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A review on the physical stability of amorphous solid dispersion

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Abstract
Solid dispersions in water-soluble carriers have piqued researchers' interest as a way to boost the dissolution rate, and thus the bioavailability, of a variety of hydrophobic drugs. Despite its many benefits, strong dispersion has a number of significant disadvantages. One of the most serious issues is the physical stability of the drug's high-energy amorphous state. Since solid dispersion aids in improving dissolution and solubility, the drug in an amorphous state can crystallise over time. This review focuses on the factors that aid in the improvement of solid dispersion's physical stability. The consequences of a better understanding of physical stability are addressed, with a focus on optimising the carrier-to-drug ratio, carrier selection, and the estimation of the glass transition temperature of the drug. The medication and the carrier, as well as the physical changes in solid dispersions that lead to crystallisation.

Keywords: solid dispersion, physical stability, glass transition temperature, amorphous state

Introduction

Solid dispersions are an effective way to increase the rate of dissolution and thus the bioavailability of a variety of poorly soluble drugs. Solid dispersion is a concept used to describe a collection of solid products made up of at least two separate elements, usually a hydrophilic matrix and a hydrophobic drug. The matrix may be crystalline or amorphous in nature. Amorphous particles (clusters) or crystalline particles may be used to distribute the drug molecularly [1]. Chion and Riegelman defined "A dispersion involving the creation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures," according to the definition of solid dispersion. Strong dispersions were divided into six categories by the researchers: Eutectic mixtures that are simple, Glass suspensions, solid solutions, solid solutions, solid solutions, solid solutions, solid solutions, solid solutions, solid solutions, solid solutions combinations of the previous five groups, amorphous precipitations in a crystalline carrier, compound or complex shape, and amorphous precipitations in a crystalline carrier. While Corrigan (1985) suggested the definition as a solid-state substance produced by converting a liquid drug-carrier mixture. This technique entails removing the crystallinity of the substance, converting the crystalline drug to an amorphous drug, and dispersing the poorly soluble compound molecularly in a hydrophilic polymeric carrier [2]. Solid dispersion is a promising method for improving hydrophobic drug dissolution and bioavailability. Changes in the preparation and storage conditions of solid dispersions can affect the active ingredients' dissolution characteristics [3]. Solid dispersions have overcome the drawbacks of previous methods such as salt formation, solubilization by co solvents, and particle size reduction to improve bioavailability of poorly water-soluble drugs. When a strong dispersion is exposed to water, it becomes aqueous. The carrier dissolves in the media, releasing the medication as fine colloidal particles. Poorly water-soluble drugs have a higher dissolution rate and bioavailability as a Result of the increased surface area. Furthermore, in solid dispersions, a portion of the drug dissolves quickly to saturate the gastrointestinal tract fluid, and the rest settles out as fine colloidal particles or oily globules of submicron size [4].

Significant properties of solid dispersion [5].

The following are some of the unique characteristics of solid dispersion:

1. Drug Particles with a Higher Porosity: It has been discovered that drug particles in stable dispersions have a higher porosity. Porosity increases depending on the properties of the carriers used; for example, solid dispersions containing linear polymers yield larger and more porous particles than those containing reticular polymers, and as a consequence, the dissolution rate and therefore bioavailability would be higher.
2. Reduced Dug Particle Size: A large surface area is formed, resulting in a higher dissolution rate and, as a result, better bioavailability.
3. Improved Wettability: Drug wettability improvement in solid dispersions has been shown to have a significant impact on drug solubility. Even carriers with no surface movement, such as urea, were found to increase medication wettability. Cholic acid and bile salts, for example, are surface-active carriers. When used correctly, it will greatly improve the wettability of medications.
4. Amorphous Drugs: Since no energy is used to break up the crystal lattice during the dissolution process, the amorphous state of the substance may normally be used to improve drug release.

Amorphous Solid Dispersion Physical Stability

During storage, the dissolution behaviour of solid dispersions must not alter. Maintaining their physical state and molecular composition is the only way to ensure this. The molecular mobility of amorphous solid dispersions should be as minimal as possible for optimum stability. Strong dispersions, whether partly or fully amorphous, are, however, thermodynamically fragile. These particles form nuclei in stable dispersions containing crystalline particles, and may serve as a starting point for further crystallisation. During storage, such solid dispersions have been found to have increasingly worse dissolution activity. The drug will crystallise in solid dispersions containing amorphous drug particles, but a nucleation step is necessary first. The drug is molecularly distributed in homogeneous solid dispersions, so crystallisation is needed. Drug molecules must move through the matrix before nucleation can occur. As a result, both diffusion and crystallisation of drug molecules in the matrix determine physical degradation. It should be remembered that a crystalline matrix is preferable in this regard because diffusion is much slower in such a matrix. Changes in the physical world are portrayed in (fig. 1). The physical stability of amorphous solid dispersions should be considered not only in terms of drug crystallisation, but also in terms of any changes in molecular structure, such as drug delivery. Furthermore, the physical state of the matrix should be tracked, as changes there will likely affect the physical state of the drug as well as drug release [6].

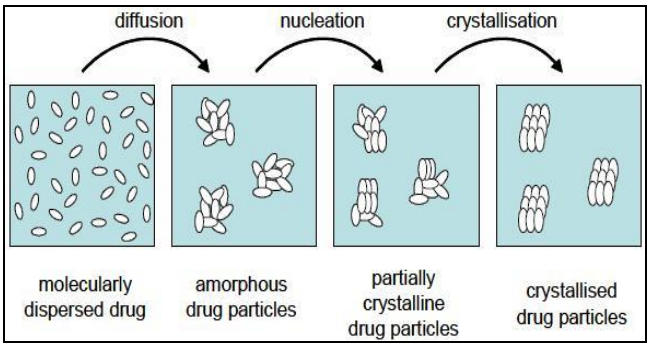

Fig 1: Crystallization occurs as a result of physical modifications in solid dispersions.

Amorphous state physical properties

Materials may exist in a variety of states. Above the melting temperature (Tm), the crystalline and liquid states are thermodynamically healthy. Since the crystalline state has a lower energy than the amorphous state, amorphous materials are thermodynamically unstable and would naturally crystallise. Amorphous materials, on the other hand, may be kinetically stable, meaning that the equilibrium state, i.e. crystalline, is not achieved within the timeframe of the experiment or the product's shelf life [7]. The physical state of an amorphous substance determines its kinetic stability. The glassy state and the rubbery state are the two physical states of amorphous materials. The most important characteristics of the various thermodynamically stable and unstable states that materials can be found in are Seen in (Table 1).

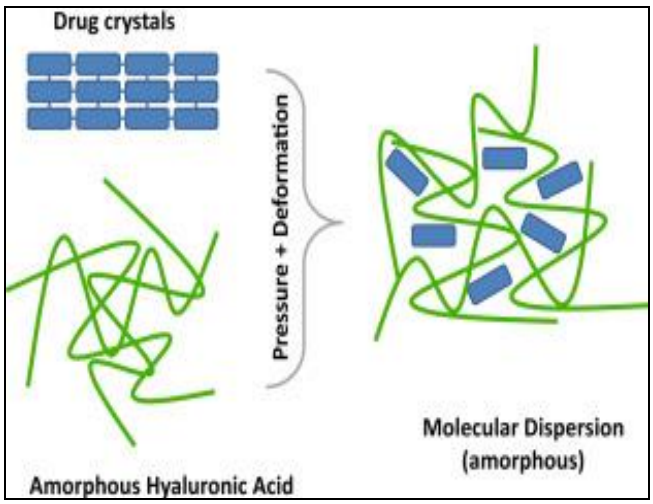

Fig 2: Molecular dispersion of drug

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 tool for determining a polymeric material's property. The temperature at which a polymer transitions from a hard, glassy state to a rubbery state is known as the glass transition. Put a rubber band (in a rubber-like state, very flexible) into a tub of liquid nitrogen to visualise this kind of transformation. As the rubber band is cut, it becomes rigid and inflexible (glass state), and it can also be broken. The rubber band would become soft and rubbery again after standing and warming to room temperature (rubber like state). The glass transformation is described by DSC as a shift in heat capacity as the polymer matrix transitions from glass to rubber. Since this is a second order endothermic transformation (which takes heat to complete), the DSC shows the transition as a phase rather than a peak, as it does for a melting transition.

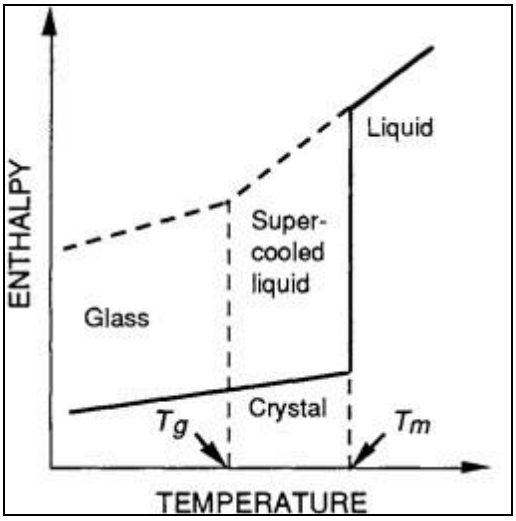

Fig 3: Temperature-dependent changes in free volume and enthalpy.

Molecular mobility in amorphous solid [12].

Physical stability and reactivity of amorphous materials are determined by molecular mobility. While molecular mobility is linked to macromolecular properties such as viscosity, it is most commonly measured in terms of mean relaxation time. The relaxation time is the amount of time it takes for a molecule or chain segment to diffuse over a single molecule or chain segment's distance. Temperature affects the recovery time. At Tg, typical relaxation times range from 100 to 200 seconds. When relaxation periods are close to or greater than experimental time frames, such as a drying or cooling cycle, the chance of crystallisation during glass formulation is reduced. The shelf life can be determined by the time it takes to relax in the storage conditions. The transition in bulk properties such as enthalpy or volume over time can be used to describe molecular relaxation times. The Kohlrausch Williams-Watts equation, as explained by Hodge, empirically describes the degree of relaxation: [13].

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

In which φ (t) represents the fraction of non-relaxated material at time t, and β is the temperature-dependent relaxation time distribution parameter. A research by six *et al*. demonstrated the functional use of this equation to describe relaxation mechanisms in various glasses. A shelf life could be calculated if the mean relaxation time and the relaxation time distribution parameter β were known. When it is expected that only 10% of the sample can enter a relaxed state, such as 10% degradation or 10% crystallisation, φ (t) must be at least 90%. Some amorphous materials exhibit non-Arrhenius behaviour, as at temperatures just above Tg, τ usually decreases by a factor of ten with every 3K temperature increase. A 33K temperature shift is needed for amorphous materials to exhibit Arrhenius behaviour. 13 Since the temperature dependence of relaxation time is closely similar to the viscosity of amorphous solids, all properties can be plotted on the same graph. The molecular relaxation time and viscosity for two forms of amorphous materials are seen in Figure 4: solid glasses and delicate glasses.

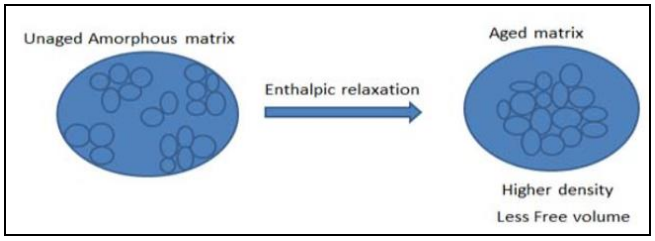

Fig 4: Relaxation of amorphous drugs with respect to time

The temperature dependency of relaxation time or viscosity above Tg is used to divide amorphous materials. The viscosity (or relaxation) versus temperature plot in the solid glasses shows Arrhenius behaviour, while the viscosity (or relaxation) versus temperature plot in the fragile glasses shows strong nonlinearity, showing a major variance from the exponential Arrhenius relation. It should be remembered that the viscosity and relaxation time of delicate materials decrease more quickly. Solid glasses will be more durable, and devitrification and crystallisation will take longer. Unfortunately, most pharmaceutical amorphous structures seem to be relatively delicate to fragile [14].

Anti-plasticization approach to molecular mobility of drug-matrix mixtures:

Another approach to investigate molecular mobility of amorphous solid dispersions is to dig at the matrix's anti-plasticizing of the drug. The solid dispersion consists of one amorphous step while the drug and matrix are homogeneously combined. The Tg of the solid dispersion is increased when the matrix is added, which normally has a higher Tg than the drug alone. As a result, the drug's molecular mobility has been limited. While defined as a different stabilisation mechanism, this anti-plasticization strategy is basically the same as Tg-dependent mobility reduction. To achieve a solid dispersion with a high Tg and hence a low molecular mobility, the Tg of of the matrix should obviously be as high as possible. The plasticizing effect of water consumed in solid dispersions should also be regarded in this regard. Since certain matrices are hygroscopic, water would be dispersed uniformly in the solid dispersion. The Tg of of the matrix can be reduced below storage temperature, causing the substance to devitrify. Water has a large plasticizing potential owing to its low Tg, which is 135 degrees Fahrenheit (K). The Tg of of a homogeneous solid dispersion determines its consistency, it can be inferred [15]. Obviously, the mobility of the two phases determines the consistency of amorphous solid dispersions of two phases. For eg, in an amorphous solid dispersion containing amorphous clusters of drug molecules, the Tg of the matrix determines drug diffusion in the matrix, while the Tg of the drug determines crystallisation of molecules within the clusters. The matrix is only capable of stabilising the drug at the cluster-matrix interface. As a result, the size of the amorphous drug clusters would have a large impact on the crystallisation rate in this form of solid dispersion [16, 17].

Crystallization and the influence of molecular properties:

Two separate processes govern the pace of crystallisation of an amorphous substance, such as a drug: nucleation and propagation, or the development of nuclei to create crystals. At lower temperatures, nucleation occurs more quickly, but

at higher temperatures, high molecular mobility favours propagation. As shown in the graph, this leads in an overall crystallisation rate (figure 5).

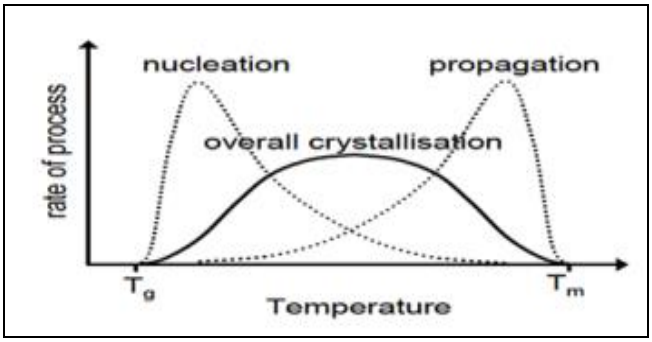

Fig 5: Temperature-dependent overall crystallisation rate.

The rate of crystallisation is also influenced by the medication molecule. Because most lipophilic medicines crystallise quickly, they are usually found in crystalline form. Some compounds, such as cyclosporine A, form a liquid crystal with molecular regularity in just two dimensions, whereas lipophilic resins, such as 9-tetrahydrocannabinol (THC), simply refuse to crystallise [18]. Similarly, the matrix PVP is resistant to crystallisation, whereas PEG and mannitol crystallise readily. The level of relaxation in glassy medicines was discovered to be dependent on the intricacy of the drug's molecular structure.

Drug-matrix mass ratio:

The influence of amorphous solid dispersion composition on physical stability is determined by several factors. With starters, for lower drug concentrations, the diffusion distance between single drug molecules to form amorphous or crystalline particles is greater. As a result, the establishment of a distinct drug phase is greatly slowed. Second, low drug concentrations reduce the possibility of surpassing solid solubility [19]. There is a driving force for phase separation when the solid solubility is smaller than the medication load. This is only applicable for partially miscible or immiscible drug-matrix combos. Finally, the composition affects the Tg of a homogenous solid dispersion. A large drug concentration lowers the Tg of the solid dispersion when the drug has a lower Tg than the matrix, increasing the danger of phase separation. Finally, if drug-matrix interaction improves stability, low drug content is desired, as drug-drug interactions will be rare and drug-matrix interactions will be common. These considerations support the use of low-drug formulations. However, a high drug concentration can reduce the solid dispersion's hygroscopicity, allowing for the production of high-dosed dosage forms. Because to its hydrophobic character, the medication is less hygroscopic than the matrix. When exposed to a specific relative humidity, a molecularly integrated medication limits the quantity of water that may plasticize the solid dispersion, lowering molecular mobility. As a result, additional medicines can diminish both the Tg of the dry solid dispersion and the plasticizing action of water. It's impossible to say which of the two competing impacts will make a bigger impact. The prevention of matrix crystallisation above a specific drug load, when drug molecules sterically hinder the migration of matrix molecules, is a second rationale for enhanced stability with increasing drug loads [20]. The consequences of a higher medication load are summarised in (Table 6).

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.

The molecular mobility should be kept to a minimum in order to generate a stable solid dispersion. The majority of the time, matrices with a high Tg are favoured. The use of matrices with a high molecular weight is appropriate for this purpose since the free volume is less, meaning that molecular movements are limited. In the literature on solid dispersion, the link between large molecular weight and great physical stability is well recognised [21]. Physical stability is suggested in most investigations mainly because dissolution profiles do not change after storage. The Tg of an amorphous matrix rises as the molecular weight rises. Before the shift from the glassy, low mobility state to the rubbery state, where drug molecules can diffuse and crystallise, higher temperatures are permitted. Depending on the monomer, the Tg has a maximum value. The influence of PEG and PVP molecular weight on their dissolving behaviour was investigated: sluggish dissolving was ascribed to crystallisation. In addition, the production of gels from high molecular weight matrices might slow down dissolution. The impact of molecular weight on physical stability during storage is a topic that has received little attention. PVP with a low molecular weight did not inhibit crystallisation, whereas PVP with a longer chain did. To achieve excellent physical stability, smaller molecular weight matrices are combined with big matrix molecules [22].

Interactions between drugs and their matrix

During the creation and dissolution of solid dispersions, drug-matrix interaction is important. Miscibility during fusion, dissolving in a shared solvent, phase separation, and dosage form dissolution are all governed by the degree and kind of interactions. The physical stability of solid dispersions during storage is also determined by drug-matrix interactions. H-bonding with PVP, for example, is frequently associated with physical stability. Chemical stabilisation was achieved by complexation after efficient insertion of the labile quinapril into the cavity of cyclodextrins [23]. Furthermore, nifedipine's photo stability might be improved by incorporating it into the cavity of cyclodextrins. Another effect of drug-matrix interactions is an increase in Tg above what the Gordon-Taylor equation predicts. Tg rises above the Tg of the individual components due to restricted molecular mobility. Borax has been shown to boost the Tg and Tg of sugar matrices when molecularly integrated. Strong contacts occurring during complex formation are said to raise Tg, resulting in improved physical stability. However, there is still debate on which factor contributes more to stability: drug-matrix interactions

or anti-plasticizing effect, i.e. a high *Tg* of the matrix [24]. Drug-matrix interactions are the same when the monomer of PVP, vinylpyrollidone, is compared to PVP, however physical stability is decreased when utilising the monomer [25]. It would be interesting to evaluate the physical stability of solid dispersions with the same Tgs but different interactions to distinguish between the two characteristics.

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].

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 which high 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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