability, of a range of hydrophobic drugs. However, despite thevarious advantages of solid dispersion, the technique has some major drawbacks. One of the major problemis related to the physical stability of the high energy amorphous state of the drug. Since solid dispersion aids in the improvement of the dissolution and solubility, the drug in the amorphous state may get converted to the crystalline state with the time period. This review mainly focuses on the factors that help in the improvement of the physical stability of the solid dispersion. The implications of a deeper understanding of the physical stability are discussed, with particular emphasis on optimizing the ratio of carrier and drug, choice of the carrier, the prediction of the glass transition temperature of drug and the carrier and the mechanism involved in the physical changes of solid dispersions resulting in crystallization.

Keywords: *Solid dispersion, Physical stability, Glass transition temperature, Amorphous state.*

INTRODUCTION

Solid dispersions is one of the efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly soluble drugs.The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles [1].

Chion and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures". They classified solid dispersions into the following six representative types: Simple eutectic mixtures, Solid solutions, Glass solutions, Glass suspensions, Amorphous precipitations in a crystalline carrier, Compound or complex formation, and Combinations of the previous five types. While Corrigan (1985) suggested the definition as being a product formed by converting a fluid drug-carrier combination to the solid state. This strategy includes complete removal of drug crystallinity, conversion of crystalline drug to amorphous drug and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier [2]. Solid dispersion is a promising approach to improve the dissolution and bioavailability of hydrophobic drugs. The preparation and storage conditions of solid dispersions are crucial since changes may alter the dissolution characteristics of the active ingredients [3]. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by co solvents, and particle size reduction. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size [4].

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Significant properties of solid dispersion: [5]

There are certain exclusive properties of solid dispersion and that may be given as follows:

1. **Higher Porosity of Drug Particle:**Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity depends on the properties of carriers used, for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate and hence bioavailability.
2. **Reduced Dug Particle Size:**A high surface area is formed, resulting in an increased dissolution rate and consequently, improved bioavailability.
3. **Improved Wettability:**A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts, when used, can significantly increase the wettability properties of drugs.
4. **Drugs in Amorphous State:**The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process.

PHYSICAL STABILITY OF AMORPHOUS SOLID DISPERSION

The dissolution behavior of solid dispersions must remain unchanged during storage. The best way to guarantee this is by maintaining their physical state and molecular structure. For optimal stability of amorphous solid dispersions, the molecular mobility should be as low as possible. However, solid dispersions, partially or fully amorphous, are thermodynamically unstable. In solid dispersions containing crystalline particles, these particles form nuclei that can be the starting point for further crystallization. It has been shown that such solid dispersions show

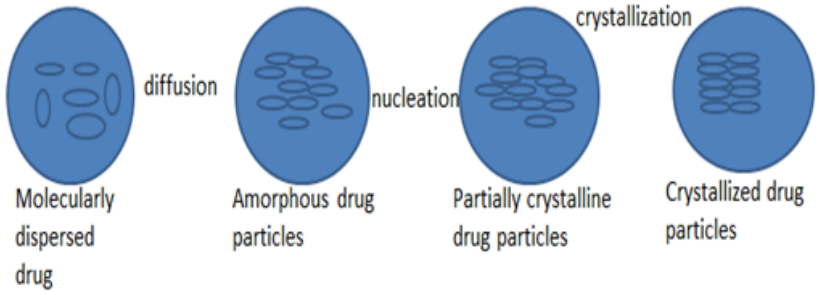

Fig.1: Physical changes in solid dispersions resulting in crystallization [6].

progressively poorer dissolution behavior during storage. In solid dispersions containing amorphous drug particles the drug can crystallize, but a nucleation step is required prior to that. In homogeneous solid dispersions the drug is molecularly dispersed, and crystallization requires another step. Before nucleation can occur, drug molecules have to migrate through the matrix. Therefore, physical degradation is determined by both diffusion and crystallization of drug molecules in the matrix. It should be noted that in this respect it is better to have a crystalline matrix, because diffusion in such a matrix is much slower. Physical changes are depicted in (fig. 1). The physical stability of amorphous solid dispersions should be related not only to crystallization of drug but to any change in molecular structure including the distribution of the drug. Moreover, the physical state of the matrix should be monitored, because changes therein are likely to alter the physical state of the drug and drug release as well [6].

Physical properties of amorphous state:

Materials can occur in different states. The crystalline state and the liquid state above the melting temperature (T_m) are thermodynamically stable. Amorphous materials are thermodynamically unstable and will have a natural tendency to crystallize, because the crystalline state has a lower energy compared to amorphous material. However, amorphous material can be kinetically stable, which implies that the equilibrium state, i.e. crystalline, is not reached within the timeframe of the experiment or shelf life of the product [7]. The kinetic stability of amorphous material depends on the physical state of the material. Two physical states can be defined for amorphous material: the glassy state and the rubbery state. (Table 1) shows the most relevant characteristics of the various thermodynamically stable and unstable states that materials may occur in.

Fig. 2: Molecular dispersion of drug [7].

Table - 1: Characteristics of thermodynamically stable and unstable physical states of material

THERMODYNAMICALLY STABLE	
CRYSTAL	LIQUID
Below the melting temperature	Above the melting temperature [8]
Molecules in crystalline lattice	Molecules randomly oriented [8]
Low molecular mobility (no translation, only rotation and vibrations	High molecular mobility (including translations) [9]
THERMODYNAMICALLY UNSTABLE	
GLASS	RUBBER/SUPER-COOLED LIQUID
Below the glass transition temperature	Above the glass transition Temperature
Molecules randomly distributed, liquid-like	Molecules randomly distributed, liquid-like
Low molecular mobility	High molecular mobility
Kinetically stable	Kinetically unstable
Crystallization and chemical reactions are absent or extremely slow	Crystallization and chemical reactions can be observed [10]

GLASS TRANSITION TEMPERATURE (Tg) [11].

Glass Transition is a method to characterize a property of a polymeric material. The glass transition is the temperature where the polymer goes from a hard, glass like state to a rubber like state. The best way to envision this type of transition is to put a rubber band (rubber like state, very flexible) into a container of liquid nitrogen. When removed the rubber band is solid and inflexible (glass state) and in fact the rubber band can be shattered. Upon standing and warming to room temperature the rubber band will again become flexible and rubbery (rubber like state). DSC defines the glass transition as a change in the heat capacity as the polymer matrix goes from the glass state to the rubber state. This is a second order endothermic transition (requires heat to go through the transition) so in the DSC the transition appears as a step transition and not a peak such as might be seen with a melting transition.

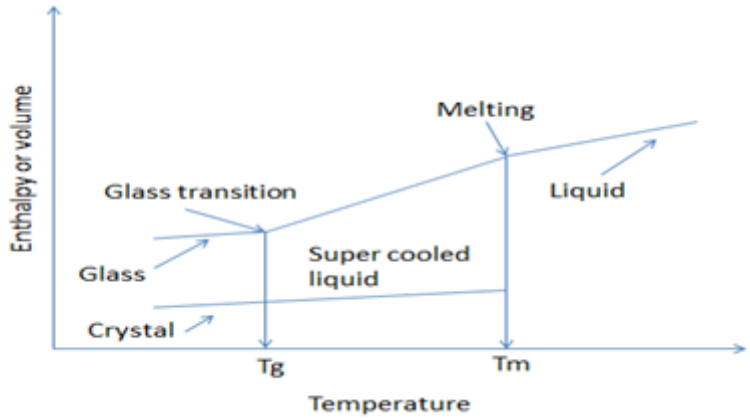

Fig. 3: Change of free volume and enthalpy with respect to temperature.

Molecular mobility in amorphous solid [12].

Molecular mobility in amorphous materials determines the physical stability and reactivity. The molecular mobility is related to macromolecular properties like viscosity but is generally quantified in terms of mean relaxation time τ. The relaxation time is defined as the time necessary for a molecule or chain segment to diffuse across the distance of one molecule or chain segment. The relaxation time varies with temperature. Typical relaxation times at *Tg* are 100-200 seconds. As a rule of thumb, the risk of crystallization during glass formation is minimized when relaxation times are similar or larger than experimental time frames, like a drying- or cooling-period. Relaxation times at the storage

conditions will be indicative for shelf life. Molecular relaxation times can be characterized by the change of several bulk properties like enthalpy or volume in time. The extent of relaxation is described empirically by the Kohlrausch-Williams-Watts equation, as discussed by Hodge: [13].

$$\phi(t) = \exp\left[-\left(\frac{t}{\tau}\right)^{\beta}\right], \quad 0 < \beta \leq 1$$

In which $\varphi(t)$ can be considered as the fraction of non-relaxated material at time t and β is the relaxation time distribution parameter which is a function of temperature. The practical application of this equation to characterize relaxation processes in different glasses was shown in a study by six et al. When the mean relaxation time and the relaxation time distribution parameter β are known, a shelf life could be predicted. When it is assumed that for example maximally 10% of the product may reached a relaxed state, i.e. 10% degradation or 10% crystallization, $\varphi(t)$ must be at least 90%. Some amorphous materials show non-Arrhenius behavior since at temperatures just above *Tg*, τ decreases typically by a factor of 10 for every 3K temperature rise. For amorphous materials showing Arrhenius behavior this would be require a 33K temperature change.[13]The temperature dependency of the relaxation time is closely related to viscosity of amorphous solids and hence both properties can be plotted in one graph. (Figure 4) shows the molecular relaxation time and the viscosity for two types of amorphous materials: strong glasses and fragile glasses.

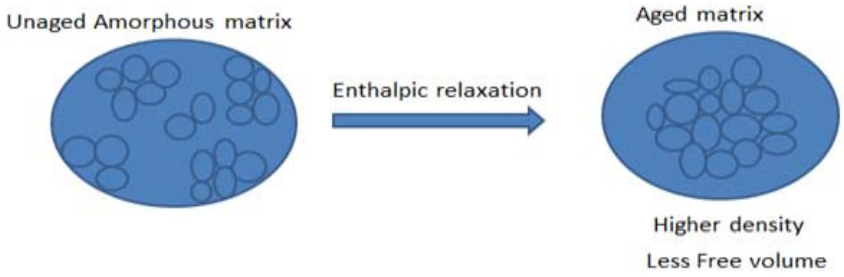

Fig. 4: Amorphous drug relaxation with respect to time

This subdivision of amorphous material is based on the temperature dependence of relaxation time or viscosity above its *Tg*. The strong glasses show Arrhenius behavior, whereas fragile glasses show strong nonlinearity in the viscosity (or relaxation) versus temperature plot, indicating significant deviation from the exponential Arrhenius relation. It should be noted that the viscosity and relaxation time decrease more rapidly in fragile materials. This implies that strong glasses will be more stable and devitrification or crystallization proceeds slower. Unfortunately, it seems that most pharmaceutical amorphous systems show moderately fragile to fragile behavior [14].

Molecular mobility in drug-matrix mixtures: anti-plasticization approach:

Another way of looking at molecular mobility in amorphous solid dispersions is by investigation of the anti-plasticizing of the drug by the matrix. When drug and matrix are mixed homogeneously, the solid dispersion consists of one amorphous phase. By addition of the matrix, usually having a higher *Tg*, the *Tg* of the solid dispersion is elevated compared to that of the drug alone. Accordingly, the molecular mobility of the drug has been reduced. This anti plasticization approach, although reported as separate stabilization mechanism, is essentially the same as *Tg*-dependent mobility reduction. It is obvious that the *Tg*of the matrix should be as high as possible in order to obtain a solid dispersion with a high *Tg* and thus a low molecular mobility. In this respect, the plasticizing effect of water absorbed in solid dispersions should be considered as well. Many matrices are hygroscopic and water will be homogeneously distributed through the solid dispersion. The *Tg*of the matrix can be decreased to below storage temperature and the material becomes prone to devitrification. The plasticizing capacity of water is huge due to its low *Tg*, i.e. 135(K). It can be concluded that the *Tg*of an homogeneous solid dispersion determines its stability [15]. Obviously, the stability of amorphous solid dispersions that consist of two phases is determined by the mobility in those two phases. For example, in an amorphous solid dispersion containing amorphous clusters of drug molecules, the diffusion of drug in the matrix is determined by the *Tg*of the matrix, whereas crystallization of molecules within the clusters will be mainly determined by the *Tg* of the drug. Only at the cluster-matrix interface, the matrix is capable of stabilizing the drug. Therefore, in this type of solid dispersions, the size of the. amorphous drug clusters will affect the crystallization rate to a significant extent [16,17].

Effect of molecular properties on crystallization:

The rate of crystallization of an amorphous material, e.g. a drug, is determined by two distinct processes: nucleation and propagation, i.e. the growth of nuclei to form crystals. Nucleation proceeds faster at lower temperatures, whereas propagation is favored by high molecular mobility, obtained at elevated temperatures. This results in an overall crystallization rate as depicted in (figure 5).

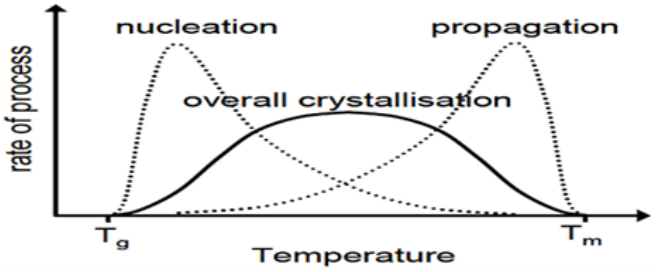

Fig. 5: Overall crystallization rate as a function of temperature.

The crystallization rate also depends on the drug molecule itself. Most lipophilic drugs easily crystallize and therefore occur generally in the crystalline state. However, some molecules like cyclosporine A form a liquid crystal with molecular regularity in only two dimensions, or lipophilic resins like Δ9-tetrahydrocannabinol (THC) simply resist crystallization [18]. Similarly, the matrix PVP resists crystallization, whereas for example PEG and mannitol easily crystallize. It was found that the extent of relaxation in glassy drugs was dependent on the complexity of the molecular structure of the drug molecule

Drug-matrix mass ratio:

Several aspects determine the effect of amorphous solid dispersion composition on physical stability. Firstly, the diffusion distance for separate drug molecules to form amorphous or crystalline particles is larger for lower drug contents. Hence, the formation of a separate drug phase is significantly retarded. Secondly, low drug contents minimize the risk of exceeding the solid solubility [19]. When the solid solubility is lower than the drug load, there is a driving force for phase separation. This is only relevant for drug-matrix combinations that are partially miscible or immiscible. Thirdly, the *Tg*of a homogeneous solid dispersion is a function of the composition. When the drug has a lower *Tg*than the matrix, a high drug content depresses the *Tg* of the solid dispersion, increasing the risk for phase separation. And finally, if drug-matrix interaction increases stability, then also low drug contents are preferred, since in that case drug-drug contacts will be rare and drug-matrix contacts omnipresent. These arguments favour the choice of low drug content. However, high drug content can decrease the hygroscopicity of the solid dispersion and enables the preparation of a high dosed dosage forms. The drug, being hydrophobic in nature, is generally less hygroscopic than the matrix. Molecularly incorporated drug reduces the amount of water that can plasticize the solid dispersion when exposed to a particular relative humidity, thereby decreasing molecular mobility. Therefore, more drugs can not only reduce the *Tg*of the dry solid dispersion but also decrease the plasticizing effect of water. Which one of the two competing effects has a larger contribution is difficult to predict. A second reason for increased stability with increasing drug loads is the inhibition of crystallization of the matrix above a certain drug load, when drug molecules sterically block the migration of matrix molecules [20]. (Table 6) summarizes the effects of an increased drug load.

Table 2: Effects of increasing drug load

Increasing drug load deteriorates physical stability because:
It alters (generally decrease) the Tg of a homogeneous solid dispersion It reduces the distance between drug molecules and hence facilitates crystallization
Increasing drug load improves physical stability because:
It reduces hygroscopicity and hence reduce plasticizing effect of water (especially for homogeneous solid dispersion)
It prevents crystallization of the matrix and hence inhibits phase separation.

To develop a stable solid dispersion, the molecular mobility should be minimized. Mostly, matrices with a high *Tg*are preferred. The selection of high molecular weight matrices is suitable for that purpose, because the free volume is smaller implying that molecular motions are restricted. The relation between high molecular weight and high physical stability is generally acknowledged in solid dispersion literature [21]. In most studies, physical stability is suggested only because dissolution profiles remain constant after storage. The *Tg*of an amorphous matrix increases with increasing molecular weight. Higher temperatures are allowed before transition takes place from the glassy, low mobility state to the rubbery state in which drug molecules can diffuse and crystallize. The *Tg*has a certain maximum value, depending on the monomer. The effect of molecular weight of PEG and PVP was investigated in relation to their dissolution behavior: slow dissolution was attributed to crystallization. Furthermore, gel formation of high molecular weight matrices can decelerate dissolution. The effect of molecular weight on physical stability during storage is scarcely investigated. It was found that low molecular weight PVP did not prevent crystallization, whereas longer chains did. Therefore, low molecular weight matrices are mixed with large matrix molecules to obtain high physical stability [22].

Drug matrix interactions:

Drug-matrix interaction is relevant during preparation and dissolution of solid dispersions. The extent and type of interactions govern miscibility during fusion, dissolution in a common solvent, phase separation and dissolution of the dosage form. Furthermore, drug-matrix interactions determine the physical stability of solid dispersions during storage. For example, H-bonding with PVP is often related to physical stabilization. Efficient insertion of the labile quinapril in the cavity of cyclodextrins resulted in chemical stabilization by complexation [23]. Furthermore; the photo stability of nifedipine could be increased by incorporation in cyclodextrins cavity as well. Another consequence of drug-matrix interactions is an increase of *Tg*to values higher than predicted by the Gordon-Taylor equation. Restricted molecular mobility increases the *Tg*to levels above the *Tg*'s of the individual components. Borax (when molecularly incorporated) is known to increase the *Tg*and *Tg*" of sugar matrices. It is claimed that strong interactions present during complex formation increase the *Tg*and hence increased physical stability. However, discussions are ongoing, which aspect more contributes to stability: drug-matrix interactions or the anti-plasticizing effect, i.e. a high *Tg* of the matrix [24]. When the monomer of PVP, vinylpyrollidone, was compared with PVP, drug-matrix interactions are the same, but physical stability was lost using the monomer [25]. To differentiate between the two aspects, it would be of interest to compare the physical stability of solid dispersions with the same *Tg*'s but different interactions.

Advantages of solid dispersion:

1. Rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic both can lead to the need for lower doses of the drug [26].
2. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and thereby bio-availability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption.
3. Processing equipment available at small and large scale [27].
4. Thermo labile products
5. Relatively high drug doses are possible
6. Most carriers can act as "solid" solvent [28].
7. Carriers (mainly surface active agents) can maintain supersaturation in GI tract
8. Downstream processing is possible.
9. provides better physical stability as compared to purely amorphous system [29].

Advantages over other strategies:

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches [31]. Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its in vivo conversion into acidic or basic forms.Moreover, these type of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE [32].

Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do. Milling or micronizations for particle size reduction are commonly performed as approaches to improve solubility, on the basis of the increase in surface area. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine and, consequently, to improve the bioavailability. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle [33].

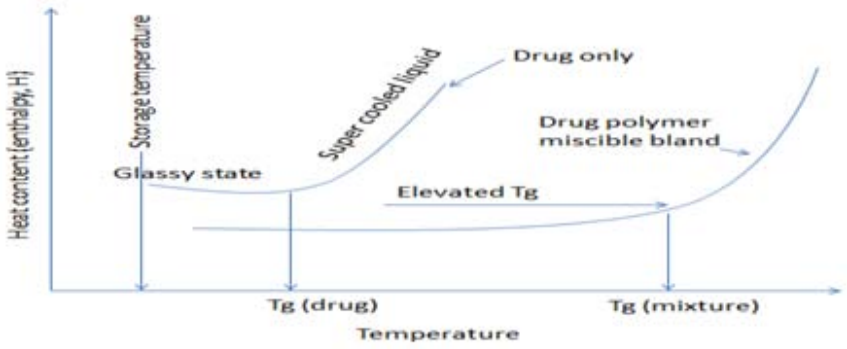

Fig. 6: Advantage of solid dispersion.

Disadvantages of solid dispersion: [34]

The limitations of this technology have been a drawback for the commercialization of solid dispersions, the limitations include:

1. Laborious and expensive methods of preparation,
2. Difficulty in incorporating into formulation of dosage forms,
3. Scale-up of manufacturing process and
4. The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. Not broadly used in commercial products due to change of amorphous state into crystallization [35].

CONCLUSION

This article has outlined some of the current means regard to the physical stability by whichhigh energy amorphous state get converted into crystalline state of solid dispersions,focusing on the solid state properties of the dispersions and the possible fates of drug particles within a solid disperse matrix. It is proposed that by optimizing the ratio of (carrier + drug), choice of the carrier, the prediction of the glass transition temperature of drug and the carrier and the mechanism involved in the physical changes of solid dispersions resulting in crystallization, the stability of solid dispersions can be increased.

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