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SOLID DISPERSION: AN OVERVIEW

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ABSTRACT

Solid dispersions have attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The poor oral bioavailability as a result of poor aqueous solubility makes drug research and its development more difficult. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new chemical entities. New chemical entities (NCEs) often show poor water solubility necessitating solid dispersion formulation. Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly aqueous soluble drugs by reducing drug particle size to the absolute minimum, increasing surface area and hence improving drug wettability, bioavailability may be significantly improved. Solid dispersion are obtained by two different methods i.e. melting and solvent evaporation usually presenting the amorphous product. To reduce the drawbacks of initial process new manufacturing processes have also been developed to obtain solid dispersions have also been developed. In this review, it is intended to discuss the recent advances in the area of solid dispersions.

KEYWORDS: Solid dispersion, Improved bioavailability, Dissolution Enhancement.

INTRODUCTION[1, 2, 3, 4, 5]

The simplest and easiest way of administering drugs is oral drug delivery. Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms offers many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form originating an effective and reproducible in vivo plasma concentration profile after oral administration. In fact, most NCEs are poorly aqueous soluble drugs, hence not well-absorbed after oral administration, which can detract from the drug's inherent efficacy. Moreover, most promising NCEs, instead of their high permeability, are usually only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window. Consequently, the incomplete release of these drugs in the gastrointestinal area, will show low bioavailability problems. Therefore, one of the major current challenges of the pharmaceutical industry is related to tactics that improve the aqueous solubility of drugs. Drug release is a crucial and rate limiting step for oral bioavailability, particularly for drugs with low solubility and low permeability i.e. BCS class IV drugs. By improving the drug release profile of BCS class IV drugs, it is possible to enhance their bioavailability and reduce side effects. Solid dispersions are one of the most promising strategies to improve drug release of poorly soluble drugs. Solid dispersion's can be defined as homogeneous molecular mixtures of poorly water soluble drugs in hydrophilic carriers, presenting a drug release profile driven by the polymer properties.

BCS CLASSIFICATION[6, 7, 8]

Biopharmaceutics classification system (BCS) is a useful tool for making decision in formulation development from a biopharmaceutical point of view. As per BCS classification system drug substances is categorized into one of four classes depending on their solubility and intestinal permeability, and these four categories are defined as follows.

Table no : 1 Biopharmaceutical classification system.

Class	Solubility	Permeability	Characteristic features
Class I	High	High	Well absorption orally
Class II	Low	High	Variable absorption due to solubility limitation.
Class III	High	Low	Variable absorption due to permeability limitation
Class IV	Low	Low	Meager absorbed due to both solubility & permeability limitation .

Biopharmaceutical Classification System: The BCS has proven to be an extremely useful guiding tool for the prediction of *in vivo* performance of drug substances and development of new drug delivery system to suit the performance of drug in the body, as also for the regulation of bioequivalence of drug product during scale up and post approval. The development of dosage form especially for prolonged release has been a challenge to formulation scientists because of many independent factors governing the absorption from the gastrointestinal tract. For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeability to biomembranes and such a classification system is called as a biopharmaceutical classification system . The BCS was first devised in 1995 by Amidon et al and since then it has become a benchmark in the regulation of bioequivalence of oral drug products. The BCS serves as a guiding tool to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of immediate release (IR) solid dosage forms, for which bioequivalence may be assessed based on *in vitro* dissolution tests and to lay the effect of excipients on drug permeability. The classification of a drug candidate depends upon its three key parameters that control absorption – solubility, dissolution rate and permeability that correlate with three respective dimensionless parameter- dose number, dissolution number, and absorption number are given in Table 1.

Table 2: BCS classification of drug based on solubility, dissolution rate, and permeability.[9]

Sr. No.	Drug property influencing absorption	Corresponding dimensionless parameter	Significance
1.	**Solubility** A drug with high solubility is the one whose largest dosage strength is soluble in 250 ml or less of water over a pH range of 1-8.	**Dose number** It is mass of drug divided by an uptake volume of 250ml and drug's solubility.	Ideally, dose ratio should be below 1if full dissolution is to be possible in princilple. Obviously, higher doses will raise the ratio and absorption less likely.
2.	**Dissolution rate** A drug product with rapid dissolution is the one when ≥ 85 % of the labelled amount of drug substance dissolves within 30 minutes using USP apparatus 1 or 2 in a volume of ≤900ml buffer solutions.	**Dissolution number** It is the ratio of mean residence time to mean dissolution time.	Ideally, dissolution number should exceed 1. In the case of solid dosage forms, a combination of inadequate solubility or diffusivity, or density can increase the time needed for full dissolution and reduce this ratio.

3.	**Permeability** A drug with high permeability is the one having extent of absorption greater than 90% of the administered dose given that the drug is stable in the gastrointestinal environment.	**Absorption number** It is the ratio of the mean residence time of drug in the GIT to the absorption time.	Ideally, absorption number should excess 1. Longer absorption times resulting from lower permeability will reduce the ratio.

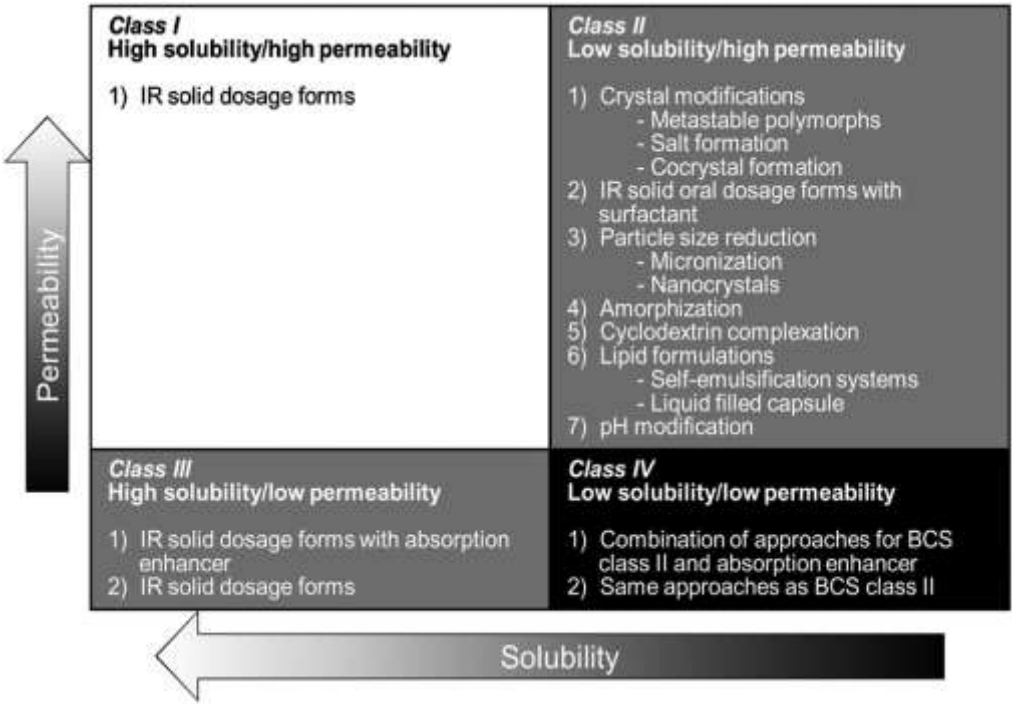


Figure 1: BCS and viable formulation option based on the BCS.[10]

Characteristics of the Drugs under BCS[7, 8]

Class I: High Permeability, High Solubility

In-vivo these drugs behave like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very fast, bioavailability and bioequivalence are unnecessary for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter in this case. Example: Metoprolol, Diltiazem, Propanolol.

Class II: High Permeability, Low Solubility: Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These drugs exhibit variable bioavailability and need enhancement in the dissolution rate by different methods for improvement in bioavailability. These are also

suitable for controlled release development. Example: Atorvastatin calcium, Lovastatin, Felodipine.

Class III: Low Permeability, High Solubility: Permeation through the intestinal membrane forms the rate-determining step for these drugs. Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. For example, the various ranitidine products having different dissolution profiles produce super-imposable plasma concentration versus time profile *in-vivo.* These drugs generally exhibit low bioavailability and permeability enhancement is generally required. These drugs are problematic for controlled release development. Example: Cimetidine, Neomycin, Captopril.

Class IV: Low Permeability, Low Solubility: Drugs of this class exhibit poor and variable bioavailability. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not suitable for oral drug delivery or else some special drug delivery technologies such as nanosuspensions will be needed. Example: Hydrochlorothiazide,Tobromycin,Furosamide .

Formulation of BCS class V drugs

Class V drugs are those that are metabolically or chemically unstable thus limiting their bioavailability. The various approaches to overcome these problems are aimed at enhancing their stability by use of methods such as.

1. Prodrug design
2. Enteric coating (Protection from stomach acid)
3. Enzyme inhibition or lymphatic delivery (to prevent presystemic metabolism)
4. Lipid technologies.

SOLUBILITY[11-17]

Basic consideration

Solid drugs administered orally for systemic activity must dissolve in GI fluids prior to their absorption. Thus the rate of dissolution can influence rate of absorption. As rate of dissolution of a solid is a function of its solubility in dissolution medium, latter could influence absorption of insoluble drugs. Compounds with an aqueous solubility of greater than 1% w/v do not show dissolution related problems. Mainly BCS class II and Class IV drugs show solubilization problems. Dissolution is the transfer of molecules or ions from a solid state into solution. The extent to which the dissolution proceeds under a given set of

experimental conditions is referred to as the solubility of the solute in the solvent. Thus, solubility is the amount of solute that passes into solution when equilibrium is established between the solution and excess solute The pharmacopoeia lists solubility in terms of solvent required to dissolve 1g of solute. If exact solubilities are not known, the pharmacopoeia provides general terms to describe a given range as shown in table 3.

Table 3: Definition of solubility as per USP/NF 2008.

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	From 10,000 and over.

Related terminology [4]

Supersaturation is an unstable state of a solution containing more dissolved substance than would exist at equilibrium under same experimental conditions.

Subsaturation is the term introduced by Sirius to describe the state of a system containing precipitate that begins to dissolve in the surrounding solution.

Absolute/Intrinsic solubility is defined as the maximum amount of solute dissolved in a given solvent under standard conditions of temperature, pressure and pH. Also it can be defined as the maximum concentration to which a solution can be prepared with specific solute & solvent. Solubility depends on the solute & solvent as well as temperature, pressure & pH. Also in simple words intrinsic solubility of any compound is the solubility of that compound in its active form that is pure.

Equilibrium solubility is the concentration of compound in a saturated solution when excess solid is present, and solution and solid are at equilibrium. The equilibrium solubility of the free acid and base form of an ionizable compound at a pH where it is un-ionized .

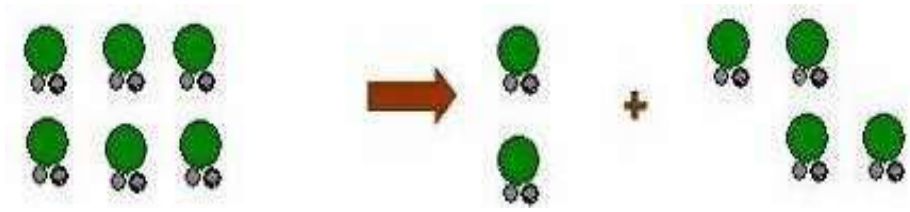
Kinetic solubility is the solubility at the time when an induced precipitate first appears in a solution**.**

Process of Solubilization [18]

Solubility process is depend on the bonding between the solute and solvent molecule. The bonds involved in solubilization are mainly dipole interaction, London forces, hydrogen bonding, ionic bonding etc.

Step 1: Holes open in the solvent

Step 2: Molecules of the solid breaks away from the bulk



Step 3: The free solid molecules are integrated into solvent holes

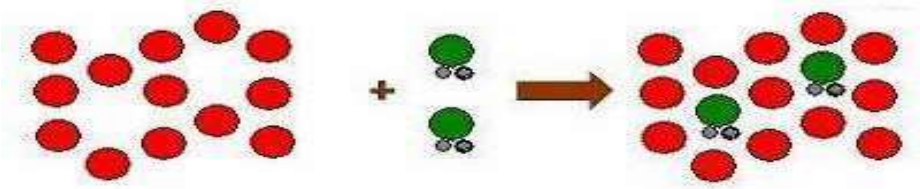


Figure 2: Mechanism of Solubility

Table 4: Factors Affecting Solubilization [19]

Particle Size	The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent.
Pressure	For solids and liquid solutes, changes in pressure have practically no effect on solubilitybut for gaseous solutes, an increase in pressure, increases solubility and a decrease inpressure, decrease the solubility. Nature of the solute and solvent only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at roomtemperature while 200 grams of zinc chloride can be dissolved. The great difference inthe solubility's of these two substances is the result of differences in their natures.
Temperature	Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased. If the solution process releases energy then solubility will decrease with increase in temperature. The situation is different for gases with increase of temperature they become less soluble in each other

	and in water but more soluble in organic solvents. Organic compounds nearly always become soluble as temperature raised in most of the solvents
Molecular size	The solubility of the substance is decreased when molecules have higher molecular weight and higher molecular size because larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.
Polarity	Polarity of the solute and solvent molecules will affect the solubility. Generally dissolves like means non-polar solute molecules will dissolve in non-polar solvents andpolar solute molecules will dissolve in polar solvents. The polar solute molecules have apositive and a negative end to the molecule. If the solvent molecule is also polar thenpositive ends of solvent molecules will attract negative ends of solute molecules. This isa type of intermolecular force known as dipole-dipole interaction. The other forces calledLondon dispersion forces where the positive nuclei of the atoms of the solute moleculewill attract the negative electrons of the atoms of a solvent molecule. This gives the nonpolarsolvent a chance to solvate the solute molecules.
Polymorphs	Polymorphs can vary in melting point. Since the melting point of the solid is related to solubility, so polymorphs will have different solubility's. Generally the range of solubility differences between different polymorphs is only 2-3 folds due to relatively small differences in free energy.

SOLID DISPERSION: DEFINITION[20]

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 either be crystalline or amorphous is having good solubility than crystalline substance because no energy is required to break up the crystal lattice of a drug during dissolution process . Drug solubility and wettability may be increased by surrounding hydrophilic carriers.

ADVANTAGES OF SOLID DISPERSIONS[20]

There are various reasons for the improvement of solubility of poorly water-soluble drug using solid dispersion technology. The reasons for solid dispersion or advantages of solid dispersions are as follows:

Particles with reduced particle size

Molecular dispersions, as solid dispersion, represent the last state on particle size reduction, and after inert carrier or matrix dissolution the drug is molecularly dispersed in the dissolution medium . A high surface area is formed which results an increased dissolution rate and further improved the bioavailability of the poorly water soluble drug.

Particles with improved wettability

The solubility enhancement of the drug is related to the drug wettability improvement verified in solid dispersion.

Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity and the increase in porosity also depends on the properties of the carrier. When polymers having linear structure are utilized it produces larger and more porous particle as compared with SDs that prepared with reticular polymers. More porous nature of the particle results higher dissolution rate.

Drugs in amorphous state

Poorly water-soluble crystalline drugs, when in the amorphous state tend to have higher degree of solubility. Drug in its amorphous state shows higher drug release because no energy is required to break up the crystal lattice during the dissolution process.

DISADVANTAGES OF SOLID DISPERSIONS[21]

The major disadvantages of SDs are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate on ageing. By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility. Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness.

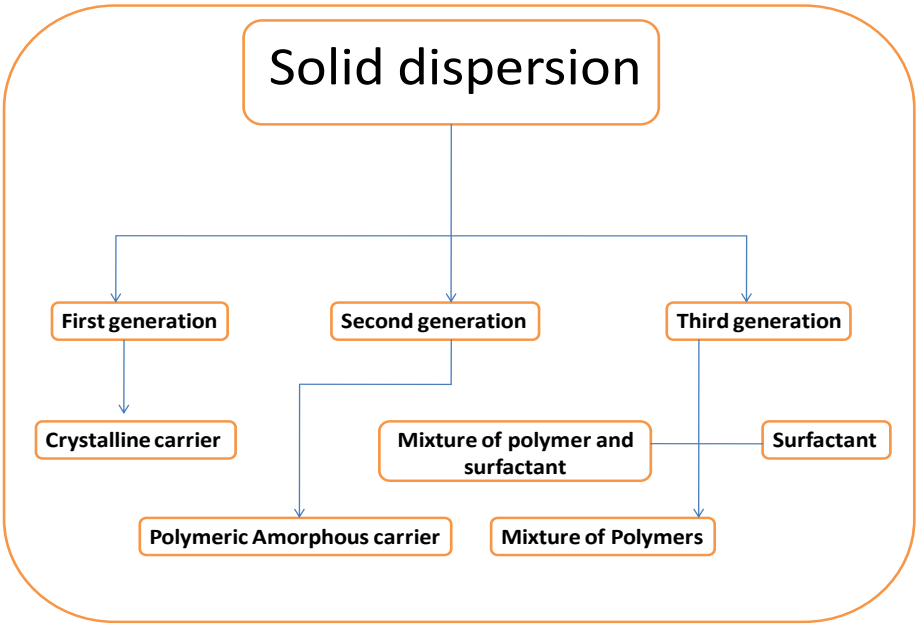
LIMITATIONS OF SOLID DISPERSIONS[22]

Although a great research interest in solid dispersion in the past four decades, the commercial utilization is very limited.

Problems of solid dispersion involve.

I. The physical and chemical stability of drugs and vehicles,
II. Method of preparation.
III. Reproducibility of its physicochemical properties,
IV. Formulation of solid dispersion into dosage forms, and
V. Scale-up of manufacturing processes .

CLASSIFICATION OF SOLID DISPERSIONS[23]



The classification of solid dispersion

1) First Generation Solid Dispersions

Solid despersion were first described by sekiguchi and obi in 1961 in which they used concept of eutectic mixtures. They mentioned that the formulation of eutectic mixtures improve the rate of drug release and thus increase bioavalibility of poorly soluble drug .Thus first generation solid dispersions were prepared using crystalline carrier like urea , mannitol . Eutectic mixtures are binary systems comprising of poorly water soluble drug and highly water soluble carrier and at eutectic point drug crystallizing out simultaneously only in the specific composition . The main disadvantage of first generation solid dispersion is crystalline nature which leads to less solubility as compare to amorphous form , however , they possess good thermodynamic stability.

2) Second generation solid dispersions

In second generation instead of crystalline carriers, amorphous carriers used to disperse drugs which are generally polymers. Polymeric carriers can be of fully synthetic origin like povidone , polyethylene glycols and polymethacryates whereas natural products based polymers comprises of cellulose or starch derivatives , like cyclodextrins. Amorphous solid dispersions are further classified as solid solutions , solid suspension or mixture of both as per molecular interaction of drug and carrier.

3) Third Generation Solid Dispersions

In the third generation solid dispersion surfactants carrier or mixture of polymer are used as carrier. If carrier has surface active or self emulsifying properties, the dissolution profile of poor soluble drug can be improved and hence result in increased bioavailability. Typically used surfactants as solid dispersion carrier are poloxamer 188,gelucire 44/14, compritol 888 ATO27, insulin.

SOLID DISPERSION MANUFACTURING TECHNIQUES[24, 25, 26, 27]

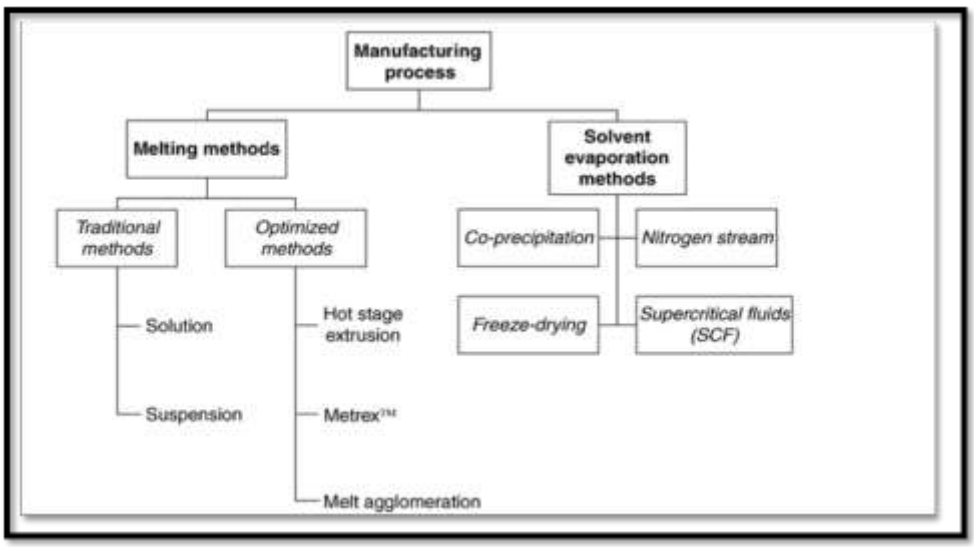


FIG.4:MANUFACTURING PROCESSES USED TO PRODUCE SOLID DISPERSION

1. Melting method/ fusion method

Sekiguchi and Obi utilized a hot melt system to plan basic eutectic mixtures. Sulphathiazole and urea were melted together at a temperature over the eutectic point and after that cooled in an ice bath . The resultant solid eutectic was then processed to reduced the particle size . Cooling leads to supersaturation, but due to solidification the dispersed drug becomes trapped within the carrier matrix and get stabilized. Whether or not a molecular dispersion can be achieved depends on the degree of supersaturation and rate of cooling attained in the process. Kanig[35] introduced the variation of spraying the hot melt onto a cold surface. A further approach is to prepare the solid dispersion by injection molding, as demonstrated by Wacker et al. An important prerequisite to the manufacture of solid solutions by the hot melt method is the miscibility of the drug and the carrier in the molten mass. When there are miscibility gaps in the phase diagram, this usually leads to a product that is not molecularly dispersed.

Limitation to fusion method

• Firstly, a major disadvantage is that 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, which results in an inhomogeneous solid dispersion. This can be prevented by using surfactants.

• 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.

• 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. Poly ethylene glycols melt at around 70°C and are therefore often used for the preparation of solid dispersions with the fusion method. ME applications include taste masking, solid-state stability enhancement, sustained drug release and solubility enhancement. While ME can result in amorphous or crystalline solid dispersions depending upon several factors, solubility enhancement applications are centered around generating amorphous dispersions, primarily because of the free energy benefits they offer. In recent years, ME has been applied to the manufacture of solid solutions. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/ carrier mix is only subjected to an elevated temperature for about 1 min, which enables thermolabile drugs to be processed. A further alternative for processing thermolabile substances is by hot-spin-melting. Here, the drug and carrier are melted together over an extremely short time in a high speed mixer and, in the same apparatus, dispersed in air or an inert gas in a cooling tower. Some drugs that have been processed into solid dispersions using hot-spin-melting to date include testosterone, progesterone and dienogest.

1. **Dropping method**

Hot melt extrusion is essentially the same asthe fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials.

2. The Solvent Method

Tachibani and Nakumara were the first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophilic b-carotene in the highly water soluble carrier polyvinylpyrrolidone (PVP) . Many investigators studied solid dispersion of meloxicam, naproxen and nimesulide using solvent evaporation technique. This technique increase solubility and stability of solid dispersions of hydrophobic drugs. The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents.

Solvents should be selected on the basis of following criteria

• Dissolve both drug and carrier

• Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.

• Ethanol is a less toxic alternative

• Water based systems preferable

• Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass.

• Transition point.

Solvents used are as following

Some solvents may also be of interest to manufacturers of excipients, drug substances, or drug products for example, Petroleum ether, and isopropyl ether. Class III solvent have less toxic effect if they are used within limit list is as following, Acetic acid, Acetone, 1-Butanol, 2-Butanol, Butyl acetate, Dimethyl sufoxide, Ethanol, Ethyl acetate, Ethyl ether, Formic acid, Heptanes, Isobutyl acetate, Isopropyl acetate ,Methyl acetate, 3-Methyl-1-Butanol, Pentane, 1- Pentanol, 1-Propanol, 2-Propanol, Propyl acetate. According to the ICH-Guidelines, these solvents belong to Class I, comprising the most toxic solvents. Therefore, the use of these solvents is unacceptable and impractical because the amount of residual solvent present in the solid dispersion after drying has to be below the detection limits. The last strategy for the dissolution of both drug and matrix is the use of solvent mixtures. Water and ethanol or dichloromethane and ethanol have been used for this purpose. However, dissolution of drug and matrix in these mixtures is not always possible in the required concentration or ratio. The second challenge in the solvent method is to prevent phase separation, e.g. crystallization of

drug. To dry the solutions, vacuum drying is often used. The solution is dried by the application of vacuum and moderate heating. Sometimes, the solvent evaporation is accelerated by using a rotary evaporator. Vacuum drying at elevated temperature bears the risk of phase separation because the mobility of drug and matrix decreases slowly. Another drying technique is spray drying. The solution is dispersed as fine particles in hot air. Due to the large specific surface area offered by the droplets, the solvent rapidly evaporates and the solid dispersion is formed within seconds, which may be fast enough to prevent phase separation. Moreover, the solid dispersions prepared by spray drying consist of particles of which the size may be customized by changing the droplet size to meet the requirements for further processing or application (e.g., free flowing particles or particles for inhalation). Spray drying usually yields drug in the amorphous state, however sometimes the drug may have (partially) crystallized during processing. An alternative to these drying techniques is freeze drying. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique.

CHARACTERIZATION OF SOLID DISPERSIONS[28, 29, 30, 31, 32]

The most important methods are thermoanalytical, X-ray diffraction, infrared spectroscopy and measurement of the release rate of the drug. In addition to characterizing the solid dispersion, these methods can be used to differentiate between solid solutions (molecularly dispersed drug), solid dispersions in which drug is only partly molecularly dispersed and physical mixtures of drug and carrier. Due to the complex composition of these preparations, it is often difficult to delineate precisely between molecularly dispersed and not molecularly dispersed systems and different analytical methods may yield disparate results. It is usually assumed that dispersions in which no crystallinity can be detected are molecularly dispersed and the absence of crystallinity is used as a criterion to differentiate between solid solutions and solid dispersions.

Thermoanalytical method

Thermoanalytical methods include all that examine a characteristic of the system as a function of temperature. Of these, differential scanning calorimetry (DSC) is the most highly regarded method. DSC enables the quantitative detection of all processes in which energy is required or produced (i.e. endothermic and exothermic phase transformations). The usual method of measurement is to heat the reference and test samples in such a way that the temperature of the two is kept identical. If an energy-requiring phase transition occurs in the

test sample, extra heat is applied to this sample so that its temperature climbs at the same rate as in the reference. The additional heat required is recorded and used to quantitate the energy of the phase transition. Exothermic transitions, such as conversion of one polymorph to a more stable polymorph, can also be detected. Lack of a melting peak in the DSC of a solid dispersion indicates that the drug is present in an amorphous rather than a crystalline form. Since the method is quantitative in nature, the degree of crystallinity can also be calculated for systems in which the drug is partly amorphous and partly crystalline. However, crystallinities of under 2% cannot generally be detected with DSC.

X- Ray diffraction spectroscopy

The principle behind X-ray diffraction is that when an Xray beam is applied to the sample, interference bands can be detected. The angle at which the interference bands can be detected depends on the wavelength applied and the geometry of the sample with respect to periodicities in the structure. Crystallinity in the sample is reflected by a characteristic fingerprint region in the diffraction pattern. Owing to the specificity of the fingerprint, crystallinity in the drug can be separately identified from crystallinity in the carrier. Therefore, it is possible with X-ray diffraction to differentiate between solid solutions, in which the drug is amorphous, and solid dispersions, in which it is at least partly present in the crystalline form, regardless of whether the carrier is amorphous or crystalline. However, crystallinity of under 5±10% cannot generally be detected with X-ray diffraction.

Infrared spectroscopy

FTIR analysis is performed on the drug-polymer dispersions to determine what specific interactions are formed and if these interactions are related to the impact of the polymer. FTIR is a well-established technique for the evaluation of hydrogen bonding interactions in amorphous systems. If an interaction between the drug and polymers occurs, then a shift in the vibrational frequencies of the functional groups involved in the interaction is expected. For a group participating in a hydrogen bond, a shift to lower wavenumbers usually indicates a stronger bond while a shift to higher wavenumbers indicates the formation of a bond that is weaker than the original bond present in the pure condensed phase. Structural changes and lack of a crystal structure can lead to changes in bonding between functional groups which can be detected by infrared spectroscopy. Since not all peaks in the IR spectrum are sensitive to crystalline changes, it is possible to differentiate between those that are sensitive to changes in crystallinity and those that are not.

Release rate experiments

Release rate experiments cannot be used on a stand-alone basis to determine whether a solid solution has been formed or not. However, in conjunction with other physicochemical data, they provide strong evidence for the formation of a molecularly dispersed or nearly molecularly dispersed system. When the goal of preparing a solid dispersion is to improve the dissolution characteristics of the drug in question, the results of the release rate experiments are obviously of prime importance in assessing the success of the approach. A well-designed release experiment will show whether the solubility of the drug and its dissolution rate has been enhanced, and also whether the resulting supersaturated solution is stable or tends to precipitate quickly. Comparison of results with those for pure drug powder and physical mixtures of the drug and carrier can help to indicate the mechanism by which the carrier improves dissolution: via solubilization and wetting effects which could be affected by a simple mixture of the components, or by formation of a solid dispersion/solution.

CONCLUSION

Experience with solid dispersion over last 25-35 years depicts its fruitfulness in improving the dissolution rate and oral bioavailability of poorly water soluble drugs. Most of the NCEs are poorly water soluble which may affect their therapeutic efficacy, due to their low bioavailability. Now a day's, solid dispersions are one of the most widely used strategy because it offers several advantages like reduction in particle size, increase in effective surface area, improved drug wettability, and dissolution rate. The most frequent concerns with solid dispersions have been the ability to scale-up the manufacturing method, the physical stability of the solid dispersion, and the amount of carrier needed to facilitate the required increase in dissolution rate when dose of drug is too high and also the compatibility of the carrier with the GI fluids. Despite the concern there are several products on market containing solid dispersions, and number is expected to increase dramatically in the next years. The advancement in manufacturing of the solid dispersions is being carried out and the best example is hot melt extrusion. The application of hot melt extrusion to the production of solid dispersion is a particularly important breakthrough for scale-up of solid dispersion manufacture. Aspect still needed to be considered in the next years include further development in manufacturing on the large scale, and better predictions of whether a particular NCEs/Carrier combination will lead to true solid solution or to a partly crystalline dispersion as well as whether the dispersion will remain physically stable during further processing and storage. Last but not the least, although this article has been devoted to use of

solid dispersion for the improvement of dissolution rate and oral bioavailability, by appropriate choice of the carrier it is also possible to delay or slow down the release pattern of a drug by formulating it as a solid dispersion. The availability of a wide variety of polymers that are themselves poorly water soluble or which swells under aqueous conditions suggests that solid dispersion has tremendous potential in the area of controlled release dosage forms.

REFERENCES

1. Noyes, A. A., Whitney, W. R. The rate of solution of solid substances in their own solutions, journal of American Chemical Society, 1897; 19: 930-934.
2. Galia, E., Nicolaides, E., Hoerter, D., Reppas, C., Dressman, J. B. Evaluation of various dissolution media for predicting invivo performance of class I and II drugs, pharmaceutical Research, 1998; 15: 698-705.
3. Hancock, B. C., Zogra, G. Characteristics and significance of the amorphous state in pharmaceutical systems Review, Journal of Pharmaceutical Science, 1997; 86: 1-12.
4. Horter, D, Dressman, J. B. Influence of physicochemical properties on dissolution of drugs in gastrointestinal tract Review, Advance Drug Delivery Review, 1997; 25: 3-14.
5. Goldberg, A.H., Gibaldi, M., Kanig, J.L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II- experimental evaluation of a eutectic mixture: urea-acetaminophen system, Journal of Pharmaceutical Science, 1966; 55: 482-487.
6. Amidon, G.L., Lennernas, H., Shah, V.P., Crison, J.R., A theoretical basis for a biopharmaceutics drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical Research, 1995; 12: 413–420.
7. Khan GM., Controlled release oral dosage forms: some recent advances in matrix type drug delivery systems. The Science, 2001; 1: 350-354.
8. Lobenberg R, Amidon GL: Modern bioavailability and bioequivalence and biopharmaceutics classification system. New scientific approaches to international regulatory standards. Eur J Pharm Biopharm, 2000; 50: 3-12.
9. Cook.,Addicks,W.,Wu,Y.H. Application of the biopharmaceutical classification system in clinical drug development – an industrial view . The AAPS journal, 2008; 10: 306-310
10. 10 .Yohei k., Koichi, W., Formulation design for poorly water-soluble drug based on biopharmaceutics classification system: Basic approaches an practical applications. International journal of pharmaceutics, 2011; 420: 1-10.

11. Indian Pharmacopoeia", Government of ministry of health & family welfare Indian Pharmacopoeia Commision , Ghaziabad, 2010; 1-147.
12. United State Pharmacopoeia", Water-Solid interaction of pharmaceutical systems, the official compendia of standard, 2008; 1: 710.
13. "British Pharmacopoeia", London The stationary office, Published by The Stationary Office on behalf of the medicines & health care products. Solubility definition, 2009; 2208.
14. Patrick J. Sinko., Solubility & Distribution Phenomenon, Martin's Physical Pharmacy & Pharmaceutical Sciences, Sixth Edition, 182-196.
15. .Remington, "The Science & Practice of Pharmacy", 21st edition, volume-I, 223.
16. Samuel H. Yalkowsky, "Solubilization of Drug's in aqueous media", Encyclopedia of pharmaceutical Technology, 2nd edition, 2458.
17. Rao M. V., Sanghvi R., Zhu H., "Solubility of pharmaceutical solids", Theories & Techniques in characterization of drug substances & Excipients. Developing Solid oral dosage form, Pharmaceutical Theory & Practise. Part I, 3-22.
18. Md . Mofizur Rahman , Abdul Bashar Ripon Khalipha JamalAhmed , Md. AbShuaib Rafashanjani Shanjida Haque . Methods of solubility & dissolution enhancement for poorly water soluble drugs : A Review, 1-23.
19. Sajid A., Chaudhary VSolubility enhancement methods with importance of Hydrotropy; Journal of drug discovery and therapeutics, 2013; 2(6): 96-101.
20. Sanjoy Kumar Das1, Sudipta Roy2 . Solid Dispersions : An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs. International Journal of Pharmacology and Pharmaceutical Technology (IJPPT), ISSN: 2277 – 3436, I (1):38 – 46.
21. N.S.Seth, Formulation and evaluation of solid despersion of olanzepine, Int J.pharm. sci,res., 2011; 2(3): 691-697.
22. H.Karanth, V.S.Shenoy and R.R.Murthy, " Industrially feasible alternative approaches in the manufacture of solid despersion : A technical report ; AAPS pharm sci Tech, 2006; 7(4): 31-38.
23. Andre B. da Fonseca Antunes, Bruno G, Gelucire 44/14 based immediate release formulation for poorly water soluble drugs, Drug Development and Industrial Pharmacy, 2012; 1-8.
24. Prasanthi N.L, Manikiran S.S, Sowmya S., Anusha B, Effect of poloxamer 188 On In Vitro Dissolution Properties Of Antipsychotic Solid Dispersion, International Journal Of Pharmaceutical Sciences Review and Research, 2011; 10(1): 15-19.

25. Singh S., A review on solid dispersion, International journal of pharmacy and life sciences, 2011; 2(9): 12-17.
26. Mayersohn, M., Gibaldi,M., New method of solid-state dispersion for increasing dissolution rates, Journal of Pharmaceutical Science, 1966; 55: 1323-1324.
27. Sekiguchi, K. and Obi, N. Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem. Pharm. Bull, 1961; 9: 866–872.
28. Tyagi S., Patel C.J., Dadrwal P., Mangukia D., Sojitra I.,Nimbiwal B.K, Sigh V., Subrahmanyam K.V.A" novel concept for solublization and bioavailibility of poorly soluble drugs: Hydrotropy. Int. J Pharm Res and Bio Sci, 2013; 2(1): 372-381.
29. Chandel P., Raj K., Kapoor A. Liquisolid technique, an approach for enhancement of solubility. Journal of Drug Delivery & Therapeutics, 2013; 3(4): 131-137.
30. Jared A. B., Taylor, S. L. Evaluation of amorphous solid dispersion properties using thermal analysis techniques, Advance Drug Delivery Review, 2012; 64: 396-421.
31. Van Drooge, D.J. et al. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. International Journal of Pharmaceutics, 2006; 310: 220–229.
32. Dressman, J., Vasconcelose, T. Solid dispersion as strategy to improve oral bioavailability of poorly water soluble drugs. Advance Drug Delivery Review, 2007; 12: 1068-1075.
33. Taylor, S. L., Baird, J. A. Evaluation of amorphous solid dispersion properties using Thermal Analytical Technique. Advance drug delivery reviews, 2012; 64: 396-421.
34. Chiou, W.L. and Riegelman, S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. Journal of Pharmaceutical Scienc, 1969; 58: 1505–1510.