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A REVIEW ON: SOLID DISPERSION FOR IMPROVEMENT OF SOLUBILITY IN PHARMACUTICAL DOSAGE FORM

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ABSTRACT

The poor oral bioavailability arising from poor aqueous solubility should make drug research and development more difficult. Various approaches have been developed with a focus on enhancement of the solubility, dissolution rate, and oral bioavailability of poor water soluble drugs. Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of the range of hydrophobic drugs. This article reviews the various preparation techniques for solid dispersion. The different types of solid dispersions based on the molecular arrangement have been highlighted. Mechanism of dissolution of solid dispersion. Some of the practical aspects to be considered for the preparation of solid dispersion, such as selection of carrier and method of physicochemical characterization along with an insight into the molecular arrangement of drugs in solid dispersions are also discussed.

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INTRODUCTION

Many compounds that are identified to have high activity during early screening have low aqueous solubility [1]. These compounds are mainly selected by high-throughput and receptor-based *in vitro* screening techniques. In the screening process, a certain degree of lipophilicity is often required for a drug to cross the cell membrane to reach the receptor site, and a lipophilic group is often needed for the drug to have an affinity with the receptor [2-4]. Unfortunately, compounds with high lipophilicity usually have low water solubility [5].

These compounds with poor aqueous solubility are increasingly posing challenges in the development of new drugs, since more numbers of poorly water-soluble drugs are introduced in the pharmaceutical pipeline. It is estimated that > 40% of marketed drugs are poorly water-soluble; among the US pharmacopeia, this share is > 30% [6]. It is well known that drug efficacy can be severely limited by poor aqueous solubility,

leading to low dissolution rate and thus results in low absorption in the gastrointestinal tract after oral administration hence compromising oral bioavailability. The ability to increase aqueous solubility is thus a valuable aid to increase the efficacy for certain drugs [7].

Based on the biopharmaceutics classification system (BCS), drug substances are classified into four categories according to their solubility and permeability properties, as shown in Figure1.1 [8,9] For the drugs exhibiting low solubility but reasonable membrane permeability, which are categorised as BCS class II, it is obvious that for Class II drugs the low ability to dissolve is a more important limitation to their overall rate and extent of absorption than their ability to permeate through the intestinal epithelia. Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. The bioavailability from conventional tablet formulations may be unacceptable for these drugs, which often have water-solubility of < 1 µg/ml [10].

Figure 1.1 Biopharmaceutics classification system of drugs

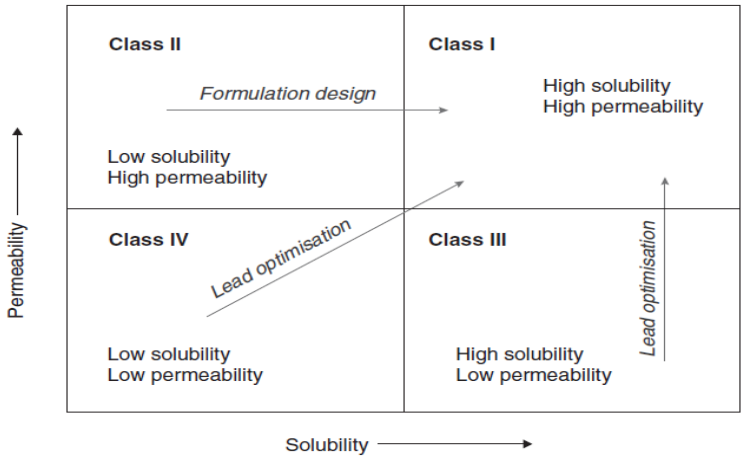
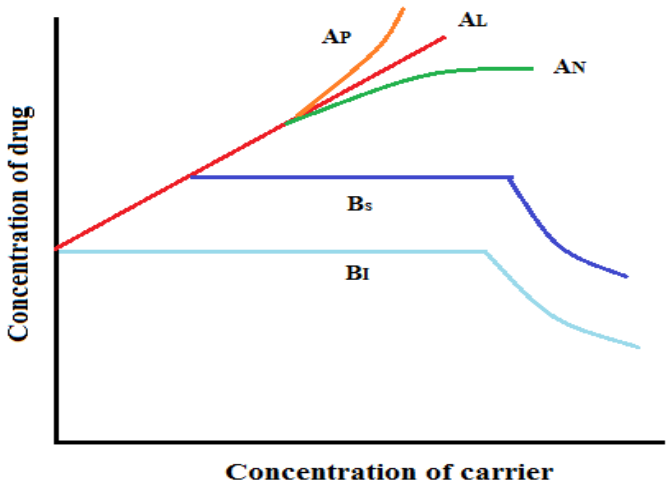


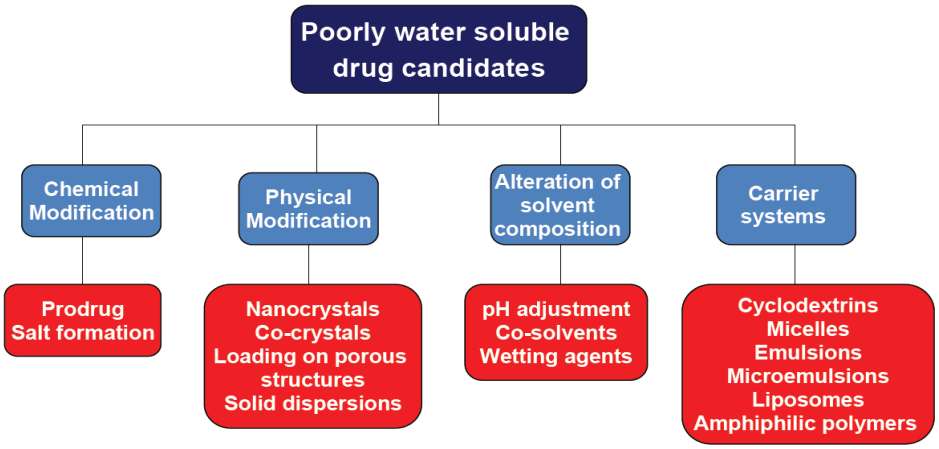
Figure 1.2 Graphical representations of A and B-type phase-solubility profiles with applicable subtypes (A_P, A_L, A_N and B_S, B_I)



To increase the amount of dissolved drug at the absorption site several strategies can be used. The most straightforward method is to use a dosage form in which drug molecules are already dissolved in an aqueous solution. However, this may require large volumes of the liquid to

dissolve the complete drug dose, which is highly unwanted. There are several pharmaceutical strategies available to improve the aqueous solubility of poorly soluble drugs: solid dispersions, solubilization using surfactants, the use of cosolvents, reduction of particle size, hydrotropy and the use of aqueous soluble derivatives or salts.These approaches to improve the solubility are classified in Chart 1[11].

Chart 1.1 Approaches to increase the solubility of drug



0Recently, Rasenack and Muller [12] presented a new method to reduce the particle size to the nanometer level. They precipitated the drug in the presence of stabilizing agents, such as hydrocolloids. The obtained dispersion was then spray-dried. Increased dissolution rate was observed in vitro for ibuprofen, itraconazole and ketoconazole. Particle size reduction is commonly used to increase dissolution rate, however the commonly used methods such as controlled crystallization and grinding have a practical limit to how much size reduction can be achieved. Furthermore, very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability. The poor wettability is most probably the result of electrostatic behavior of very fine hydrophobic particles.

Nanopowders have been of extreme interest in the pharmaceutical field. Drug delivery has been impacted in several ways due to the advances in nanopowder technology. Smaller particles are able to be delivered in new ways to patients, through solutions, oral or injected, and aerosol, inhaler or respirator. New production processes allow for encapsulation of pharmaceuticals which allow for drug delivery where needed within the body. Dosing of pharmaceuticals is also improved. Smaller particles mean better absorption by the body therefore less drug is needed. Because of a combination of these, side effects are lessened due to better use of pharmaceuticals.

The use of aqueous soluble derivatives or salts can improve solubility and dissolution properties, and may also enhance the oral absorption. Salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. Even when salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms.

The term hydrotropy has been used to designate the increase in solubility of various substances in water, due to the presence of large amounts of additives. Sodium benzoate, niacin amide, sodium salicylate, sodium acetate, sodium citrate, and urea, have been employed to enhance the aqueous solubility of many poorly water soluble drugs.

Alternatively, solid dispersions can be used to increase the dissolution rate of poorly soluble

drugs [13-15] and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability [16-18]. Solid dispersions are investigated in many studies because they are highly versatile in their application. They can form the basis of products applied for various routes of administration and for various dosage forms, including the most popular dosage form the tablet.

SOLID DISPERSION

A solid dispersion can be defined as a dispersion of an active ingredient in an inert carrier in the solid state. A solid dispersion is the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting-solvent method [19].

In 1961, Sekiguchi and Obi [20] developed the first solid dispersion as a practical method to reduce particle size and enhance drug dissolution and absorption by the melting method. This method, which was later termed "solid dispersion", involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures.

In 1966, Goldberg e t al. [21, 22] proved that the drug in a solid dispersion might be present in a microcrystalline state and/or be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because the surface area of the drug was greatly enhanced after being prepared into a solid dispersion, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

PHYSICOCHEMICAL CLASSIFICATION OF SOLID DISPERSIONS [23]

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. They are described in Table 1.1.

Table 1.1 Classification of solid dispersions in six subtypes

Solid dispersion type		Matrix	Drug	Remark	No. of Phases
I	Eutectics	C	C	the first type of solid dispersions	2
II	Amorphous precipitations in crystalline matrix	C	A	rarely encountered[25, 26]	2
III	Solid solutions				
	Continuous solid solutions	C	M	Miscible at all compositions, never prepared	1
	Discontinuous solid solutions	C	M	partially miscible, 2 phases even though drug is molecularly dispersed	2

	Substitutional solid solutions	C	M	molecular diameter of drug (solute) differs less than 15% from matrix (solvent) diameter. In that case the drug and matrix are substitutional. Can be continuous or discontinuous. When discontinous: 2 phases even though drug is molecularly	1 or 2
	Interstitial solid solutions	C	M	drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinous. Example: Drug in helical interstitial spaces of PEG	2
IV	Glass suspension	A	C	particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
V	Glass suspension	A	A	particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
VI	Glass solution	A	M	requires miscibility/solid solubility, complex formation or upon fast cooling/evaporation during preparation, many (recent) examples especially with PVP	1

Moreover, certain combinations can be encountered, i.e. in the same sample, some molecules are present in clusters while some are molecularly dispersed. Confusingly, in various studies the designation of solid dispersions is based on the method of preparation. However, since different preparation methods can result in the same subtypes or similar preparation methods can result in different subtypes, it can be argued that solid dispersions should preferably be designated according to their molecular arrangement. Moreover, not the preparation method but the molecular arrangement governs the properties of solid dispersions.

Knowledge about the molecular arrangement will enlarge comprehension of the properties and behavior of solid dispersions. Furthermore, it will facilitate optimization of their properties required for a specific application. For example, the mechanism underpinning the dissolution of solid dispersions is poorly understood. Many case studies showed accelerated dissolution of hydrophobic compounds using solid dispersions but mechanisms are rarely discussed. The most important reason for that is the lacking knowledge about the mode of incorporation of the hydrophobic drug in the matrix, despite numerous efforts to clarify this. A question like, “is the drug present as a crystalline phase or as amorphous nano-particles or molecularly dispersed throughout the matrix” is rarely discussed. All three situations result in different drug concentrations at the dissolving interface. Still it has not been fully elucidated how this affects dissolution behavior of solid dispersions. Secondly, the physical and chemical stability of the matrix or the incorporated drug depends on the

mode of incorporation. If drug molecules, for example, are present in amorphous nano-particles, crystallization requires only rotational rearrangement.

On the other hand, for a molecularly dispersed drug, translational diffusion is necessary before crystallization can occur by rotational rearrangements. The physical state of the matrix is also important for the chemical stability of the drug: the crystalline of the matrix influences the translational and rotational rearrangements of the drug necessary for degradation reactions. Finally, the influence of drug load and method of preparation on dissolution behavior and stability of solid dispersions can only be understood and predicted when the relation between these characteristics and the mode of incorporation is known.

METHODS FOR PREPARATION OF SOLID DISPERSION

Various preparation methods for solid dispersions have been reported in literature. These methods deal with the challenge of mixing a carrier and/or carriers and a drug, preferably on a molecular level, while carrier and drug are generally poorly miscible. During many of the preparation techniques, demixing (partially or complete), and formation of different phases is observed. Phase separations like crystallization or formation of amorphous drug clusters are difficult to control and therefore unwanted. It was already recognized in one of the first studies on solid dispersions that the extent of phase separation can be minimized by a rapid cooling procedure[18, 19]. Generally, phase separation can be prevented by maintaining a low molecular mobility of matrix and drug during preparation. On the other hand, phase separation is prevented by maintaining the driving force for phase separation low for example by keeping the mixture at an elevated temperature thereby maintaining sufficient miscibility for as long as possible.

1. Fusion method

The fusion method is sometimes referred to as the melt method, which is correct only when the starting materials are crystalline. Therefore, the more general term fusion method is preferred. The first solid dispersions for pharmaceutical applications were prepared by the fusion method[19]. The dispersion consisted of sulfathiazole and urea as a matrix which were melted using a physical mixture at the eutectic composition, followed by a cooling step. The eutectic composition was chosen to obtain simultaneous crystallization of drug and matrix during cooling. This procedure resulted in solid dispersions of type I .Poly(ethylene glycol) (PEG) is a hydrophilic polymer often used to prepare solid dispersions with the fusion method. This often results in solid dispersions of type III since many drugs are incorporated as separate molecules in the helical structure present in a crystalline PEG. The helices are aligned in orderly fashion, illustrating that PEG easily crystallizes. Another polymer frequently applied as a matrix in the fusion method is poly(vinyl pyrollidone) PVP. PVP, supplied in the amorphous state, is heated to above its Tg. The drug has to fuse with or dissolve in the rubbery matrix, which is subsequently cooled to vitrify the solid dispersion. When PVP is used as matrix, solid dispersions of type V or VI are obtained. The mode of incorporation of the drug depends on the PVP-drug miscibility and the preparation procedure. Grinding is required to obtain the solid dispersion as powder that is easy to handle.

Although frequently applied, the fusion method has serious limitations.

1. The method can only be applied when drug and matrix are compatible and when they mix well at the heating temperature. When drug and matrix are incompatible two liquid phases or a suspension can be observed in the heated mixture [37,38] which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants [39, 40].
2. Secondly, a problem can arise during cooling when the drug-matrix miscibility changes. In

this case phase separation can occur. Indeed, it was observed that when the mixture was slowly cooled, crystalline drug occurred, whereas fast cooling yielded amorphous solid dispersions[41, 42]. Thirdly, degradation of the drug and or matrix can occur during heating to temperatures necessary to fuse matrix and drug. For example, to melt a sugar matrix of galactose a temperature of
169°C was required and in order to get the glassy PVP in the rubbery state a temperature of about 170°C is required. PEG"s melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method.

2. Solvent method

The solvent method aims to dissolve the drug and carrier (often a polymer)simultaneously in a common solvent, followed by the removal of solvent by evaporation**,** evaporation procedure is often accomplished in a rotavapor, but the solvent can also be removed by other methods e.g. freeze-drying, spray drying or using supercritical fluids. The drug used in solid dispersions is usually hydrophobic and the carrier is hydrophilic. It is often difficult to identify a common solvent to dissolve both components. Frequently used solvents include, ethanol, methanol and methylene chloride. In some cases, large volumes of solvents as well as heating may be necessary to enable complete dissolution of both components. To minimize the volume of organic solvent necessary, some investigators reported the use of cosolvents[43].

Thermal decomposition of drug and carrier can be prevented or reduced using low boiling solvents, evaporation at reduced pressure, freeze-drying or supercritical fluid technology. However, solvent methods show multiple disadvantages due to the use of organic solvents;

- Expensive
- Ecological and environmental problems
- Difficult to find a common and removable solvent
- Residual solvent, which can cause health risks and can have an effect on the physico-chemical stability of drug, carrier and dispersion

3. Melting-solvent method

The melting-solvent method is a combination of the two methods mentioned above. It is performed by dissolving the drug in a suitable solvent and mixing of this solution with the molten carrier followed by cooling, resulting in solidification[44-46].The advantage of this method is that it can reduce maximum temperature and time at maximum temperature and result in less decomposition of thermolabile drugs. However, only a low drug loading is possible for this method.

4. Hot melt extrusion

Melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. When compared to melting in a vessel, the product stability and dissolution are similar[47], but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms[48]. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem.Solubility parameters are investigated to predict the solid-state miscibility and to select matrices suitable for melt extrusion
High shear forces resulting in high local temperatures in the extruder be a problem for heat sensitive materials[49, 50]. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, the product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.

5. Kneading

It consists of forming a paste starting from the addition of the low amount of liquid (water or hydroalcoholic solutions) enough to moisten the powdered mixture of drug and CD. In laboratory scale it is accomplished in a mortar/pistil. In

industry scale can be use extruders and other machines it is the most common method to obtain inclusions. This method presents very low cost of production.

Other methods

Evaporative precipitation into aqueous solutions (EPAS) was used to coat a colloidal suspension of carbamazepine with block-copolymers as stabilizing surfactants. A solution of drug in dichloromethane was sprayed in an aqueous solution containing polymeric surfactants as stabilizers. The obtained colloidal suspension was spray dried, freeze dried or spray freeze dried, resulting in solid dispersions of type IV/V. It was concluded that the amorphous state of the drug was best preserved with the spray freeze drying process[51].

In another process called supercritical fluid impregnation, the drug is dissolved in a supercritical fluid and exposed to solid matrix material that swells and absorbs the supercritical solution. By varying the pressure and the time of exposure, the diffusion process can be controlled. The absorption stops when the pressure is reduced. This process is investigated for poly(methyl methacrylate) but can be applied for other polymers as well[52].

MECHANISM OF DISSOLUTION OF SOLID DISPERSION

The enhancement in dissolution rate by formation of solid dispersion, relative to the pure drug was reviewed by Corrigan [53] the current understanding of the mechanism of release from solid dispersions. The increase in dissolution rate for solid dispersions can be attributed to a number of factors. It is difficult to demonstrate experimentally that any one particular factor is more important than other. The main reasons postulated for the observed improvements in dissolution of these systems are as follows: [11]

- Reduced drug particle size and hence increased surface area in two phase solid dispersions
- Reduced crystallinity or creation of amorphous system
- Carrier material may improve wettability and dispersibility of drug in the dissolution media and this should retard any agglomeration or aggregation of the particles, which can slow the dissolution process
- Elimination of drug particles in solid solutions, drug is dispersed molecularly

CARRIERS FOR SOLID DISPERSION

Desirable properties of a carrier for solid dispersions[11]

- Water soluble in common solvent with intrinsic rapid dissolution properties
- Non toxic, pharmacologically inert
- Heat stable with low melting point
- Soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method
- Chemically compatible with the drug and not form a strongly bonded complex with the drug
- High molecular weight with high Tg - less molecular mobility- improved stability

Materials used as a carriers for solid dispersion

Various different kinds of materials are being examined and user for their potential of enhancing intrinsic dissolution rate of poorly soluble drugs. List of various materials used as carrier for preparation of solid dispersions is enlisted in table 1.2.

Table 1.2 List of materials used as carriers

Category of material	Exampls
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Xylitol, Mannitol, Lactose
Acids	Citric acid, Succinic acid

Polymeric materials	Polyvinylpyrollidone, Poly ethylene glycol, Hydroxylethyl cellulose, Hydroxypropylmethyl cellulose,Methyl cellulose, Cyclodextrins, Hydroxyl propyl cellulose, Pectin, Polyethylene oxide, Microcrystalline cellulose, Starch, Avicel, Galactomannan
Insoluble or enteric polymer	Hydroxypropylmethyl cellulose phthalate, Eudragit RL, Eudragit RS, Eudragit L-100, Eudragit S-100

Solubilizing effects of carriers

Phase–solubility analysis of the effect of carrier on the compound being solubilized is a traditional approach to determine not only the value of the stability constant but also to give insight into the stoichiometry of the equilibrium. Experimentally, an excess of a poorly water-soluble drug is introduced into several vials to which a constant volume of an aqueous vehicle containing successively larger concentrations of the carriers are added. The need for excess drug is based on the desired to maintain as high a thermodynamic activity of the drug as possible. The vials are shaken or otherwise agitated at constant temperature until equilibrium is established. The suspensions are then filtered and the total concentration of the drug determined based on appropriate analytical techniques (UV spectrophotometry, HPLC, etc). The phase–solubility profile is then constructed by assessing the effect of the carrier on the apparent solubility of the drug. The practical and phenomenological implications of phase–solubility analysis were developed by Higuchi and Connons in their pioneering work published in 1964[54], and as later reviewed by Connons[55]. Based on the shape of the generated phase solubility relationships, several types of behaviors can be identified[56]. Phase–solubility diagrams fall into two major types, A and B.

A-type profiles: In A systems, the apparent solubility of the substrate increase as a function of carrier concentration. Three subtypes have been defined: A_L profiles indicate a linear increase in solubility as a function of solubilizer concentration, A_P systems indicate an isotherm wherein the curve deviates in a positive direction from linearity (i.e. the solubilizer is proportionally more effective at higher concentrations) and A_N relationships indicate a negative deviation from linearity (i.e. the carrier is proportionally less effective at higher concentrations).

B-type profiles: Type B phase–solubility profiles are indicative of the formation of complexes with limited water solubility and are traditionally observed with naturally occurring CDs, especially β-CD. Two subclasses have been described including B_S and B_I systems. B_S-type isotherms have been interpreted in the following manner: as the carrier concentration increases, a soluble complex forms which increase the total solubility of the substrate. At some point, all of the solid drug will have been consumed in the above described process and further addition of the carrier results in the formation of additional insoluble inclusion complex which precipitates and further depletes the total drug concentration. B_S-type solubility isotherms results in the precipitation of insoluble complexes of drug and carrier.

CHARACTERIZATION OF SOLID DISPERSIONS

Solid dispersions are characterized for crystallanity and molecular structure in amorphous solid dispersion. Various different types of analytical methods are available to characterize solid dispersions.

Detection of crystallinity in solid dispersions

Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. For that purpose many techniques are

available which detect the amount of crystalline material in the dispersion. The amount of amorphous material is never measured directly but is mostly derived from the amount of crystalline material in the sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecules.

1. Powder X-ray diffraction (XRD)
2. Infrared spectroscopy (IR)
3. Water vapour sorption
4. Isothermal Microcalorimetry
5. Dissolution Calorimetry
6. Differential Scanning Calorimetry (DSC)

Detection of molecular structure in amorphous solid dispersions

The properties of a solid dispersion are highly affected by the uniformity of the distribution of the drug in the matrix. The stability and dissolution behavior could be different for solid dispersions that do not contain any crystalline drug particles, i.e. solid dispersions of type V and VI or for type II and III.

However, not only the knowledge on the physical state (crystalline or amorphous) is important; the distribution of the drug as amorphous or crystalline particles or as separate drug molecules is relevant to the properties of the solid dispersion too.

Nevertheless, only very few studies focus on the discrimination between amorphous incorporated particles versus molecular distribution or homogeneous mixtures. Currently, the following techniques are available to detect molecular dispersion in amorphous solid dispersion:

1. Confocal Raman Spectroscopy
2. Temperature Modulated Differential Scanning Calorimetry (TMDSC)
3. Infrared or Fourier Transformed Infrared Spectroscopy (FTIR)

LIMITATIONS OF SOLID DISPERSION SYSTEMS

Problems limiting the commercial application of solid dispersion involve

1. Method of preparation
2. Reproducibility of its physicochemical properties,
3. Formulation into dosage forms,
4. Scale up of manufacturing processes, and
5. Physical and chemical stability of drug and vehicle.

CONCLUSION

Several types of approaches have been purposed to improve the aqueous solubility of poorly water soluble drugs. In particular, for BCS class II drugs, increasing their solubility or dissolution rate would be a promising approach to enhance the oral bioavailability. Solid dispersion systems have been realized as extremely useful tool in improving the dissolution properties of poorly water-soluble drugs. In recent year, a great deal of knowledge has been accumulated about solid dispersion technology, but their commercial application is limited due reproducibility of its physicochemical properties. Scale up of manufacturing processes, physical and chemical stability of drug and vehicle.

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