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Review: physical chemistry of solid dispersions

Sandrien Janssens and Guy Van den Mooter

Laboratorium voor Farmacotechnologie en Biofarmacie, Katholieke Universiteit Leuven, Leuven, Belgium

Abstract

Objectives With poorly soluble drug candidates emerging in the drug discovery pipeline, the importance of the solid dispersion formulation approach is increasing. This strategy includes complete removal of drug crystallinity, and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier. The potential of this technique to increase oral absorption and hence bioavailability is enormous. Nevertheless, some issues have to be considered regarding thermodynamic instability, as well in supersaturated solutions that are formed upon dissolution as in the solid state.

Key findings After a brief discussion on the historical background of solid dispersions and their current role in formulation, an overview will be given on the physical chemistry and stability of glass solutions as they form supersaturated solutions, and during their shelf life.

Conclusions Thorough understanding of these aspects will elicit conscious evaluation of carrier properties and eventually facilitate rational excipient selection. Thus, full exploitation of the solid dispersion strategy may provide an appropriate answer to drug attrition due to low aqueous solubility in later stages of development.

Keywords carrier selection; crystallization; glass solution; molecular mobility; solid solubility; supersaturation

Introduction

Due to the nature of current drug selection procedures, such as high throughput screening and combinatorial chemistry, new drug candidates tend to have a high affinity and selectivity for their targets. However, a downside of such strategies is that they also tend to sub-select for unfavourable drug-like properties with respect to drug delivery, which leads to drug attrition in later stages of development. Therefore current drug discovery and development programmes are being adapted to the philosophy 'fail early, fail cheaply'. On the other hand this phenomenon has led to the development of several new formulation strategies that aim at increasing the oral bioavailability.[1]

Bioavailability

A drug is orally active if it dissolves into the gastrointestinal juices, then permeates the gut wall, passes through the liver without being inactivated and finally enters the systemic blood flow. For the majority of new chemical entities this trajectory contains a number of bottlenecks, of which dissolution is the major problem for drugs with a poor aqueous solubility. Based on the possible rate-limiting steps of absorption, Amidon *et al.* classified active compounds into four groups according to their solubility and permeability. This is generally known as the Biopharmaceutical Classification System (BCS).[2] Class I compounds have a high solubility and permeability, therefore their bioavailability will depend solely on the gastric emptying rate. For class II compounds with a low aqueous solubility and sufficient permeability the dissolution will be the rate limiting step. Class III compounds have sufficient solubility but poor permeability and hence the absorption rate will be determined by passage through the gut wall. In the case of class IV compounds with both low solubility and permeability, the rate limiting step will differ case by case.

Dissolution

A drug's solubility is problematic if the required dose cannot dissolve into the available volume of gastrointestinal juices. A well-studied example of such a drug is itraconazole, which is a weak base that is expected to dissolve primarily in the stomach, with an

Correspondence: Mr Guy Van den Mooter, Laboratorium voor Farmacotechnologie en Biofarmacie, Katholieke Universiteit Leuven, Leuven, Belgium.
E-mail: guy.vandenmooter@pharm.kuleuven.be

aqueous solubility of 1 ng/ml at neutral pH, 4 μg/ml at pH 1 and a dose of 100 mg.[3] Therefore, 25 L would be required to dissolve the dose at pH 1. A consequence of low aqueous solubility is a slow dissolution rate, which is especially important for drugs with an absorption window, since they might have passed their absorptive sites by the time they have dissolved. The relation between solubility and dissolution rate is given by the Noyes–Whitney equation (Equation 1):[4]

$$dM/dt = AD(C_s - C_t)/h \quad (1)$$

where dM/dt is the dissolution rate, A is the specific surface area of the drug particle, D is the diffusion coefficient, h is the diffusion layer thickness, C_s is the saturation solubility and C_t is the drug concentration at time t. The diffusion coefficient depends on the molecular weight of the drug and the viscosity of the gastrointestinal fluids, which varies in the fed and fasted state and is subject to large intra- and inter-subject variability. The same is true for the diffusion layer thickness, which is largely dependent on the hydrodynamics during gastrointestinal transit. Therefore these parameters are less suitable targets for bioavailability optimization. Manipulation of the saturation solubility and specific surface area, however, has given rise to a large variety of formulation strategies. The surface area in contact with the dissolution medium is increased via particle size reduction and improved wetting. The saturation solubility can be increased not only by chemically modifying the active compound (e.g. by preparing prodrugs or salts) but also by changing the physical state of the drug in the formulation. Indeed, metastable polymorphic modifications and the amorphous state all have a higher free energy than the most stable crystal state. Therefore, these forms have a higher apparent solubility that can be utilized in formulations of poorly water soluble compounds. The downside of such high energy states, however, is their thermodynamic instability and that conversions to more stable physical states will also lead to changes with respect to solubility and dissolution rate. Finally, formulation ingredients can also be utilized to solubilize the poorly soluble active compound upon dissolution or to stabilize supersaturated drug solutions.

Solid dispersions

Formulation of poorly soluble compounds as solid dispersions is one strategy to tackle dissolution-rate-limited oral absorption. Chiou and Riegelman have defined solid dispersions as 'a dispersion of one or more active ingredients in an inert carrier at the solid state, prepared by the melting, the solvent or the melting solvent method'.[5] Formulation of poorly soluble compounds as solid dispersions might lead to particle size reduction, improved wetting, reduced agglomeration, changes in the physical state of the drug and possibly dispersion on a molecular level, according to the physical state of the solid dispersion. The physical state of the solid dispersion will depend on the physicochemical properties of the carrier and the drug, the drug–carrier interactions and the preparation method. Chiou and Riegelman were also the first to introduce a solid dispersion classification system based on the possible physical states,[5] which will be briefly discussed below (interested readers are encouraged to look up the excellent reviews by Ford, Chiou and Riegelman, Leuner and Dressman, Vasconcelos and Serajuddin[5–10]). However, over the years, the development of formulation strategies for poorly soluble compounds, such as nanosuspensions, cocrystals, semi-solid and solid lipid formulations have made the line between solid dispersions and the above-mentioned formulation types less clear. Indeed, nanoparticles can be stabilized in solid matrices,[11] cocrystals might be considered as substitutional solid solutions[12] and in semi-solid and solid lipid formulations the drug can also be dispersed or dissolved in the solid state.[13] Nowadays, the term solid dispersion is mostly linked to glass solutions of poorly soluble compounds, using amorphous carriers with high glass transition temperatures. Recently, some new solid dispersion formulations have entered the market (Table 1): Kaletra (Abbott), Intelence (Tibotec), Certican (Novartis), Isoptin SR-E (Abbott), Nivadil, Prograf (Fujisawa Pharmaceutical Co., Ltd) and Rezulin (Sankyo). All of these new formulations utilize amorphous polymers as a carrier. Therefore, this review will focus on this particular subtype of solid dispersion – amorphous glass solutions with hydrophilic polymeric carriers for fast release. For this subtype, the molecularly dispersed drug will be released as the hydrophilic carrier dissolves, to form a supersaturated solution. Therefore, dissolution is generally sufficient for amorphous

Table 1 Examples of commercially available solid dispersions

Brand name	Manufacturer	Drug	Carrier
Gris-PEG	Pedinol Pharmacal Inc.	Griseofulvin	PEG6000
Cesamet	Valeant Pharmaceuticals	Nabilone	PVP
Kaletra	Abbott	Lopinavir, ritonavir	PVPVA
Sporanox	Janssen Pharmaceutica	Itraconazole	HPMC
Intelence	Tibotec	Etravirin	HPMC
Certican	Novartis	Everolimus	HPMC
Isoptin SR-E	Abbott	Verapamil	HPC/HPMC
Nivadil	Fujisawa Pharmaceutical Co., Ltd	Nivaldipine	HPMC
Prograf	Fujisawa Pharmaceutical Co., Ltd	Tacrolimus	HPMC
Rezulin	Developed by Sankyo, manufactured by Parke-Davis division of Warner-Lambert	Troglitazone	PVP

HPMC, hydroxypropylmethylcellulose; HPC, hydroxypropyl cellulose; PVP, polyvinylpyrrolidone; PVPVA, polyvinylpyrrolidone-co-vinylacetate.

glass solutions. The formation of a supersaturated solution on the other hand, often requires stabilizing formulation compounds to prevent precipitation. This aspect will be discussed in detail since it is an important factor when it comes down to excipient selection. Currently, much research is also focused on the physical stability of amorphous solid solutions, which is still one of the main reasons why only a few amorphous solid solutions have made it to the market. Therefore, the carriers' influence on molecular mobility, crystallization of the drug from its amorphous state and finally solid state solubility will be discussed as well. This review will thus summarize the most fundamental aspects of glass solutions with respect to release characteristics and stability. Eventually, thorough understanding will lead to rational selection and design of carriers, either by blending or by synthesizing new materials.

Preparation and classification of solid dispersions

Preparation of solid dispersions by the melting or fusion method

In general, heating all components above their melting or glass transition temperatures, followed by mixing and cooling, is covered by the term 'melting method'. The first to report on solid dispersions, Sekiguchi and Obi[14] used a fusion method to prepare a sulfathiazole–urea solid dispersion of eutectic composition and noticed a significantly higher release than that obtained with conventional formulation methods. In this study the solid dispersion was obtained by simply melting the sulfathiazole–urea mixture, cooling it on an ice bath and pulverizing it to obtain a powder. A scalable and industrially applicable variation of this method is 'hot stage' or 'hot melt' extrusion. In the most common set-up a powder blend is introduced via a hopper into a heated barrel with a co-rotating twin-screw, where the powder blend is intensively mixed in the liquid state and moved towards a die that shapes the melt as films, granules or pellets. Interesting work on the optimization of the melt extrusion process as a manufacturing tool has been done by Doelker.[14] Nakamichi described in detail the equipment set-up for manufacturing solid dispersions.[15,16] Further research regarding the influence of formulation factors on melt extrusion, such as plasticization by drugs and plasticizers, and optimization of the process towards thermolabile compounds, has been done by the group of McGinity.[17–20] Another application is spray congealing, which is defined as a process by which a melt is transformed into solid particles of spherical shape by spraying the melt into a cooling chamber through which ambient or cooled, low-temperature air is passing. The advantage of this process is that pellets can be obtained immediately. Physicochemical modifications due to additional processing steps are thus prevented.[21–24] In direct capsule filling, the drug–carrier melt is directly filled into hard gelatin capsules. This way, better weight and content uniformity is achieved than with the powder fill technique, since solid dispersions are often difficult to handle due to their waxy consistence. Polyethylene glycols (PEGs) are well suited for this procedure because of their low melting points. However, phase separation and crystallization often occurs upon solidification, due to the general low solid solubility of drugs into PEGs. Therefore, surfactants can be added to the PEG matrix to solubilize the dispersed drug.[25–28] Goldberg *et al.* reported on the potential drawbacks of the melting methods, such as thermal degradation, sublimation and polymorphic modifications.[29] Also, miscibility gaps in the liquid state influence the degree of dispersion in the solid state.[30] The advantage of the fusion method is that no organic solvents are involved, which reduces production costs.

Preparation of solid dispersions by the solvent method

With the solvent method, solid dispersions are obtained by evaporating the common solvent from a drug–carrier solution. Since, in solid dispersions for fast drug release, hydrophilic carriers are combined with hydrophobic drugs, finding a common solvent is not always straightforward. Also, a secondary drying step is imperative to reduce the residual solvent to below acceptable levels for toxicity issues and the chemical stability of the drug. Furthermore, even a small amount of solvent can plasticize the solid dispersion matrix and hence lead to physical instability. The advantage of solvent techniques is that in general they are operated at lower temperatures than melting methods, and therefore they are more suitable for processing thermolabile compounds. The temperature, the evaporation rate and the type of solvent have an influence on the physical state of the obtained solids.[31] The first report on a solid dispersion prepared by a solvent method was done in 1965 by Tachibana and Nakamura, who dissolved β-carotene and polyvinylpyrrolidone (PVP) in a common solvent, chloroform, and obtained solid dispersions upon evaporation.[32] Practical applications of the solvent method are spray drying and freeze drying. In both procedures the solvent is removed rapidly. In spray drying, the drug–polymer solution is atomized and dispersed into hot gas, which causes the solvent to evaporate and leads to the generation of spherical particles.[33] Freeze drying or lyophilization is a technique in which the drug–carrier solution is frozen and the solvent is sublimed under reduced pressure.[34,35] In another application the fluidized bed system can be used to coat beads with drug–polymer solutions and, hence, generate pellets that are coated with solid dispersion.[36,37] The marketed form of itraconazole, Sporanox, is prepared by spraying an itraconazole–hydroxy propylmethylcellulose (HPMC) coating onto sugar beads from a dichloromethane–ethanol solution.

Non-conventional methods for solid dispersion manufacturing

A number of new techniques that have emerged from the polymer industry have been introduced to manufacture solid dispersions. Electrostatic spinning involves the use of high voltages to induce surface charges sufficient to overcome the surface tension in a pendant polymer droplet, and hence trigger the formation of a jet that solidifies as a fine fibre. This method has been used to produce solid dispersions with polymeric carriers.[38,39] The application window of hot-stage extrusion has been broadened by using sub- or

supercritical carbon dioxide as a temporary plasticizer, allowing thermolabile drug–polymer blends to be extruded at lower temperatures.[40–43] A detailed review on the pharmaceutical applications of techniques using supercritical fluids is given by Pasquali *et al.*[44]

Classification

A physicochemical classification of solid dispersions was first introduced by Chiou and Riegelman.[5] This classification included simple eutectic mixtures, solid solutions and glass solutions.

Eutectic mixtures

Eutectic mixtures are formed from two components that are miscible in the liquid state and immiscible in the solid state. At the eutectic composition the two components cocrystallize at the eutectic temperature. At any other composition, one of the two components will start crystallizing before the eutectic temperature is reached.[45] For the simple eutectics, the enhanced release characteristics are mainly due to the dispersion of the drug as fine crystals, improved wetting because of the presence of the carrier, in some cases solubilization of the dissolved drug, and impeded agglomeration of the fine drug particles.

Solid solutions

The term solid solution was introduced to explain the fact that for extreme compositions of a drug and a crystalline carrier, either a high or a very low drug load, a certain degree of solid solubility of one compound into the other was often observed. This was referred to as discontinuous solid solutions. Indeed, the phase diagram of the eutectic sulfathiazole–urea system introduced by Sekiguchi and Obi[14] was later interpreted by Goldberg *et al.*[29] as a system with limited solid solubility, with the maximum solid solubility of sulfathiazole in urea being ca. 10% w/w and the maximum solid solubility of urea into sulfathiazole ca. 8% w/w. This implies that the eutectic that is formed at a sulfathiazole weight percentage of 52 is in theory a physical mixture of two solid solutions. It is expected that a limited solid solubility exists for all binary systems. The continuous solid solution, a system in which a solid solution of two components is obtained at any composition ratio, was introduced as well.[46] The theoretical ground for such systems was adapted from the field of metals and alloys, but to date no such system has been reported for pharmaceuticals. A second criterion in the classification of solid solutions is the relative molecular size of the drug and the carrier, by which the subclasses of interstitial and substitutional solid solutions are defined. The former consists of a large carrier molecule (e.g. a polymer) and a small active compound and the latter of a drug and carrier of similar size.[47,48] As it was hypothesized that drugs could be molecularly dispersed into the crystalline moieties of PEG, solid solutions of drugs in PEGs were considered to be interstitial.[5] Later, however, it was observed that molecularly dispersed drugs reside predominantly in the amorphous parts of PEG.[49–52] Note that the term 'solid solution' refers to systems with crystalline carriers.

Glass solutions

The third class is that of the glass dispersions or solutions. These systems consist of amorphous carriers and the drug can be either molecularly dispersed or form an amorphous precipitate into its carrier, which can possibly crystallize upon time. Examples of carriers that favour the formation of glass solutions are sugars, such as dextrose, fructose, galactose, trehalose, sucrose, and different types of inulin,[53–55] or amorphous polymers such as PVP, Polyvinylpyrrolidone-co-vinylacetate (PVPVA) and HPMC. The earliest examples of such glassy dispersions were prepared with PVP[56] and currently this class represents the most intensively studied and applied solid dispersion system.

Release

In the case of solid solutions and glass solutions, the size of the drug particle is reduced to the absolute minimum since the drug is molecularly dispersed. In terms of release this holds an advantage. Indeed, upon dissolution no energy will have to be delivered to break down the drug's crystal lattice, which is the case for eutectics where fine drug crystals are still present. Therefore, the drug molecules will be released as the hydrophilic carrier dissolves and hence form a supersaturated solution. In such metastable solutions, the drug is prone to precipitation. On the other hand both the carrier and biological factors, such as bile salts and fatty acids from digestive products, can influence the in-vivo precipitation behaviour or solubilize the drug.[57–61]

Physicochemical properties

Most drug–carrier systems are only partially miscible, with phase separation occurring as the drug weight fraction increases.[62–64] This way either amorphous or crystalline drug clusters precipitate into a glassy drug–carrier solution. Upon time, glassy drug clusters can crystallize, leading to a decrease in the apparent solubility and hence in dissolution rate.[65] Indeed, amorphous compounds generally have a higher apparent solubility than their crystalline counterparts. However, accurate (apparent) solubility measurements are scarce since amorphous compounds tend to crystallize during dissolution.[66] If a drug is formulated as a glass solution, the absence of drug neighbours and the viscous environment in the dissolving interface will impede drug cluster formation and, therefore, nucleation and crystal growth. The ease of crystallization of a drug from its amorphous state depends on the driving force for crystallization given by the free energy difference between the amorphous and the crystalline state, the mobility of the amorphous state and the crystallization mechanism.[67] Therefore, amorphous formulations benefit from the presence of an amorphous stabilizer, with respect to dissolution, as well as the shelf-life stability. To obtain a single amorphous drug–polymer phase, a certain degree of solid solubility, miscibility and kinetic stabilization is required.[68] The term 'solid solubility' refers to the thermodynamic solubility of one solid into the other, 'miscibility' refers to the miscibility of two amorphous compounds in their (super-cooled) liquid state and 'kinetic stabilization' refers to immobilizing supersaturated drug concentrations into a highly viscous matrix and hence preventing phase separation and crystallization. This type

of kinetic stabilization is generally referred to as the anti-plasticizing effect. Since glass solutions are often supersaturated, kinetic stabilization plays an important role. The importance of kinetic stabilization is the main reason for the popularity of the 'Tg – 50°C' rule that states that the molecular mobility of an amorphous solid becomes negligible 50°C below the glass transition temperature (Tg).[69] Hence, the physical stability improves since phase separation and crystallization require mobility.

The glass transition

Glass solutions of a miscible drug–carrier system typically display a glass transition at a temperature that is between the glass transition temperatures of the pure amorphous compounds. The exact position can give additional information on the nature and size of the adhesive forces in the mixture compared with the cohesive forces within the pure amorphous components. Provided that the adhesive interactions are of the same order of magnitude as the cohesive forces, and the volumes of the mixture components are additive, there is a relationship between the glass transition temperature and the composition of the mixture. This relationship is expressed by the Gordon–Taylor/Kelly–Bueche equation (Equation 2), in combination with the Simha–Boyer rule (Equation 3).[70–72] These equations have originally been derived for polymer blends but they have been proven to be applicable to small molecule–polymer systems as well.

$$Tg_{mix} = (w_1 Tg_1 + \mathrm{K} w_2 Tg_2)/(w_1 + \mathrm{K} w_2) \qquad (2)$$

Equation 2 is the Gordon–Taylor equation in which w stands for the weight fraction and Tg for the glass transition temperature (in K); subscripts 1 and 2 represent the amorphous compounds with the lowest and the highest glass transition temperature, respectively; and K is a constant that can be estimated with the Simha–Boyer rule:

$$\mathrm{K} \cong \rho_1 Tg_1/\rho_2 Tg_2 \qquad (3)$$

in which ρ is the density of the amorphous components. Deviation from the theoretical values can indicate undetected phase separation and hence a different composition, non-volume additivity, strong specific interactions or the presence of an additional plasticizer such as water.[63]

In addition to surface adsorption, molecules in an amorphous phase are capable of adsorbing considerable amounts of water. Since water has a Tg of 136 K, it will significantly plasticize, and potentially destabilize, amorphous materials.[73] Temperature, partial vapour pressure and properties of the substrate determine the magnitude of water-vapour adsorption. The larger water-vapour adsorption into PVP as compared with polyvinylacetate points to the importance of the type and number of functional groups capable of forming hydrogen bonds with water vapour.[74] Also changes in the free volume of amorphous materials affect the magnitude of water adsorption.[75–78]

There are other equations to describe the composition dependence of glass solutions (i.e. the Fox equation[69] and the Couchman–Karasz equation)[79,80] but the Gordon–Taylor equation is the most widely used. In a recent paper by Pinal, a comment has been formulated with respect to the fact that none of these widely used equations includes an entropy of mixing term. Therefore, a modification of the Couchman–Karasz equation has been proposed with a term that accounts for the residual entropy of mixing, which is minimal for slowly cooled glasses. Kinetic effects due to the preparation methodology are thus accounted for as well.[81]

Criteria for carrier selection

The primary aim of fast release glass solutions is to 'molecularly' release the drug in the intestinal fluids and to generate a supersaturated solution from which the drug will move to the gut wall, permeate and finally appear in the blood. On the other hand the formulation should remain chemically and physically stable upon storage. Hence utilization of these high-energy states to obtain both an adequate bioavailability and an acceptable shelf-life stability is the challenge to meet. The choice of carrier has a tremendous impact on the success rate of the solid dispersion strategy. Table 2 gives an overview of the most important carrier properties and Table 1 gives an overview of the polymers that are being used in marketed formulations (i.e. PEG, PVP, PVPVA, HPMC and hydroxypropylcellulose (HPC)). To obtain sufficient kinetic stabilization in the mostly supersaturated glass solutions, a high glass transition temperature is an invaluable property for a good carrier. The presence of functional groups that are either donors or acceptors for hydrogen bonds is an additional benefit, since specific interactions increase the solid solubility of the drug into its carrier and also seem to play an important role in inhibiting phase separation and crystallization of a drug from a glass solution.[68,82] The carrier should be inert and generally recognized as safe (GRAS). Also, with respect to manufacturing solid dispersions, thermal stability and thermoplasticity are advantageous for systems prepared by hot-stage extrusion, whereas solubility in organic solvents is a prerequisite for carriers that are used for producing solid dispersions via the solvent method. In terms of release, it is obvious that the carrier should be soluble in water. Water-insoluble carriers that swell rather than dissolve are being used to produce solid dispersions for sustained release. In a fast-release molecular dispersion formulation, the drug is released upon dissolution of the carrier. Therefore, the role of

Table 2 Desired carrier properties for solid dispersion formulation

Safety	Inert
	GRAS (generally recognized as safe)
Preparation	Melting methods:
	Thermally stable
	Thermoplasticity (hot melt extrusion)
	Solvent methods:
	Soluble in organic solvents
Release	Water soluble
	Solubilizing properties
	Stabilizing properties
Stability	High Tg
	High fragility
	Hydrogen donors/acceptors

the carrier goes further than the initial release. Indeed, the dissolved carrier will still influence the supersaturated drug solution that is formed. Some carriers solubilize the released drug, whereas other carriers will stabilize the supersaturated drug solution. A thorough insight into all of these aspects is imperative to develop a rational strategy for the selection of formulation compounds.

Drug release

In a clinical study performed by Six *et al*.,[83] a variety of itraconazole glass solutions prepared by hot-stage extrusion was compared with the commercially available formulation of itraconazole, Sporanox. The in-vivo results indicated that in-vitro dissolution profiles are not necessarily reflected in the in-vivo behaviour. Correlations between physicochemical properties and dissolution behaviour will not be discussed in this paper since interesting reviews on drug release from solid dispersions are given by Corrigan and Craig.[10,84] In general, it can be stated that dissolution of drugs that are molecularly dispersed in hydrophilic carriers is rather good since no energy is required to break up the drug's crystal lattice. Upon contact with the gastrointestinal fluids, the hydrophilic carrier will start to dissolve and thereby release the molecularly dispersed drug into a supersaturated solution. Indeed, in the case of poorly soluble compounds (i.e. compounds that cannot be dissolved in the available volume of gastrointestinal fluids), the solution that is generated this way will, in most cases, have a higher concentration than the thermodynamic solubility. The influence of formulation compounds on installation and maintenance of supersaturated drug solutions is important and will therefore be discussed further. The thermodynamic solubility is defined as the concentration of a solution in equilibrium with the most stable crystalline state of the solute. The apparent solubility is then defined by the solubility of a compound in solution that is in equilibrium with one of its metastable states. In supersaturated solutions the concentration of the solute exceeds its thermodynamic solubility and the degree of supersaturation, σ, is given by Equation 4:[85]

$$\sigma = \ln(c_s/c_{eq}) = \ln(S) \tag{4}$$

where c_s is the concentration of the crystallizing substance in the supersaturated solution and c_{eq} is the solubility. To attain equilibrium, the solute will have to crystallize until the equilibrium concentration is reached. *In vivo*, the formation of poorly soluble crystals would impede further dissolution and absorption. Therefore, it is desirable that the supersaturated state that is generated upon dissolution is preserved until transepithelial transport is completed.

The co-dissolved carrier will influence the degree of supersaturation as well as the precipitation behaviour.[86] Indeed, many carriers improve the solubility of poorly soluble drugs and therefore they decrease the degree of supersaturation. In addition to that, many formulation compounds have solubilising properties and will, together with bile salts, further solubilize the dissolved drug and decrease the free drug concentration.[60,61] Also, the sum of both the gastric emptying rate and the release rate of the drug from the formulation will determine the maximal concentration of the drug and hence the degree of supersaturation, which is the thermodynamic driving force for crystallization, in the stomach. The sum of the gastric emptying rate and permeation through the gut wall will determine the degree of supersaturation in the small intestine. Therefore, the dissolution rate of a drug from its formulation has an influence on the intraluminal degree of supersaturation.[87–89] Also, the stability of the supersaturated solution will be influenced by the presence of formulation compounds.[86] To understand the underlying mechanisms of crystallization inhibition, nucleation and crystal growth will be discussed in detail.

Nucleation

Even though in a supersaturated solution crystallization is favoured, the activation energy for nucleation will have to be surmounted. This activation energy can be mainly attributed to the high interfacial tension between small particles with high curvature and the medium. This means that until a certain degree of supersaturation is reached, the activation energy will not be overcome and, therefore, no new nuclei will be formed (at least for a certain time span). This supersaturated concentration range where no nucleation occurs is called the metastable zone, and a conscious choice of excipients can expand this region. The rate for homogeneous nucleation of spherical clusters is given by Equation 5:

$$J = N_o\, v \exp(-\Delta G^*/k_bT) \tag{5}$$

where J is the number of nuclei formed per unit of time and volume, N_o is the number of molecules of the crystallizing phase in a unit volume, v is the frequency of molecular transport at the solid–liquid interface, ΔG^* is the maximum change in Gibbs free energy for the formation of nuclei with a critical radius, k_b is the Boltzman constant and T is the absolute temperature. ΔG^* is given by Equation 6:

$$\Delta G^* = 16\pi v^2 \gamma_{ns}^3/3(k_bT ln(S))^2 \tag{6}$$

in which v is the frequency of atomic or molecular transport at the nucleus–liquid interface and γ is the interfacial energy per unit area between the medium and the nucleating cluster. The transport frequency, v, depends on the fluidity, $1/\eta$ of the solution. Combination of Equations 5 and 6 renders Equation 7.

$$J = N_o\, v \exp[-16\pi v^2 \gamma_{ns}^3/3(k_bT)^3 (ln(S))^2] \quad \text{and} \quad v \sim 1/\eta \tag{7}$$

This equation expresses how the nucleation rate depends on the degree of supersaturation S and the interfacial energy γ_{ns} between the nucleus and the solvent.[57,85,90,91] The nucleation rate will increase with increasing degree of supersaturation and with a decrease in the interfacial energy. The degree of supersaturation will be influenced by formulation compounds as discussed above and the interfacial tension will decrease in the presence of surfactants. Therefore non-surface-active compounds that increase solubility could unambiguously reduce the nucleation rate. Surfactants, however, might on one hand reduce the degree of supersaturation by solubilizing the drug and hence decrease the free drug concentration, while

on the other hand they will decrease the interfacial tension between the nuclei and the solvent. Hence, their influence on the nucleation rate will depend on their relative contribution to both S and γ_{ns}. Furthermore, the presence of formulation compounds might alter the frequency of atomic or molecular transport at the nucleus–liquid interface by changing the viscosity, η, of the solution.

In reality, surfaces, particles and interfaces will decrease the activation energy and therefore facilitate the nucleation process. Due to the difficulty in modelling this process the discussion was limited to the case of homogeneous nucleation, even though heterogeneous nucleation is of practical importance. Once the nuclei are formed, macroscopic crystals can start growing.

Crystal growth

Crystal growth consists of two steps: (1) diffusion of molecules from the bulk of the solution towards the crystal interface, and (2) integration of the molecules into the crystal lattice, which is accompanied by desolvation. The increase of the crystal radius, r, is given by Equation 8:

$$dr/dt = [DvN_A/(r + D/k_+)](C - C_{eq}) \quad (8)$$

where D is the diffusion coefficient of the molecule, k_+ is the surface integration factor, N_A is Avogadro's constant and $(C - C_{eq})$ is the difference between the bulk concentration and the concentration in the liquid layer surrounding the growing crystal. Consequently, the process will be diffusion-controlled if $r >> D/k_+$ and controlled by surface integration if $r << D/k_+$. With respect to crystal growth, the presence of formulation compounds could alter the viscosity of the solution and hence the diffusion constant D, and v, the frequency of atomic or molecular transport at the nucleus–liquid interface. Also, the equilibrium concentration and the free drug concentration in the bulk as well as the liquid layer surrounding the growing crystal will be influenced. Finally the surface integration factor, k_+, will change in the presence of compounds that adsorb onto the crystal surface.[57]

Influence of formulation compounds on supersaturation

The use of excipients can influence the nucleation as well as the crystal growth rate. For this reason, screening for stabilizing agents has become a vital step in the development of formulations for poorly soluble compounds. With respect to screening, it is important to distinguish between thermodynamic stabilization, which refers to lowering the degree of supersaturation, and kinetic stabilization, which refers to delaying nucleation and crystal growth. Supersaturation screenings are commonly carried out by the co-solvent method. This involves adding a small volume of a concentrated solution of the poorly soluble test compound in an organic solvent to a relevant test medium in the presence or absence of various potential stabilizers.[92,93] It is important that the thermodynamic solubility of the test compound into the mixture of the organic solvent and the test medium is exceeded to create supersaturation. The influence of the formulation compounds on the generation and stabilization of supersaturation is then determined from the time–concentration profiles.

In general, polymers are reported to be good stabilizers. Their influence on the solubility of poorly soluble drugs is usually limited so their stabilizing potential is mainly kinetic. Most reports indicate that nucleation and crystal growth are delayed due to drug–polymer interactions in solution and by adsorption of the polymer on the nucleus or the growing crystal.[58,94,95] Some polymers that have been thoroughly investigated for their stabilizing characteristics are PVP, PEG, methylcellulose (MC) and HPMC.[57–59,93]

Above their critical micellar concentration, surfactants will solubilize poorly soluble compounds and thereby decrease the degree of supersaturation. Apart from that, they are also capable of delaying the nucleation and crystal growth process. This has been demonstrated by a study performed by Overhoff *et al.*,[88] where it was found that sodium dodecyl sulfate stabilizes supersaturated solutions of tacrolimus below its critical micellar concentration and impedes coalescence by adsorption onto embryonic crystals. The same author hypothesized that surfactants increase the activation energy for molecules to desolvatize and nucleate or integrate into the crystal lattice, due to their solubilizing activity. An excellent review on supersaturating drug delivery systems is given by Brouwers *et al.*[96]

Stability of glass solutions

Preparation of glasses

Selection of suitable carriers for the formulation of glass solutions with a glass transition temperature well above room temperature is another important issue. To elucidate this aspect of solid dispersions, a closer look should be taken at the glass transition phenomenon itself.

A glass transition is the fingerprint of a glassy material and is most easily understood by looking at it as the state that is formed upon quench cooling from a melt. From a thermodynamic point of view a melt should crystallize once it is cooled below the melting point. This would be marked by a discontinuous step in the entropy, enthalpy or volume curve. At high cooling rates, however, crystallization is often suppressed and in such cases the enthalpy, entropy and volume curve of the liquid is being followed. The material is now in the super-cooled liquid state. As temperature decreases, molecular mobility in the liquid decreases as well. This causes the super-cooled liquid to set off from the liquid line at the point where molecular mobility is insufficient to allow the system to equilibrate within the time scale of the cooling process (Figure 1). This point is referred to as the glass transition. A glass typically has the molecular conformation of a frozen-in higher temperature liquid. Due to its high viscosity, molecular motions and relaxation processes become very slow. Therefore, glasses have the appearance of a solid.[97] Next to the above-described super-cooling method (as in hot-stage extrusion), glasses can be prepared via several other routes as well, such as solvent evaporation (spray drying and freeze drying), precipitation from solution, dehydration from hydrates and as a consequence of mechanical stress, which is induced

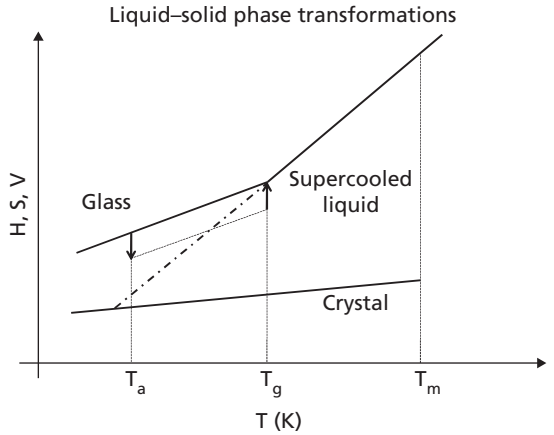

Figure 1 Schematic diagram depicting the enthalpy, entropy and volume changes of the liquid, crystal and the amorphous state as a function of temperature. The arrows indicate structural relaxation at annealing temperature T_a and recovery of the relaxed glass at T_g.

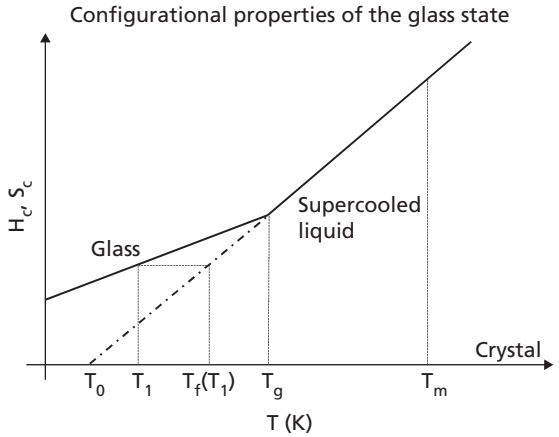

Figure 2 Schematic diagram depicting configurational enthalpy (H_c) and entropy (S_c) changes as a function of temperature (T) and the determination of the initial fictive temperature $T_f(T_1)$ for an amorphous material annealed at temperature T_1.

during compaction, compression or intense grinding of crystals.[98,99] Common routes to prepare mixed glasses are based on solvent and quench-cooling methods.

Molecular mobility

Since the glassy state is a non-equilibrium state with respect to the crystalline state, the glass will relax towards lower configurational enthalpy (ΔH_{conf}) and entropy and increased density. This process is time and temperature dependent. The temperature dependence of the relaxation phenomenon relates to decreased molecular mobility as the glass is annealed at a temperature further below Tg. Relaxation is also time dependent since it is known that the relaxation time constant, τ, increases upon time.[100] The reason for the interest in the relaxation behaviour of glasses is because of the correlation with molecular mobility, which is to a certain extent coupled to phase separation and crystallization from the amorphous state. Indeed, phase separation and crystallization involve diffusion and nucleation, which both require molecular mobility.

The Kohlrausch–William–Watts equation

Several calorimetric methods, of which differential scanning calorimetry (DSC) has been the most frequently used technique so far, have been developed to determine molecular mobility in amorphous materials at a temperature below Tg. The Kohlrausch–William–Watts (KWW) equation relates 'relaxation recovery enthalpy' to the average relaxation time constant, τ, and a stretch parameter, β.[101,102] The relaxation recovery enthalpy can be detected in a DSC experiment as an endothermic event that overlaps with the glass transition. It represents the energy that the glass has to take up from its environment to become a super-cooled liquid. In Figure 1 it is indicated how the freshly prepared glass relaxes to point b. As the relaxed or 'aged' glass is reheated, its entropy, enthalpy and volume will have to increase at Tg to become a metastable super-cooled liquid. By determining the relaxation recovery endotherm as a function of time at certain temperatures (annealing) below Tg, the KWW equation can be fitted:

$$\Phi = 1-(\Delta H_{relax}/\Delta H_{\infty}) = \exp[(-t/\tau)^{\beta}] \qquad (9)$$

in which Φ is the extent of relaxation at a certain annealing temperature, which decays from 1, indicating no relaxation, to 0 when relaxation is complete. ΔH_{∞} is the energy available for relaxation, which can be obtained by extrapolating the liquid line to below Tg and integrating the difference of the configurational heat capacities of the liquid and the glass from the annealing temperature to the Tg as a function of temperature. In Figure 2 the configurational heat capacity is represented by the slopes of the glass and the liquid lines. The term 'configurational' with respect to enthalpy and entropy, refers to the difference between the enthalpy and entropy of the glass and the most stable crystal.[100] For this reason, the configurational heat capacity of the crystal state coincides with the x-axis. A quick estimation of ΔH_{∞} can also be obtained from the heat capacity change ΔCp.[103] ΔH_{relax} is the relaxation recovery enthalpy (measured as the peak area), τ is the average relaxation time constant and β is a stretch parameter that describes the distribution of molecular relaxation times with a value ranging from 0 to 1, with 1 indicating a single relaxation time for all molecules. Relaxation time constants of several amorphous drugs and amorphous solid solutions have been determined in this manner.[82,104–107] The above-discussed relaxation enthalpy study can be performed with isothermal microcalorimetry (TAM) as well.[108] The disadvantage of the KWW method is the fact that to reduce analysis time, glasses are annealed at temperatures that are not far below Tg in order to obtain a sufficiently large recovery endotherm signal. Therefore results are extrapolated from temperatures right below Tg to temperatures far below Tg, which correspond to the actual storage temperatures. Since the structural relaxation of organic compounds often follows non-Arrhenius behaviour, such extrapolations are rather arbitrary. Also, at temperatures

far below Tg, the relaxation is slow and as relaxation progresses it slows down even more. Therefore, it seems that at temperatures far below Tg, an estimation of the initial relaxation time constant will give more relevant information than an average relaxation time constant.

The Adam–Gibbs equation

Mao *et al*. proposed a different calorimetric method to obtain the initial relaxation time constant at relatively low temperatures with respect to Tg.[109] This method is based on the non-linear Adam–Gibbs equation that requires an estimation of the fragility parameters of a glass and its fictive temperature:[110]

$$\tau = \tau_0 \exp\{DT_0/[T(1-T_0/T_f)]\} \quad (10)$$

where τ is the initial relaxation time constant, T is the annealing temperature and τ_0 is a pre-exponential factor often taken as being of the order of the lifetime of atomic vibrations, 10^{-14} s. The fragility parameters, D and T_0, describe the deviation from linear Arrhenius behaviour in (super-cooled) liquids as the temperature approaches Tg. These parameters, D and T_0 can be calculated from the activation energy, E_a, for the transition from the glassy to the super-cooled liquid state.[111] This value can be obtained by determining the scanning rate dependence of the glass transition temperature using DSC.[112] The fictive temperature represents the temperature where the observed configurational properties of the non-equilibrium state at a certain annealing temperature below Tg correspond to the configurational properties of the super-cooled liquid state. As indicated in Figure 2, the position of the fictive temperature of the freshly prepared glass (the initial fictive temperature) depends on the difference in the heat capacity between the crystal and the amorphous state. Indeed, in the case that the glassy and the crystalline state have the same heat capacity, which would be visually represented by a horizontal line for the glass, the fictive temperature would be equal to Tg. In reality, however, the glass often has a greater heat capacity than the crystal state and has therefore a faster decrease of configurational properties than the stable (crystal) form does. Therefore, the initial fictive temperature is in most cases lower than Tg. The initial fictive temperature can be estimated by measuring the heat capacity of the glass, the supercooled liquid and the most stable crystal form and is used to estimate the initial relaxation time constant.[113,114] The fictive temperature of an aged glass can be derived from a configurational enthalpy ($-\Delta H_{conf}$) versus T plot by taking the intersection between the tangents of the super-cooled liquid and the glass (Figure 3). Descamps *et al.*[115] used this plot to compare maltodextrin glasses that were obtained via different routes and demonstrated that, depending on the preparation method and annealing conditions, glasses will be entrapped in different local minima of the potential energy landscape. A disadvantage of all the above-described calorimetric methods for fictive temperature determinations is that none of them is suited for amorphous polymers or amorphous drug–polymer mixtures, since the heat capacity of the corresponding crystalline form does not exist in these cases. Therefore, configurational entropy and enthalpy data cannot be obtained.

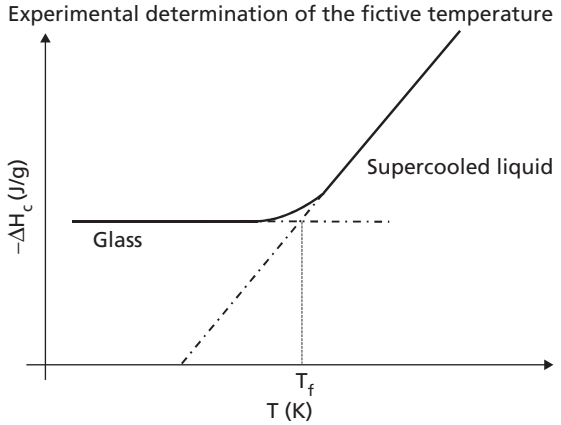

Figure 3 Schematic representation of a configurational enthalpy, −ΔHconf (J/g), versus temperature (K) plot. The fictive temperature is obtained from the intersection of the extrapolated liquid and glass lines.

Fragility

In another study by Mao *et al*., the influence of the glass transition temperature, the fragility and the heat capacity of the glass, the super-cooled liquid and the crystal on the evolution of the relaxation time constant was evaluated.[109] It was found that for two compounds with similar Tg but different fragility, the relaxation time constant can differ by several orders of magnitude. For glasses with similar Tg, the glass with the highest fragility will be more stable. With respect to the evolution of the relaxation time constant, it was found that glasses with a higher fragility will experience a more rapid increase in τ, and structural relaxation will therefore stabilize faster. How the fragility of a multi-component system relates to the fragility of the pure amorphous compounds is an intriguing topic with respect to formulation and excipient selection.

Alpha and beta mobility

Apart from the frequently studied glass-transition-related α mobility, several studies report on another type of mobility that is observed at temperatures far below the glass transition, which is referred to as β mobility. Alpha mobility is associated with slow motions on a large length scale, similar to those involved in viscous flow. Beta mobility on the other hand is related to faster motions on the length scale of local molecular motions such as rotations of side chains. In a study performed by Alie *et al*., dynamic dielectric spectroscopy (DDS) and thermo-stimulated current spectroscopy (TSC), collectively referred to as dielectric spectroscopy (DS), were used to study molecular mobility.[116] DDS detects the complex dielectric permittivity and the dielectric loss factor. TSC is performed by polarizing the sample in an electrostatic field at a temperature that allows orientation, followed by a cooling step that brings the sample to a temperature where polarization can be retained. The depolarization current can then be measured as temperature is increased at a constant heating rate. With both of these techniques a beta-type

mobility as well as an alpha type of mobility could be resolved. Based on correlations between the type of temperature dependence of the crystallization process and the two types of molecular mobility, it was hypothesized that crystallization is more likely to be dominated by beta-like molecular motions. Indeed, molecules that are localized in an amorphous phase in the vicinity of crystalline surfaces can adjust their conformation to allow inclusion into the nearby crystal. Some other studies report correlations between beta mobility and crystallization as well.[117,118] The pharmaceutical significance of local mobility in amorphous pharmaceuticals has recently been highlighted in an excellent review by Bhattacharya and Suryanarayanan.[119]

Spin-lattice relaxation times recorded via nuclear magnetic resonance (NMR) are also linked to molecular mobility.[120–122] However, different techniques might capture different types of mobility. Calorimetric techniques measure viscosity and glass transition related mobility, whereas dielectric spectroscopy, TSDC and NMR are also sensitive for mobility related to localized molecular motions. A better insight into the type of mobility measured by different techniques is required to fully understand the relation between mobility and physical stability.

Crystallization from the amorphous state

With respect to bioavailability, crystallization of the molecularly dispersed drug from its glass solution leads to loss of both high dissolution rates and creation of supersaturated solutions. The role of molecular mobility in crystallization lies in the fact that it is necessary to allow diffusion and surface integration, which are required in phase separation and crystallization. In glass solutions, crystallization of the drug is generally preceded by phase separation and thus the formation of a drug rich amorphous phase. A glass of a pure compound or a drug–polymer system with a high drug load, can relax towards molecular conformations that precede nucleation. Therefore, formulation of glass solutions with a high polymer weight percentage is a sensible approach to increase the kinetic barrier for phase separation and subsequent crystallization. Regarding pill burden, however, formulation scientists will attempt to achieve the highest possible drug load to reduce the tablet size. Therefore it is interesting to pinpoint mechanisms of phase separation and crystallization in glass solutions with high drug loads as well as low drug loads.

The classical nucleation theory

According to the classical nucleation theory (CNT), the rate of homogeneous nucleation, I, depends on the Gibbs free energy change that is associated with the formation of a nucleus of critical size, ΔG^*, which is the balance between the reduction in Gibbs free energy associated with forming a crystalline phase, and the increase in Gibbs free energy, necessary to form a new surface, and on the activation energy for transport from the amorphous phase to the nucleus, ΔG_a.[123,124]

$$I = A \exp[-(\Delta G^* + \Delta G_a)/kT] \qquad (11)$$

A is a constant, k is the Boltzman constant, and T is the absolute temperature. This equation describes how the thermodynamic driving force for nucleation increases with the degree of super-cooling, whereas the kinetic factors become less favourable with decreasing temperature due to restricted molecular mobility. The influence of hydrogen bonds is also reflected in the activation energy for the formation of new surfaces and transport. Currently, several studies focus on the mechanism of nucleation and crystal growth in the presence of additives.

The role of hydrogen bonds

Matsumoto and Zografi investigated the influence of low levels of PVP on the crystallization behaviour of indometacin.[82] Since the glass transitions of the molecular dispersions were all very close to the glass transition of pure indometacin and the molecular mobility of the molecular dispersions was only slightly decreased, they concluded that the antiplasticizing effect of the polymer played only a minor role in the stabilization of indometacin. FT-IR spectroscopy showed that the formation of carboxylic acid dimers of indometacin, which is the required conformation for the nucleation and growth of the γ-polymorph, was impeded in the presence of minimum 5% of polymer, due to the formation of drug–polymer hydrogen bonds. Therefore, this study illustrates the importance of drug–polymer interactions as a stabilizing factor in glass solutions, other than the antiplasticizing effect of polymers with high glass transition temperatures.

In a study by Marsac *et al.*, the factors affecting the crystallization tendency of nifedipine and felodipine, and PVP glass solutions thereof, were investigated.[107] It was found that nifedipine crystallizes more easily than felodipine alone as well as in the presence of PVP, despite the fact that their glass transition temperatures, their average relaxation time constant and their hydrogen bonding patterns with PVP were very similar. For nifedipine, a higher crystallization driving force, which was mainly due to enthalpic contributions, was found. This contradicts another report wherein it was concluded that differences in crystallization driving force were mainly due to entropic contributions.[125] The larger enthalpic contribution for nifedipine compared with felodipine can be explained by their drug–drug hydrogen bonding patterns. Indeed, as nifedipine crystallizes, the hydrogen bonding strength increases compared with the amorphous state, whereas felodipine crystallizes with a reduction in the strength of the hydrogen bonding interactions. This study illustrates the importance of the thermodynamic driving force in addition to the more commonly used descriptors of the amorphous phase such as the glass transition and molecular mobility.

From these studies it appears that the formation of hydrogen bonds between the molecularly dispersed drug and the carrier is a major factor in the stabilization of glass solutions, apart from antiplasticizing effects. Indeed, the formation of drug–polymer hydrogen bonds can prevent the formation of drug–drug hydrogen bonds. Also, the relative strength of drug–drug hydrogen bonds in the amorphous versus the crystalline state plays a role with respect to the thermodynamic crystallization driving force. Such effects explain the lack of complete correlation between molecular

mobility and crystallization, as reported in the studies of Matsumoto and Zografi[82] and Marsac *et al*.[107]

Correlation between crystallization and molecular mobility

With respect to correlation between molecular mobility and crystallization, some research has been done by the group of Pikal. Most of these studies have been performed on single component systems.[126–128] In one particular publication, however, they included solid dispersions of phenobarbital with 8% w/w of PVP or l-proline.[129] The crystallization rates were followed using microscopy at different temperatures above Tg, and one point below Tg, after crystallization was first induced above Tg. The result was a continuous Arrhenius plot for pure phenobarbital as well as its solid dispersions over the studied temperature range. The molecular relaxation time was determined using dielectric spectroscopy above Tg, and calorimetry below Tg. Again a continuous Arrhenius plot was obtained for relaxation times above and below Tg. This indicates that both techniques probe similar kinds of mobility. To determine to what extent the crystal growth rate was coupled with molecular mobility, the crystal growth rates were plotted as a function of relaxation times to determine the coupling coefficient. A coupling coefficient of unity suggests a perfect correlation between relaxation and nucleation, which is controlled by diffusion and, by virtue of the Stokes–Einstein relationship, by viscosity. In this particular study the results suggest that there is only a weak correlation between alpha mobility and crystallization. Therefore, the diffusion–viscosity relationship might be more complicated than predicted by the Stokes–Einstein relationship. Or, other factors could play a role in crystallization. Indeed, nucleation and crystal growth require the right orientation of the molecules, controlled by alpha mobility, but also the right conformation, possibly controlled by beta mobility. It is worth mentioning that the lowest coupling constants were obtained for the solid dispersions. However, it should be noted that the studied solid dispersions contained only 8% of carrier. In more diluted systems, which are pharmaceutically more relevant, diffusion and thus alpha mobility, might play a larger role. Furthermore, as described above, specific interactions such as hydrogen bonds also play an important role in the crystallization process.

Phase separation and solid solubility

In drug–polymer systems with low drug loads, physical instability is in most cases initiated by amorphous–amorphous phase separation. Consequently, crystallization will start to occur from the drug-enriched amorphous phase. To date, not much research has been done about the kinetics and thermodynamics of amorphous–amorphous phase separation. However, a theoretical frame regarding the thermodynamic basis of phase separation as a result of supersaturation in the solid state has been proposed by Marsac *et al*.[68] Based on the Flory–Huggins lattice theory that was originally developed for polymer solutions, the relative influence of the polymer weight grade and the Flory–Huggins interaction parameter, χ, on the energy of mixing was modelled for two miscible drug–polymer systems: nifidipine–PVP and felodipine–PVP.[130–132]

$$\Delta G_{mix}/RT = n_{drug} ln\Phi_{drug} + n_{polymer} ln\Phi_{polymer} + n_{drug}\Phi_{polymer}\chi \tag{12}$$

Where ΔG_{mix} is the Gibbs free energy of mixing, R is the gas constant, T is the absolute temperature, n is the number of moles, and Φ is the volume fraction. The interaction parameter, χ, describes the relative strength of cohesive and adhesive interactions and a negative value signifies favourable heterogeneous interactions. Based on simulations with different polymer weight grades it was demonstrated that for any typical active compound with a molecular weight ranging from 200 to 600 g/mol, and any typical polymer with a molecular weight between 10 000 and 1 500 000 g/mol, the entropy of mixing contribution towards the Gibbs free energy of mixing is relatively constant. Therefore, using lower weight grades of polymers will not significantly improve drug–polymer miscibility. The interaction parameter, on the other hand, had a large influence on the Gibbs free energy of mixing and will essentially determine whether or not the system is miscible. Therefore, low miscibility can be anticipated by utilizing polymers that will likely interact with the drug.

Finally, the Flory–Huggins lattice theory was further adapted to describe the solid solubility of a crystalline active compound in a glassy polymer:

$$ln\gamma_{drug}x_{drug} = -\frac{\Delta H_{fus}}{RT}\left[1 - \frac{T}{T_M}\right] - \frac{1}{RT}\int_{T_M}^{T}\Delta C\mathrm{p}^{config}\mathrm{d}T + \frac{1}{R}\int_{T_M}^{T}\frac{\Delta Cp^{config}}{T}\mathrm{d}T \tag{13}$$

in which γ_{drug} is the activity coefficient, x_{drug} is the mole fraction, ΔH_{fus} is the enthalpy of fusion, T_{M} is the melting temperature of the drug, and $\Delta C_{\mathrm{p}}^{\mathrm{config}}$ is the configurational heat capacity. This equation was originally derived to describe the solubility of a crystalline material into a low-molecular-weight solvent and can be expanded to predict solid solubility in API–polymer systems, in which the glassy polymer is considered to be the solvent. Therefore the drug's activity coefficient is described by the Flory–Huggins lattice theory for an API–polymer system by the following equation:

$$ln\gamma_{drug} = ln(\Phi_{drug}/\chi_{drug}) + (1 - 1/m)\Phi_{polymer} + \chi\Phi^2_{polymer} \tag{14}$$

In which m is the ratio of the volume of the polymer to that of the fictive Flory–Huggins lattice site (defined here by the molecular volume of the drug). Based on the predicted solid solubility values for nifedipine, <10% w/w, thermodynamically stable formulations would have to consist of more than 90% of polymer, even though nifedipine and PVP are miscible in all compositions. Therefore the authors hypothesized that for most miscible drug–polymer glass solutions, kinetic stabilization will play a large role. It should be noted

that even though in this case χ served as a good measure to point out the importance of enthalpic interactions, χ varies with temperature and in some cases also with composition (e.g. in the case of specific interactions such as hydrogen bonds). Therefore, the Wertheim lattice thermodynamic perturbation theory, which accounts not only for nonspecific interactions but also for specific saturable interactions, might be more suited to describe systems with specific drug–polymer interactions.[133,134]

Vasanthavada *et al*. used a more practical approach to study solid solubility.[135] The authors investigated amorphous–amorphous phase separation in trehalose–dextran and trehalose–PVP blends as a function of time, using perfectly mixed amorphous blends. Due to an enrichment of polymer in the amorphous phase, the glass transition increased to arrive at a constant temperature, which was below the Tg of the pure polymer. Since these results were independent from the initial blend composition, this was suggested to be due to the solid solubility of trehalose into dextran and PVP. Due to the challenging storage conditions (i.e. elevated temperature and humidity), the increased molecular mobility allowed the systems to equilibrate to reach thermodynamic solid solubility in the amorphous phase and to form a crystalline fraction of the excess amount of trehalose. The thermodynamics of the model systems were interpreted with the Couchman–Karasz theoretical equations[80] and it was found that the enthalpy of mixing was unfavourable, whereas the entropy of mixing was favourable. Therefore, negative Gibbs free energy values were found for mixtures with low trehalose contents. This study was followed by a second one using griseofulvin, indoprofen and PVP. The stability study revealed similar behaviour of the glass transitions as the drugs crystallized. However, for the non-hydrogen-bonding model compound, griseofulvin, no significant solid solubility was found, since the Tg increased up to the value of pure PVP. For indoprofen, the equilibrium Tg was far below that of pure PVP, indicating a certain degree of solid solubility due to the presence of drug–polymer hydrogen bonds. The phase separation kinetics were interpreted with the Kolmogorov–Johnson–Mehl–Avrami (KJMA) equation that is usually applied to obtain rate constants of crystallization.[136,137] The phase-separated drug fraction $(1-\alpha)_t$ was obtained from the following equation:

$$(1-\alpha)_t = 1-[(Tg_{(polymer)}-Tg_{2(t)})/(Tg_{(polymer)}-Tg_{(initial)})] \quad (15)$$

where $Tg_{(polymer)}$ is the glass transition temperature of the polymer, $Tg_{(initial)}$ is the initial glass transition temperature of the mixture and $Tg_{2(t)}$ is the glass transition temperature of the mixture as a function of time. The phase-separated fraction was then substituted into the KJMA equation:

$$[-\ln(1-\alpha)] = kt \quad (16)$$

in which t is time and k is the rate constant for solid-state transformation, or phase separation in this case. From the calculated rate constants it could be concluded that the phase separation rate increased with increasing degree of supersaturation, which results from high drug loads and low solid solubility. Based on these results and the study of Marsac *et al.*,[68] it appears that, in reality, many glass solutions must be supersaturated. Therefore, stabilization by an antiplasticizing effect should play a large role. However, conclusions drawn from crystallization studies (i.e. that the formation of drug–polymer hydrogen bonds increase the crystallization activation energy for surface integration and transport), also stand for the inhibition of amorphous–amorphous phase separation. Another relevant question is, to what extent the crystallization driving force of the pure amorphous drug will drive amorphous–amorphous phase separation.

Conclusions

With the amount of marketed solid dispersions increasing rapidly in the past few years, decades of intensive research finally yields results. However, to reduce development times and to arrive at a more rational excipient selection strategy, understanding fundamental aspects of solid dispersions is imperative. Formulation compounds should be selected based on their stabilizing effect on supersaturated solutions formed upon release, as well as their effect on the shelf life stability of the glass solutions. The following formulation compound properties were identified as having a positive effect on the stability of supersaturated solutions: high solubilizing potential, the formation of specific drug–excipient interactions in solution and the ability of the formulation compound to adsorb onto the growing nucleus or crystal. Reduction of the interfacial tension between the nucleus and the solution, as often obtained with surfactants, will increase the nucleation rate and hence destabilize supersaturated solutions. From a biopharmaceutical point of view, the interplay between formulation compounds and in-vivo factors is not well understood.

With respect to the solid-state stability of glass solutions, both kinetic and thermodynamic aspects should be evaluated. Reduced mobility, and hence slowed kinetics, are obtained via formulation compounds with an antiplasticizing effect (i.e. compounds with a high glass transition) and by formulating glass solutions with high fragility. The influence of additives on localized molecular motion (i.e. beta mobility), might also play an important role in physical stabilization, as it has been shown that typical glass-transition-related mobility is not the only factor related to crystallization. From a thermodynamic point of view, determining the level of solid solubility is important since the degree of solid-state supersaturation will determine the kinetics of amorphous–amorphous phase separation. Some studies indicate the importance of the crystallization driving force of the pure amorphous compound as being determinant for the physical stability of glass solutions. Specific drug–polymer interactions play an important role, first of all since they increase the thermodynamic solid solubility and, secondly, because they increase the activation energy for crystallization and phase separation. The relative importance of all of these aspects is still poorly understood. Also, phase separation and crystallization mechanisms in pharmaceutically relevant glass solutions (i.e. solutions with a sufficient amount of stabilizing carrier) are still poorly studied. Eventually, continuous exploration of all these issues related

to stability in solution, as well as in the solid state, will enable full exploitation of the solid dispersion formulation strategy.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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