



SOLID DISPERSION: AN EFFICIENT TOOL FOR INCREASING BIOAVAILABILITY OF POORLY SOLUBLE DRUGS

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ABSTRACT

Despite tremendous development in the field of pharmaceuticals, oral solid dosage forms today also remain the most popular among all. However in recent years due to application of combinational chemistry and high-throughput screening during drug discovery, a majority of New Drug Candidates (NCE's) exhibits poor aqueous solubility which compounds to be a very challenging job for formulation scientists in development of bioavailable dosage forms for such drugs. Several researchers have employed different methods to improve the dissolution behavior of such drugs. Solid dispersion is one of such method which has attracted considerable interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of hydrophobic drugs. The present article reviews the basic concept about solid dispersion, various types of solid dispersion based upon the molecular arrangement, the methods of preparation, characterization, their advantages, limitations and applications. Furthermore a novel drug solid dispersion technique has also been reviewed wherein a hydrophobic drug can be solid dispersed into a hydrophilic drug with which the former is already available in a fixed dose combination.

Keywords: Solid dispersion, Bioavailability, Dissolution, Solubility, Carrier.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion and it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route.^{1, 2} Among them tablets and capsules are most frequently given by this route. From a patient's perspective, swallowing a dosage form is far more comfortable and a familiar means of taking medication than getting injected. As a result, patient compliance and hence drug treatment is typically more effective with orally administered medications as compared with other routes of administration, for example, parenteral.

Although the oral route of administration is having many advantages, for many drugs it can be a problematic and inefficient mode of delivery for a number of reasons. The attributes include

1. Poor absorption, rapid degradation, and lamination (peptides and protein) resulting in insufficient concentration,
2. Drug distribution to other tissues with high drug toxicities (anticancer drugs),
3. Poor solubility of drugs, and
4. Fluctuations in plasma levels owing to unpredictable bioavailability.

Moreover with the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has risen sharply and the

formulation of poorly soluble compounds for oral delivery now days presents one of the most frequent and greatest challenges to formulation scientists.^{3,4} It is also estimated that about 40% or more of New Chemical Entities (NCEs) which are being identified through combinatorial screening programs are poorly soluble in water⁵, which itself is a critical determinant of oral bioavailability and thus solubility of many newly developed high-potential drugs is an obstacle in formulation development, in addition Biopharmaceutical Classification System (BCS) also highlights dissolution as the rate-limiting step for oral absorption of class II and IV drugs. Conventional dosage forms of these drugs, therefore, often have an erratic and variable performance in preclinical and clinical evaluation leading to sub-optimal therapeutic concentration.⁶

A poorly water soluble drug, more recently, has been defined in general terms as a drug which requires more time to dissolve in the gastrointestinal fluid than it may take to get absorbed in the gastrointestinal tract and thus the ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry.⁷

Relative to highly soluble compounds, low drug solubility often manifests itself in a host of in vivo consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the

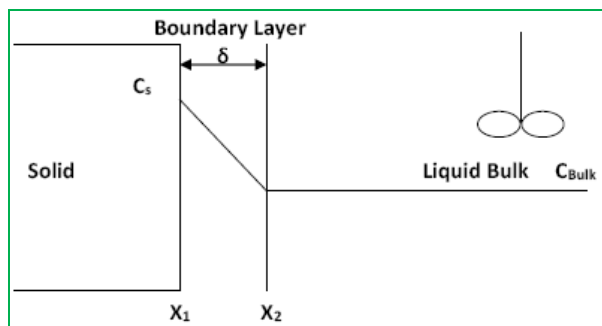


dosage form and higher inter-patient variability. Poorly soluble compounds also present many in vitro formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption.⁶ Thus a greater understanding of dissolution and absorption behaviors of drugs with low aqueous solubility is required to successfully formulate them into bioavailable drug products.

Orally administered drugs should undergo dissolution in the gastro-intestinal fluids before absorption can commence. Insoluble or poorly soluble drugs are generally poorly absorbed from the gastro-intestinal tract after oral administration. The absorption behavior of such drugs can be best studied by in-vitro dissolution characteristics. In other words, in-vitro dissolution is considered the index of in-vivo absorption of poorly soluble drugs.⁸

A description commonly used to explain the dissolution of a solid, was originally developed by Noyes and Whitney.⁹ They claimed that the dissolution rate was proportional to the difference between bulk concentration and concentration at the dissolving interface. Nernst and Brunner were the first to propose the diffusion layer model. They assumed that dissolution at the solid-liquid interface is rapid and transport of the solute to the bulk is completely determined by diffusion through a stagnant boundary layer surrounding the dissolving interface.¹⁰ These assumptions are depicted in Figure 1.

Figure 1: Schematic representation of Dissolution of a solid



The process of drug dissolution involves the transfer of individual molecules from a solid state into an aqueous environment. The underlying principles involved in the solubility process are diffusion, chemical reactivity and hydrodynamic behaviour¹¹.

The rate of dissolution of drug particles as explained by Nernst and Brunner equation is:

$$\frac{dm}{dt} = \frac{D \cdot A}{\delta} (C_s - C_{bulk}) \quad \text{----- Eq.1}$$

Where,

$\frac{dm}{dt}$ = Rate of dissolution of the drug particles.

D = Diffusion coefficient of drug in solution in the g.i. fluids.

A = Effective surface area of the drug particles in contact with the g.i. fluids.

h = Thickness of the diffusion layer around each drug particle.

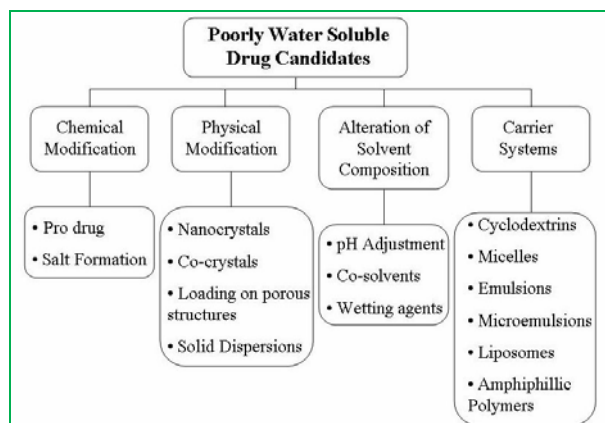
C_s = Saturation solubility of the drug in the diffusion layer.

C_{bulk} = Concentration of the drug in solution in the bulk of the gastrointestinal fluids.

From the Noyes Whitney and Nernst and Brunner equation, it is well understood that the rate of solution of the drug particles in the immediate vicinity of the layer surrounding the drug particle seems to influence the dissolution and absorption of drugs. And thus it can be said that dissolution is the rate – limiting step for the absorption of poorly soluble drugs^{8, 11, 12, 13}.

Enhancement of bioavailability of poorly water soluble drug remains one of the most challenging aspects of drug development. Several researchers have employed different methods to improve the dissolution behavior of such drugs which includes Use of adjuvant, use of salts, pH effect, particle size reduction, polymorphism, and crystal form, use of solvates and hydrates, complexation, use of surface active agents, drug-exciptent interaction and solid dispersion as shown in Figure 2. This article focuses on solid dispersion technology and the use of solid dispersion technology to improve the dissolution characteristics of poorly water-soluble drugs and in turn their oral bioavailability.

Figure 2: Approaches to Increase solubility/Dissolution



Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

SOLID DISPERSIONS

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. Chiou and Riegelman defined the term solid dispersion as: "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures"¹⁴.

The term solid dispersion refers to the dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state¹⁵, after few years Goldberg et.al. reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution.¹⁶ Exposure of this type of solid dispersion system to the gastrointestinal fluids results in dissolution of water soluble matrix (carrier). As the matrix dissolves, it exposes the dispersed poorly soluble drug in an extremely fine state of subdivision, to the aqueous gastrointestinal fluids. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal

particles or oily globules of submicron size. Hence because of the greatly enhanced surface area obtained in this way the poorly soluble drug is presented to the aqueous fluids in a form which facilitates its dissolution rate and bioavailability¹².

Because of the simplicity of manufacturing and scale up processes, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared by using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. Single or combination of carriers may also be essential for development of solid dispersion.^{7,17}

Solid dispersions are binary solid products consisting two or more 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.¹⁸ Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished²⁰. They are described in Table 1.

Table 1: Classification of Solid Dispersions according to Molecular arrangement²¹

Solid Dispersion Type		Matrix*	Drug**	Remarks	No. of Phases	Ref. to Literature
I	Eutectics	C	C	The first type of solid dispersions prepared	2	14
II	Amorphous Precipitations in crystalline matrix	C	A	Rarely encountered	2	22, 23
III	Solid Solutions					
a	Continuous Solid Solutions	C	M	Miscible at all compositions, never prepared	1	24
b	Discontinuous Solid Solutions	C	M	Partially miscible, 2 phases even though drug is molecularly dispersed	2	15
c	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 discontinuous: 2 phases even though drug is molecularly dispersed	1 or 2	25, 26
d	Interstitial Solid Solutions	C	M	Drug (solute) molecular diameter less than 59% of matrix (solvent) diameter. Usually limited miscibility, discontinuous. Example: Drug in helical interstitial spaces of PEG.	2	14, 27
IV	Glass Suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2	14, 28
V	Glass Suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2	14, 28
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	29

*: A: matrix in the amorphous state

C: matrix in the crystalline state

** : A: drug dispersed as amorphous clusters in the matrix

C: drug dispersed as crystalline particles in the matrix

M: drug molecularly dispersed throughout the matrix



ADVANTAGES OF SOLID DISPERSIONS

1. Particle size: Molecular dispersions, as solid dispersions, represent the last state on particle size reduction and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers.

2. Wettability: A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity such as cholic acid and bile salts when used can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects.²¹

3. Porosity: Particles in solid dispersions have been found to have a higher degree of porosity. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and therefore, result in a higher dissolution rate. The increased porosity of solid dispersion particles also hastens the drug release profile.³⁰

4. Amorphous state: Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form³¹. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them.^{21,32}

DISADVANTAGES

The limitations of this technology have been a drawback for the commercialization of solid dispersions, the limitations include³³

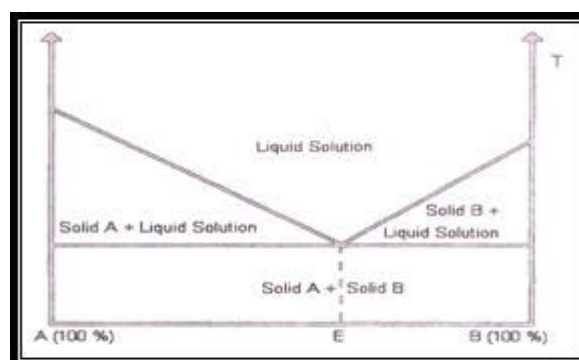
1. Laborious and expensive methods of preparation,
2. Reproducibility of physicochemical characteristics,
3. Difficulty in incorporating into formulation of dosage forms,
4. Scale-up of manufacturing process and Stability of the drug and vehicle.

Various methods have been tried recently to overcome the limitations and make the preparation more practically feasible while, at the same time, retaining both the physicochemical and bioavailability enhancing properties of solid dispersions. Some of the suggested approaches to overcome the aforementioned problems and lead to industrial scale production are reviewed in the Alternative strategies section.

TYPES OF SOLID DISPERSIONS

I. Eutectics: These are prepared by rapid solidification of the fused melt of two components that show complete liquid miscibility and negligible solid-solid solubility. Thermodynamically, such a system is an intimately blended physical mixture of its two crystalline components. Thus the X-ray diffraction pattern of a eutectic constitutes an additive composite of two components.

Figure 3: Phase diagram for a eutectic system



When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug.^{15, 34} The large surface area of the resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

II. Solid solutions: In a solid solution the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than the corresponding eutectic mixture. Solid solutions can be classified by two methods.

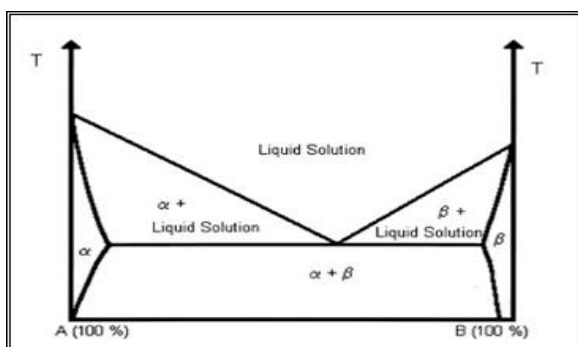
According to the extent of miscibility of the two components, they may be classified as continuous or discontinuous.

i. Continuous solid solutions: In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the

individual components. Solid solutions of this type have not been reported in the pharmaceutical literature to date.

ii. Discontinuous solid solutions: In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. A typical phase diagram is shown in Figure 4 shows the regions of true solid solutions. In these regions, one of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of the two components start to decrease. Due to practical considerations it has been suggested by Goldberg²⁴ that the term 'solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g. Assuming that the solubility of the drug in the carrier is 5%, doses of above 50 mg would not be feasible with this strategy. Obviously, if the drug solubility in the carrier is significantly higher than 5%, larger doses can be entertained.

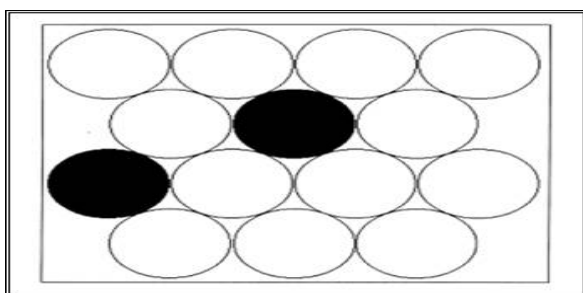
Figure 4: Phase diagram for a discontinuous solid solution



According to the criterion of molecular size of the two components, the solid solutions are classified as substitutional or interstitial.

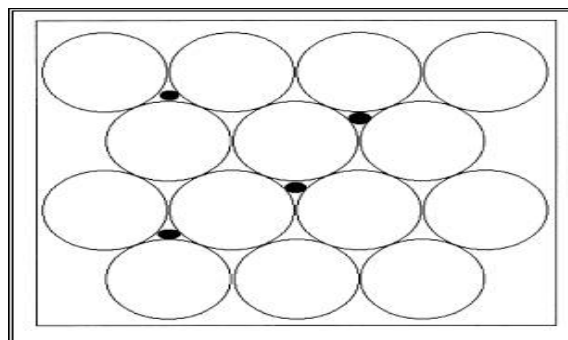
iii. Substitutional solid solutions: A substitutional crystalline solid dispersion is depicted in Figure 5. In the substitutional type, the solute molecule substitutes for the solvent molecule in the crystal lattice. The molecular size of the two components should not differ by more than 15%.³⁵ This class is represented by solid solutions of p-dibromobenzene-p-chlorobromobenzene.

Figure 5: Substitutional solid solution



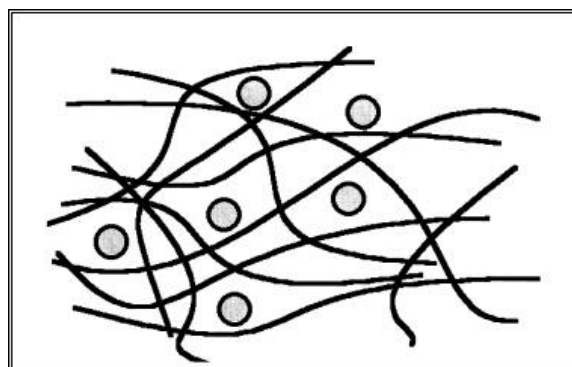
iv. Interstitial solid solutions: An interstitial solid solution is obtained when the solute (guest) molecule occupies the interstitial space in the solvent (host) lattice. (Figure. 6) For this to occur, the solute molecule diameter should be less than 0.59 that of solvent molecule; therefore, the volume of the solute molecule should be less than 20% of the solvent molecule.³⁶ Owing to their large molecular size, polymers favour the formation of interstitial solid solutions. Examples of this type include solid solutions of digitoxin, methyltestosterone, prednisolone acetate and hydrocortisone acetate in the matrix of PEG 6000. They all exhibit a faster rate of dissolution.

Figure 6: Interstitial solid solution



v. Amorphous solid solution: In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent (Figure. 7) Using griseofulvin in citric acid, Chiou and Riegelman²⁷ were the first to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose. Polymer carriers are particularly likely to form amorphous solid solutions as the polymer itself is often present in the form of an amorphous polymer chain network. In addition, the solute molecules may serve to plasticize the polymer, leading to a reduction in its glass transition temperature.

Figure 7: Amorphous solid solution



III. Glass Solutions and Glass Suspensions: Chiou and Riegelman first introduced the concept of formation of a glass solution as another potential modification of dosage forms in increasing drug dissolution and absorption. A

glass solution is a homogeneous glassy system in which a solute dissolves in the glassy system. A glass suspension refers to a mixture in which precipitated particles are suspended in a glassy solvent. The familiar term glass however, can be used to describe either a pure chemical or a mixture of chemicals in a glassy or vitreous state. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. The glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting points, instead, they soften progressively on heating.³⁶ The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions.

METHOD OF PREPARATION OF SOLID DISPERSIONS

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 created for pharmaceutical applications were prepared by the fusion method. The dispersion consisted of sulfathiazole and urea as a matrix¹⁵ which were melted using a physical mixture at the eutectic composition, followed by a cooling step.

This method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.^{16, 33}

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

2. 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. The drug/carrier mix is typically processed with a twin-screw

extruder. 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.

When compared to melting in a vessel, the product stability and dissolution are similar,³⁷ but melt extrusion offers the potential to shape the heated drug-matrix mixture into implants, ophthalmic inserts, or oral dosage forms.²² Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. 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. High shear forces resulting in high local temperatures in the extruder could be a problem for heat sensitive materials.^{37, 38} 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 drugs that are somewhat thermo labile to be processed.

3. Solvent method: Solid dispersion prepared by solvent method was termed by Bates as coprecipitates. In this method drug & carrier is dissolved in a volatile organic solvent with help of magnetic stirrer to get a clear solution and solvent is removed at room temperature, obtained mass is dried in a desiccator over anhydrous calcium chloride for 1-2 days depending on the removal rate of solvent at room temperature. The product is crushed, pulverized & sieved through a suitable mesh number sieve.^{39, 40} The common organic solvents used are summarized in Table 2.

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as

- The higher cost of preparation.
- The difficulty in completely removing liquid solvent.
- The possible adverse effect of traces of the solvent on the chemical stability
- The selection of a common volatile solvent.
- The difficulty of reproducing crystal form.
- In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.



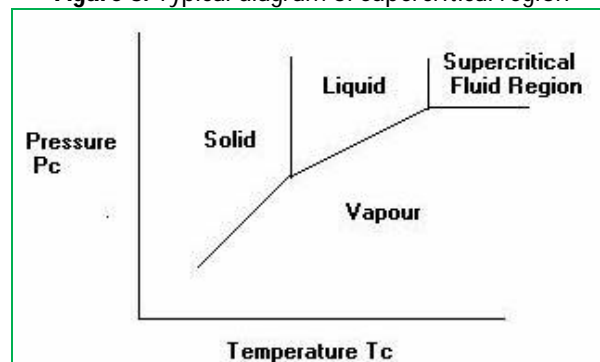
Table 2: An overview of common organic solvents²¹

Solvent	Melting point (°C)	Boiling point (°C)	Vapour pressure at 25°C (kPa)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
Dimethylsulphoxide (DMSO)	19	189	0.08
Acetic acid	17	118	1.64
1,4-dioxane	12	102	4.92
2-methyl-2-propanol (TBA)	25	82	5.49

4. Melt agglomeration method: This technique has been used to prepare Solid Dispersions wherein the binder itself acts as a carrier. In addition, Solid Dispersions are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt-in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer⁴¹. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates⁴².

The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration, since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles⁴³.

5. Supercritical fluid method:²¹ SCF techniques can be applied to the preparation of solvent-free solid dispersion dosage forms to enhance the solubility of poorly soluble compounds. Traditional methods suffer from the use of mechanical forces and excess organic solvents. A solid dispersion of Carbamazepine in polyethylene glycol 4000 (PEG-4000) increased the rate and extent of dissolution of carbamazepine. In this method, a precipitation vessel was loaded with solution of Carbamazepine and PEG-4000 in acetone, which was expanded with supercritical Carbon Dioxide from the bottom of the vessel to obtain solvent-free particles.

Figure 8: Typical diagram of supercritical region

The physical and thermal properties of SCFs fall between those of the pure liquid and gas. SCFs offer liquid-like densities, gas-like viscosities, gas-like compressibility properties and higher diffusivities than liquids. The properties of SCFs, such as polarity, viscosity, and diffusivity, can be altered several-fold by varying the operating temperature and/or pressure during the process. This flexibility is enabling the use of SCFs for various applications in the food and pharmaceutical industries. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water (Table 3) of these, Carbon Dioxide is a widely used SCF in the pharmaceutical processing due to its unique properties. This review summarizes the general SCF techniques used for particle formation, advantages and pharmaceutical application.

Table 3: Critical condition for some solvent

Substance	Tc, K	Pc, atm	Density (g/ml)
Ammonia	405.6	112.5	0.24
Benzene	562.1	48.3	0.30
Carbon dioxide	304.2	72.9	0.47
Ethane	305.5	48.2	0.20
Ethanol	516.6	63.0	0.28
Methane	190.6	45.8	0.16
Propane	370.3	41.9	0.22
Chloroform	299.3	47.9	0.62
Water	647.3	218.3	0.32

As described above, carbon dioxide is one of the most commonly used SCFs because of its low critical temperature ($T_c = 31.1^\circ\text{C}$) and pressure ($P_c = 73.8$ bar). Apart from being nontoxic, nonflammable, and inexpensive, the low critical temperature of Carbon Dioxide makes it attractive for processing heat-labile molecules (eg, products of biotechnology). The ability to rapidly vary the solvent (or antisolvent) strength and, thereby, the rate of supersaturation and nucleation of dissolved compounds is exploited as an alternative technology for particle formation under various names that are essentially based on 3 key process concepts:

1. Precipitation from supercritical solutions-Rapid Expansion of Supercritical Solution (RESS)
2. Precipitation from saturated solutions using SCF as an Antisolvent - Gas Antisolvent (GAS), Precipitation with Compressed Antisolvent (PCA), Supercritical Antisolvent (SAS), Aerosol Solvent Extraction System (ASES) and Solution Enhanced Dispersion by Supercritical fluids (SEDS) process and
3. Precipitation from gas-saturated solutions-Particles from Gas-Saturated Solutions (PGSS).

SCF technology provides a novel alternative method of generating small particles, with higher surface areas, that are free flowing and very low in residual organic solvent.⁴⁴ The formation of small particles is however, highly dependent on the materials in question and requires optimization of processing conditions. These aspects of the technology can be applied to formulate coprecipitates of drug in water-soluble carrier and thus overcome many aforementioned problems of conventional methods⁴⁵. The solid dispersion prepared from this method has been found to increase the dissolution considerably. This technique has also been used to precipitate homogeneous antracene phenanthrene crystals of solid solution⁴⁶. The applicability of RESS for preparation of solid dispersions is limited by the very low or negligible solubility of most drugs and polymers in the commonly used supercritical Carbon Dioxide.

Another advantage of this method is that the amount of the impregnated drug can be controlled and the process can be immediately stopped, by depressurizing the high-pressure cells once the desired level of impregnation is achieved. In addition, the process of impregnation that depends on the drug diffusion rate can be easily "tuned" by the pressure of the SCF solution, which influences the sorption and polymer swelling.⁴⁷

Particle formation in a light-free, oxygen-free, and possibly moisture-free atmosphere minimizes their confounding effect during scale-up. Advances in understanding the mechanism of supercritical particle/co precipitate formation and SCF mass transfer form the basis for efficient scale-up. Industrial units, such as Bradford Particle Design (Bradford, West Yorkshire, UK) have resources for the annual production of 1 ton of cGMP material. The cost of manufacturing in pilot scale

with SCF technology is comparable with (or may be better than) conventional techniques such as single-stage spray drying, micronization, crystallization, and milling batch operations.

6. Dropping method:²¹ The dropping method was developed by Ulrich et al.⁴⁸ to facilitate the crystallization of different chemicals, is a new procedure for producing round particles from melted solid dispersions. This technique may overcome some of the difficulties inherent in the other methods.

A solid dispersion of a melted drug- carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette, because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape. The important advantage of the dropping method does not use organic solvents and therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method, only thermo stable drugs can be used and the physical instability of solid dispersions is a further challenge.

Although there is still much work to do in this field (better size distribution, uniformity and stability), the dropping method is a promising approach in the formulation of solid dispersions. Simplifying the formulation process for the dropping method may overcome manufacturing difficulties.

7. Direct capsule filling method: The filling of semisolid materials into hard gelatin capsules as melts, which solidify at room temperature, was first done in 1978⁴⁹. It was not until much later that the potential application of the technique for solid dispersions was fully realized. Laboratory-scale semiautomatic equipment and large-scale manufacturing equipment for direct capsule filling are commercially available. Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug. The filling of hard gelatin capsules has been feasible in molten dispersions of Triamterene - PEG 1500 using a Zanasi LZ 64 capsule-filling machine (Zanasi Co, Bologna, Italy). This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross-contamination and operator exposure in a dust free environment, better fill weight and content uniformity was obtained than with the powder fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug. A surfactant must be mixed with the carrier to avoid formation of a drug rich surface layer (eg, polysorbate- 80



with PEG, phosphatidylcholine with PEG). The temperature of the molten solution should not exceed -70°C because it might compromise the hard gelatin capsule shell.²¹

8. Surface active carriers (Surfactants): The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobicity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization,

detergency, and enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions^{50, 51}. Commonly used surfactants are listed in Table 4.

Table 4: Commonly used surface active carriers for solid dispersions⁷

Carrier	Drug	Scientist
Poloxamer 188	Ibuprofen	Passerini et al
Poloxamer 188	ABT-963	Chen et al
Poloxamer 407	Nifedipine	Chutinawarapan et al
Poloxamer 188, Gelucire 50/13	Nifedipine	Vippagunta et al
Gelucire 44/14	REV 5901	Sheen et al
Gelucire 44/14	LAB-687	Serajuddin et al
Mixture Gelucire 44/14-lecithin	Ubidecarenone	Pozi et al
Gelucire 44/14 and PEG 6000	Glibenclamide	Tashtoush
Gelucire 44/14, Vitamin E TPGS	Carbamazepine	Squillanate et al
Gelucire, Capmul, Capmul MCM C10	Ceftriaxone	Seong-Wan CHO et al
Polyethylene glycol	DMP 323	Aungst et al
Mixture of Gelucire 50/13, Polysorbate 80, Polyoxyl 35 castor oil	Ritonavir	---
PEG 3350- Labrasol-Polysorbate 80	RP 69698	Sheen et al
PEG, Myrj 2, Eudragit E 100	Indomethacin	Hadi et al

9. 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.

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.

In an electrostatic spinning process a drug-matrix solution is pumped through an orifice and then subjected to an electrical field to form fibers with a diameter of micro- or nano-scale. This process is restricted to a limited amount of matrices, because only a few high molecular weight materials are fiber forming materials. The fiber diameter can be adjusted by surface tension, electrical field and dielectric constant. After rapid evaporation of the solvent,

the fibers can be directly used or milled and further processed.^{10, 52}

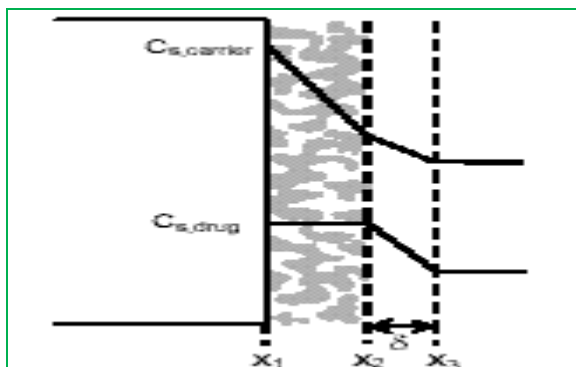
Another very promising approach is Kneading method. In this method a mixture of drug and carrier is wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste is dried under vacuum for 24 hours. Dried powder is passed through sieve no. 60 and stored in a desiccator. Solid dispersion involving PVP and valdecoxib were prepared by kneading technique. However this method cannot be applied to all poorly water soluble drugs.^{21, 53}

DISSOLUTION OF SOLID DISPERSION

The Nernst-Brunner equation (Eq.1) is applicable for pure solids but the dissolution of a binary solid is more complex. The dissolution rate of two components, intimately mixed in solid dispersions, mutually affect each other. Higuchi investigated a uniform, intimate, non-disintegrating mixture of two dissolving compounds both in crystalline state. One of the compounds (e.g. the matrix: C) dissolves faster, resulting in a porous layer consisting of the other compound (e.g. the lipophilic drug: D) (see Figure 9).



Figure 9: Schematic representation of dissolution of a solid dispersion like binary mixture.



Higuchi investigated the effect of this layer and the composition of the mixture on the dissolution rate of the fast dissolving component C. In fact, the deceleration of the dissolution of C was discussed while dissolution of D was considered to remain unchanged. He considered only the steady state portion of the problem and assumed that in the porous layer the concentration of D is equal to its solubility ($C, \text{Drug} = C_s, \text{Drug}$). This implies that no super saturation of D occurs in the liquid compartment of the porous layer. It also implies a constant flux of D to the bulk, since the thickness of the stagnant boundary layer δ will be constant. It is unlikely that amorphous solid dispersions can be described in this way: firstly because D will be supersaturated during dissolution of a solid dispersion. Without super saturation it is impossible to obtain accelerated dissolution from a non disintegrating solid dispersion tablet. A second complication is that the degree of super saturation can increase in time especially when C dissolves rapidly. And thirdly, due to this super saturation, crystallization of the lipophilic drug at the tablet surface can occur. It has been observed that crystallization can influence dissolution behavior of solid dispersions. Both super saturation and crystallization kinetics will affect the time needed to reach steady state dissolution. It has been described that the initial non-steady state portion of the problem, assumed to be negligible in Higuchi's description, in fact largely determines the dissolution rate especially when a large solubility difference exists between matrix and drug.^{10, 39, 54}

POSSIBLE MECHANISM FOR ENHANCEMENT OF DISSOLUTION RATE

1. Reduction in particle size provides the larger specific area, thereby increasing the dissolution and oral absorption of poorly soluble drugs.
2. A possible solubilization effect by the carrier may operate in the microenvironment (diffusion layer) immediately surrounding the drug particles in the early stage of dissolution, since the carrier completely dissolves in a short time.
3. The absence of aggregation between fine crystallites of the pure hydrophobic drug plays an important role in increasing rate of dissolution. Drug surface area is

markedly reduced because of aggregation and agglomeration. Serious drawbacks of aggregations, agglomeration and lumping in the dissolution medium between pure drug and particle are, however, rarely present in most solid dispersions, because individually dispersed particles are surrounded in the matrix by carrier particles.

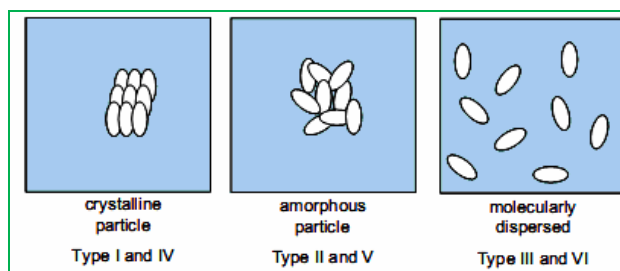
4. Excellent wettability and dispersibility of a drug from an eutectic or other solid dispersion system prepared with water soluble matrix result in an increased dissolution rate of the drug in aqueous media. This is due to the fact that each single crystalline particle of the drug is very intimately encircled by the soluble carrier which can readily dissolve and cause the water to contact and wet the drug particle. As a result a fine homogeneous solution of a drug can be easily obtained with minimum stirring.
5. An increased dissolution and absorption may also occur if a drug crystallized in a metastable form after solidification which in turn leads to faster dissolution rate.⁷

CHARACTERISATION OF SOLID DISPERSIONS

A. Detection of crystallinity in solid dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions (see Figure 10). Many attempts have been made to investigate the molecular arrangement in solid dispersions. However, most effort has been put in discrimination between amorphous and crystalline material. Consequently, 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 sample⁵⁵. 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, e.g. solid dispersions of type II or III and V or VI (see previous section).

Figure 10: Schematic representation of modes of incorporation of the drug in a SD's



Currently, the following techniques are available to detect (the degree of) crystallinity

1. Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction

peaks indicate more crystalline material. Recently developed X-ray equipment is semi quantitative.

2. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix⁴⁹. Sharp vibrational bands indicate crystallinity⁵⁶. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99% in pure material^{57, 58}. However in solid dispersions only qualitative detection was possible⁵⁹.

3. Water vapor sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different⁶⁰. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

4. Isothermal Micro calorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (T_g)⁶¹. However, this technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

5. Dissolution Calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample⁶². Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

6. Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids.

7. A frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC)⁶³. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material. Possibly, the recrystallization energy can be used to calculate the amount of amorphous material provided, that all amorphous material is transformed to the crystalline state. If during DSC-measurements, amorphous material crystallizes, information is obtained on the crystallization kinetics and on the physical stability

of the amorphous sample. To quantify the amount of crystalline material, measurements should be completed before crystallization of amorphous material has started. In some cases, this can be established applying high scanning rates.

B. 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 (type II or V) versus molecular distribution or homogeneous mixtures (type III or VI).

1. Confocal Raman Spectroscopy was used to measure the homogeneity of the solid mixture of ibuprofen in PVP⁶⁴. It was described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 μm³, uncertainty remains about the presence of nano-sized amorphous drug particles.

2. Using IR or FTIR, the extent of interactions between drug and matrix can be measured. The interactions are indicative for the mode of incorporation of the drug, because separately dispersed drug molecules will have more drug-matrix interactions than when the drug is present in amorphous clusters or other multi-molecule arrangements^{65, 66}.

3. Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the T_g is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC⁶⁷. Therefore this technique can be used to assess the amount of molecularly dispersed drug⁶⁸, and from that the fraction of drug that is dispersed as separate molecules is calculated⁶⁹.

EVALUATION OF SOLID DISPERSIONS

1. Phase-solubility studies

For phase-solubility analysis an excess amount of drug is added to the aqueous solutions of carrier in specific dissolution medium containing increasing concentrations of the carrier. After that the flasks is sealed and shaken at



37 °C for 48 h in a thermostatically controlled water bath and the samples are filtered through a 0.45 µm cellulose nitrate membrane filter. The filtrate is suitably diluted and analyzed spectrophotometrically at suitable wavelength.³⁹

2. Microscopy

Optical microscopy- the optical microscopy method using calibrated ocular and stage micrometer can be utilized for particle size analysis of powder. A number of particles are measured and mean diameter is calculated.

Scanning electron microscopy (SEM) - Electron microscopy techniques such as SEM are very useful in ascertaining the particle size and morphology of solid particles. It uses electron transmitted from the specimen surface.³⁹

3. Drug carrier miscibility

Drug carrier miscibility study is carried out to find out the complex formation between drug and carrier. There are number of techniques used to carry out this study like Hot stage microscopy, DSC (conventional and modulated), pXRD (conventional and variable temperature), NMR 1H.²¹

4. Drug carrier compatibility

This study is done to determine the interactions if any between the drug and carrier and to determine the formation of inclusion complexes²¹. Methods used for this purpose are:

- a. Fourier Transform Infra Red (FTIR) Spectroscopy
- b. Differential Scanning Calorimetric (DSC) Analysis
- c. Raman Spectroscopy
- d. Solid State NMR studies

5. Surface properties

The study of surface properties includes the study of morphology and the degree of crystallinity in the solid dispersions²¹. Methods used for this study includes:

- a. Dynamic vapor sorption
- b. Inverse gas chromatography
- c. Atomic force microscopy
- d. Raman microscopy

6. Drug content

In this method definite amount of solid dispersion is taken and dissolved in a suitable solvent in which drug is freely soluble, then after appropriate dilution concentration are measured by UV spectrophotometry.

HPLC is also very useful tool for drug content measurement. Standard solution is prepared by diluting the stock solution with mobile phase to give solutions containing drug in the concentration range of 10-100mg/ml and appropriate quantity (approx 20ml) of the

standard solutions is injected manually under operating chromatographic conditions and absorbance is measured at specific wavelength. Calibration graph is constructed by plotting peak areas versus concentration of drug and the regression equation is calculated.³⁹

7. Stability studies

Stability studies are mainly done to characterize the stability of the solid dispersions on long term storage in real time. Stability studies also give an idea about the degree of crystallinity in solid dispersions²¹. The methods used to evaluate the stability of solid dispersions include:

- a. Humidity studies
- b. Isothermal calorimetry
- c. Saturated solubility studies
- d. DSC (Tg, temperature recrystallization)
- e. Dynamic vapor sorption

8. Dissolution studies

Dissolution studies are the most significant evaluation parameter for any solid dosage form. Dissolution study is carried out to determine the rate and extent of dissolution. An improved dissolution of drug will only justify the formulation of solid dispersion²¹. Dissolution enhancement can be studied by methods listed below:

- a. Dissolution
- b. Intrinsic dissolution
- c. Dynamic solubility
- d. Dissolution in bio relevant media

APPLICATIONS OF SOLID DISPERSIONS IN PHARMA FIELD

Apart from absorption enhancement, the solid dispersion technique may have numerous pharmaceutical applications, which should be further explored.

It is possible that such a technique be used²¹:

1. To obtain a homogeneous distribution of a small amount of drug in solid state.
2. To stabilize the unstable drug.
3. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
4. To formulate a fast release primary dose in a sustained released dosage form.
5. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
6. To reduce pre systemic inactivation of drugs like morphine and progesterone.
7. Polymorphs in a given system can be converted into isomorphous, solid solution, eutectic or molecular addition compounds.



NOVEL DRUG - DRUG SOLID DISPERSION

Earlier studies reveal that solid dispersion approach has been extensively used by the researchers for enhancing the dissolution characteristics of poorly soluble drugs and encouraging results have been reported by them.

Sekiguchi and obi⁷⁰ were the first to report an improved dissolution of the drug from sulfamethazole-urea solid dispersion. Following their findings, more works in this direction started pouring into the literature. The enhanced dissolution of poorly soluble drugs such as griesiofulvin⁷¹, Prednisone⁷², naproxen⁷³ and triamterene⁷⁴ from solid dispersion has been well documented. In the recent past, similar studies have been performed on glibenclamide⁷⁵, clofibrate⁷⁶, zolpidem⁷⁷, albendazole⁷⁸, allopurinol⁷⁹ and promising results were reported.

On careful analysis of the literature on the solid dispersion of several drugs, it is obvious that in all studies a physiologically inert carrier has been employed as a solid solvent in which is incorporated a solid drug to effect solid dispersion⁸⁰.

In the modern clinical practice, single drugs are seldom prescribed for the treatment of acute or chronic ailment. Fixed dose combination of drugs has become a rule rather than exception in combating many clinical disorders; in all combination of drugs the therapeutic benefits have been justified. In other words, the relationships between the physiological interactions between the drugs that are used in combinations have been well explored. However, whether the pharmaceutical factors related to the drugs in combinations seems to have been given better consideration need to be examined.

The fixed dose combination of drugs is effective in the treatment of essential hypertension and of systolic hypertension in the elderly patient⁸¹. The following drugs are used either alone or in combination in the treatment of hypertension. Amlodipine, Atenolol, Bisoprolol, Captopril, Chlorthiazide derivatives, Diltiazem, Doxazosin, Enalapril, Indapamide, Losartan potassium, Nitroglycerin, Nifedipine, Propranolol, Spironolactone and Verapamil.

Considering the above factors a novel solid dispersion approach is now being researched by the scientists around the world wherein the poorly soluble drug can be solid dispersed in the water soluble drug (both type of drugs available in a fixed dose combination) that improves dissolution of the poorly soluble drug and hence its absorption. Recently similar work has been reported by Padma Priya S.⁵³ who have developed drug – drug solid dispersion of Hydrochlorothiazide by solid dispersing poorly soluble Hydrochlorothiazide in water soluble Captopril and have reported satisfactory results.

In their work, a novel drug – drug solid dispersion approach was applied to prepare solid dispersions in proportions similar to commercial preparations of Hydrochlorothiazide and Captopril (HCT-CAP) combination. The poorly soluble hydrochlorothiazide was

solid dispersed in soluble Captopril by kneading method. The solid dispersion was characterized for TLC, Spectrophotometric assay, Infra-red spectra, DSC and X ray diffractometry. The influence of Captopril on solubility of hydrochlorothiazide was assessed by solubility studies. The solid dispersions were evaluated for *in vitro* dissolution characteristics and the results were compared with that of physical mixtures of HCT-CAP and pure hydrochlorothiazide. The dissolution rate of hydrochlorothiazide from solid dispersions was found to be faster than that of physical mixtures and pure drug. They reported that Particle size reduction, micro-environmental solubilization, change in the crystalline nature of hydrochlorothiazide and formation of solid solution were the probable mechanisms for enhanced dissolution of hydrochlorothiazide.

The novel drug – drug solid dispersion approach applied by Padma Priya S. proposes the view that wherever a poorly soluble drug is combined with the soluble drug in the therapy of clinical disorders, the soluble drugs can play the role of physiologically inert carriers to effect solid dispersion for enhanced dissolution and absorption of poorly soluble drugs. This gives a signal to extending this approach to similar combinations of drugs used in clinical practice so as to improve bioavailability of poorly soluble drugs through improved dissolution. However a detailed assay on the therapeutic integrity of the drugs is essential for viability of this novel approach for development of formulations with improved bioavailability. Also such a drug - drug solid dispersion will be very cost effective which will a huge benefit to the patients in country like India.

CURRENTLY MARKETED SOLID DISPERSION PRODUCTS

In spite of almost thirty years of research on solid dispersions, their commercial application is limited. Only a few products have been marketed so far. Amongst these are:

1. Sporanox (Itraconazole)
2. Intelence (Etravirine)
3. Prograf (Tacrolimus)
4. Crestor (Rosuvastatin)
5. Gris-PEG (Griseofulvin)
6. Cesamet (Nabilone)
7. Solufen (Ibuprofen)
8. Ritonavir capsules produced by Norvir, Abott has been temporarily withdrawn from market due to crystallization.

FUTURE PROSPECTS

One major focus of future research will be identification of new surface-active carriers and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers



that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion system may be the inadequate drug solubility in carriers, so a wider choice will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from supersaturated systems. Attention should also be given to any physiological and pharmacological effects of carriers used. Many of the surface-active and self-emulsifying carriers are lipoidal in nature, so potential roles of such carriers on drug absorption, especially on their p-glycoprotein-mediated drug efflux, will require careful consideration. In addition to bioavailability enhancement, much recent research on solid dispersion systems was directed towards the development of extended-release dosage forms. It may be pointed out that this area of research has been reinvigorated by the availability of surface-active and self-emulsifying carriers and the development of new capsule filling processes. Because the formulation of solid dispersion for bioavailability enhancement and extended release of drugs may employ essentially similar processes, except for the use of slower dissolving carriers for the later use, it is expected that the research in these two areas will progress simultaneously and be complementary to each other.

CONCLUSION

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up, and stability limited its use in commercial dosage forms for poorly water-soluble drugs. However successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. Because of the simplicity of manufacturing and scale up processes, the popularity of the solid dispersion systems to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Also because the dosage form can be developed and prepared using small amounts of drugs substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation.

REFERENCES

- Lachman L., Liberman H.A, theory and practice of industrial pharmacy, 3rd edition, 1998; 462-464
- Encyclopedia of Pharmaceutical Technology, Marcel Dekker, 2002; 2458-2478
- Leuner, C. and Dressman, J., Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm, 2000; 47-60.
- www.worldsscibwks.com
- Lipinski CA Avoiding investment in doomed drugs, is poor solubility an industry wide problem? Curr Drug Dis., 4: 2001; 17-19.
- Birdar V. S., Arpana R. Patil, Guditi V. Sudarshan and Varsha B. Pokharkar, A comparative study of approaches improve solubility of roxithromycin, Int. J. Pharm., 2006; 22-32
- Chaudhari P.D., Current trend in solid dispersion techniques, www.pharmainfo.net, 2006; 2-12
- Milo Gibaldi. Bio pharmaceuticals and clinical pharmacokinetics; Gastrointestinal absorption-physicochemical consideration. 4th Edition, 1991; 46, 75-78
- Remingtons Pharmaceutical Sciences, 1980
- Dirk-Jan van Drooge, Wouter L.J. Hinrichs, Bastiaan H.J. Dickhoff, Marco N.A. Elli, Marine Spray freeze drying to produce a stable 9-tetrahydrocannabinol containing inulin-based solid dispersion powder suitable for inhalation, Eur. J. Pharm. Biopharm, 2005; 231-240.
- Brahmankar DM, Jaiswal SB. Absorption. In Brahmankar DM editors. A text book of Bio pharmaceuticals and pharmacokinetics A Treatise; 1st Edition, Vallabh Prakashan New Delhi; 1995, 20, 297
- Michael Aulton in pharmaceuticals- A science of dosage form; particle size reduction; 1991 150-160
- Leon Lachman, Herbert A Liberman and Joseph L. Kanig. Biopharmaceutics. In theory and practice of industrial pharmacy; 3rd ed. 1991; 221
- Chiou, W.L., Rigelman, S., 1971. Pharmaceutical application of solid dispersion system. J. Pharm. Sci. 60, 1281-1302.
- Sekiguchi, K; Obi, N. Studies on absorption of eutectic mixture. I A comparison of the behavior of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem. Pharm. Bull., 1961, 9, 866-872.
- Goldberg, A. H.; Galbaldi, M.; Kanig, K, L. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures III. Experimental evaluation of griseofulvin-succinic acid solution. J. Pharm. Sci. 1966, 55, 487-492.
- Christensen KL, Design of Redispersible Dry Emulsion: A Potential Oral Drug Delivery System. PhD Thesis 2000: 35-45.
- Pouton CW. "Lipid formulations for oral administration of drugs: non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems". Eur. J. Pharm. Sci. 2000; 11 Suppl. 2; 93-98
- David J. H, "Lipid-Based Systems for Oral Drug Delivery. Enhancing the Bioavailability of Poorly Water Soluble Drugs" APR, 2002; 5; 88-93.
- Muhammad J. Habib, Pharmaceutical solid dispersion technology, Technomic publication, USA, 2000; 27 – 95
- V. Kamalakkannan et al. Solubility enhancement of poorly soluble drugs by solid dispersion technique – A review Journal of Pharmacy Research 2010, 3(9), 2314-2321
- Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur. J. Pharm. Biopharm., 2002; 54(2): 107-117.



23. Mullins JD and Macek TJ. Some pharmaceutical properties of novobiocin. *J. Am. Pharm. Assoc. Sci.Ed.*, 1960; 49: 245-248.
24. Goldberg AH, Gibaldi M and Kanig JL. Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures. I. Theoretical considerations and discussion of the literature. *J. Pharm. Sci.*, 1965; 54(8): 1145-1148.
25. Rastogi RP and Rama Varma KT. Solid-liquid equilibria in solutions of non-electrolytes. *J. Chem.Soc.*, 1956; 2: 2097-2101.
26. Wilcox WR, Friedenberg R and Back N. Zone melting of organic compounds. *Chem. Rev.*, 1964; 64: 187- 220.
27. Chiou WL and Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 1969; 58(12): 1505-1510.
28. Sarkari M, Brown J, Chen X, Swinnea S, Williams RO. Enhanced drug dissolution using evaporative precipitation into aqueous solution. *Int. J. Pharm.*, 2002; 243(1-2): 17-31.
29. Simonelli AP, Mehta SC and Higuchi WI. Dissolution rates of high energy polyvinylpyrrolidone (PVP)-sulfathiazole coprecipitates. *J. Pharm. Sci.*, 1969; 58(5): 538-549.
30. Jain R K, Sharma D K, Jain S, Kumar S and Dua J S. Studies on solid dispersions of nimesulide with pregelatinized starch. *Biosciences, biotechnology research Asia* 3(1a), 2006, 151-153.
31. Kakumanu VK, Bansal AK. Supercritical fluid technology in pharmaceutical research. *CRIPS*. 2003; 4:8-12. (83)
32. Tanaka N, Imai K, Okimoto K, Ueda S, Rinta Ibuki Y T, Higaki K and Kimura T. Development of novel sustained-release system, disintegration-controlled matrix tablet (DCMT) with solid dispersion granules of nilvadipine (II): In vivo evaluation. *Journal of controlled release* 122, 2006, 51- 56. (3)
33. Rahul Ghaste, *Solid Dispersions: An Overview, Latest Reviews; 2009, Vol. 7, Issue. 5*
34. Goldberg A, Gibaldi M, Kanig 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", *J. Pharm. Sci.* 1966; 55; 482-487
35. Hume-Rotherly W, Raynor G V, "The Structure of Metals and Alloys", Institute of Metals, London , 1954.
36. Reed-Hill R E, "Physical Metallurgy Principles", Van-Nostrand, Princetown, NJ , 1964.
37. Forster A, Hempenstall, J, Tucker I and Rades T. Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. *Int. J. Pharm.*, 2001; 226(1- 2): 147-161.
38. Langer M, Höltje M, Urbanetz NA, Brandt B, Höltje HD and Lippold BC. Investigations on the predictability of the formation of glassy solid solutions of drugs in sugar alcohols. *Int. J. Pharm.*, 2003; 252(1-2): 167-179.
39. Patidar Kalpana et al. Solid Dispersion: Approaches, Technology involved, Unmet need & Challenges *Drug Invention Today* 2010, 2(7),349-357
40. Karanth H, Shenoy VS, Murthy RR. Industrially Feasible Alternative Approaches in the Manufacture of Solid Dispersions: A Technical Report. *AAPS Pharm Sci Tech.* 2006; E1-E8.
41. Tsinontides S C, Rajniak P, Hunke W A, Placek J, "Freeze drying-principles and practice for successful scale-up to manufacturing", *Int. J. Pharm.*, 2004;280(1): 1-16.
42. Vilhelmsen T, Eliassen H, Schaefer T. "Effect of a melt agglomeration process on agglomerates containing solid dispersions" *Int. J. Pharm.*, 2005; 303(1- 2); 132-142.
43. Seo A, Schaefer T., "Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer" *Eur. J. Pharm. Biopharm.*, 2001; 52(3); 315-325.
44. Bai J, Yaoxian L, Songtao Y, Jianshi D, Shugang W, Jifu Z, Yongzhi W, Qingbiao Y and Xuesi C X J. A simple and effective route for the preparation of poly (vinyl alcohol) (PVA) nanofibers containing gold nanoparticles by electrospinning method. *Solid State Communications* 141, 2007, 292 295
45. Johnson, D. M. and W.F.Taylor. Degradation of feprostalene in polyethylene glycol 400 solution. *Eur. J. Pharm Sci*73: 1984. 1414–1417.
46. Law SL, Lo WY, Lin FM, Chaing CH. Dissolution and absorption of nifedipine in poly (ethylene glycol) solid dispersion containing phosphatidylcholine. *Int J Pharm.* 1992; 84:161-166.
47. Verreck G, Chun I, Peeters J, Rosenblatt J and Brewster ME. Preparation and characterization of nano fibers containing amorphous drug dispersions generated by electrostatic spinning. *Pharm. Res.*, 2003; 20:810-817.
48. Hayes, Davis, Morella and Angelo Mario. Pharmaceutical compositions for poorly watersoluble drugs. United States Patent. No. 6881745, 2005.
49. Forster, A., J. Hempenstall, and T. Rades. 2001. Characterization of glass solutions of poorly water soluble drugs produced by melt extrusion with hydrophilic amorphous polymers *J.Pharm Pharmacol* 53: 303–315.
50. Ghebremeskel A N, Vemavarapu C and Lodaya M., "Use of surfactants as plasticizers in preparing solid dispersions of poorly soluble API: Selection of polymer surfactant combinations using solubility parameters and testing the processability", *Int. J. Pharm.*,2007;308; 119-129.
51. Zhang R, Somasundaran P, "Advances in adsorption of surfactants and their mixtures at solid/solution interfaces. *Advances in colloid and interface science*", *Int. J. Pharm.* 2006;123; 213-229
52. Dharendra k, Lewis S, Udupa N and Atin K, *Solid Dispersions: A Review Pak. J. Pharm. Sci.*, Vol.22, No.2, April 2009, pp.234-246
53. Padma Priya S, A Novel Captopril Hydrochlorothiazide Solid Dispersion, *International Journal of Pharmacy and Pharmaceutical Sciences* Vol 2, Issue 2, 2010
54. Van Drooge, D.J., Hinrichs, W.L.J., and Frijlink, H.W., Anomalous dissolution behaviour of tablets prepared from sugar glass-based solid dispersions. *J. Controlled Release*, 2004;64-78.



55. Kaushal AM, Gupta P and Bansal AK. Amorphous drug delivery systems: molecular aspects, design, and performance. *Crit. Rev. Ther. Drug Carrier Syst.*, 2004; 21(3): 133-193.
56. Bugay DE. Characterization of the solid-state: spectroscopic techniques. *Adv. Drug Deliv. Rev.*, 2001; 48(1): 43-65.
57. Taylor LS and Zografi G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.*, 1997; 14: 1691-1698.
58. Taylor LS and Zografi G. The quantitative analysis of crystallinity using FT-Raman spectroscopy. *Pharm. Res.*, 1998; 15(5): 755-761.
59. Broman E, Khoo C and Taylor LS. A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water soluble drug. *Int. J. Pharm.*, 2001; 222(1): 139-151.
60. Buckton G and Darcy P. The use of gravimetric studies to assess the degree of crystallinity of predominantly crystalline powders. *Int. J. Pharm.*, 1995; 123: 265-271.
61. Sebhatu T, Angberg M and Ahlneck C. Assessment of the degree of disorder in crystalline solids by isothermal microcalorimetry. *Int. J. Pharm.*, 1994; 104: 135-144.
62. Pikal MJ, Lukes AL, Lang JE and Gaines K. Quantitative crystallinity determinations for betalactam antibiotics by solution calorimetry: correlations with stability. *J. Pharm. Sci.*, 1978; 67(6): 767-73.
63. Kerc J and Srcic S. Thermal analysis of glassy pharmaceuticals. *Thermochim. Acta.*, 1995; 248: 81-95.
64. Breitenbach J, Schrof W and Neumann J. Confocal Raman-spectroscopy: analytical approach to solid dispersions and mapping of drugs. *Pharm. Res.*, 1999; 16(7): 1109-1113.
65. Li J, Guo Y and Zografi G. The solid-state stability of amorphous quinapril in the presence of beta-cyclodextrins. *J. Pharm. Sci.*, 2002; 91(1): 229-243.
66. Rogers TL, Hu JH, Brown J, Young T, Johnston KP and Williams RO. A novel particle engineering technology to enhance dissolution of poorly water soluble drugs: spray-freezing into liquid. *Eur. J. Pharm. Biopharm.*, 2002; 54(3): 271-280.
67. De Meuter P, Rahier H and Van Mele B. The use of modulated temperature differential scanning calorimetry for the characterisation of food systems. *Int. J. Pharm.*, 1999; 192(1): 77-84.
68. Cilurzo F, Minghetti P, Casiraghi A and Montanari L. Characterization of nifedipine solid dispersions. *Int. J. Pharm.*, 2002; 242(1-2): 313-317.
69. Vasanthavada M, WQ Tong, Y Joshi and MS Kislalioglu. Phase behavior of amorphous molecular dispersions I: Determination of the degree and mechanism of solid solubility. *Pharm. Res.*, 2004; 21(9): 1598-1606.
70. Sekiguchi and obi, chem. "Mechanism of dissolution of fast release solid dispersion." *pharm. Bull*; 1961; 9, 866
71. Toshiaki Nishihata, Yoshiko Chigawa, Akira Kamada, Kiyoshi Sakai, Koichi Mastumoto, Kazuhoko Shinozaki, Yujin Tabata, "Griseofulvin- Hydrogenated Soya Phospholipid Coprecipitates" *Drug Development and Industrial Pharmacy*, Volume 14, Issue 9 June 1988 , pages 1137 – 1154.
72. Darío Leonardi, María Gabriela Barrera, María Celina Lamas, and Claudio, Javier Salomón. "Development of Prednisone:Polyethylene Glycol 6000 Fast- Release Tablets From Solid Dispersions: Solid-State Characterization, Dissolution Behavior, and Formulation Parameters". *AAPS PharmSciTech* 2007; 8 (4) Article 108.
73. P. Mura, A. Manderioli, G. Bramanti, L. Ceccarelli, "Properties of Solid Dispersions of Naproxen in Various Polyethylene Glycols". *Drug Development and Industrial Pharmacy*, Volume 22, Issue 9 & 10 September 1996, pages 909 – 916.
74. Arias MJ, Gines JM, moyano JR, Preze Barrales MJ and Vela MT Rabasco AM. "Improvement of the diuretic effect of triamterene via solid dispersion technique with PEG 4000." *EUR-J-Drug Metab Pharmacokinet*; 1994; 19(4), 295-302.
75. Mariko Iwata, Haruhisa Ueda, "Dissolution Properties of Glibenclamide in Combinations with Polyvinylpyrrolidone" *Drug Development and Industrial Pharmacy*, Volume 22, Issue 11 November 1996, pages 1161 – 1165.
76. S. Anguiano-Igea, F. J. Otero-Espinar, J. L. Vila-Jato and J. Blanco-Méndez; "The properties of solid dispersions of clofibrate in polyethylene glycols". *Pharmaceutica Acta Helvetiae*; Volume 70, Issue 1, April 1995, Pages 57-66.
77. Trapani.G.;Franco M.;Latrofa A;Pantaleo M.R;Provenzano M.R.; Sanna E.; Maciocco E; Iiso G; "Physicochemical characterization and in vivo properties of Zolpidem in solid dispersions with polyethylene glycol 4000 and 6000". *International journal of pharmaceutics*; 1999, vol. 184, pp. 121-130
78. Kohri N, Yamayoshi Y, Xin H, Iseki K, Sato N, Todo S and Miyazaki K, "Improving the oral bioavailability of albendazole in rabbits by the solid dispersion technique". *J Pharm Pharmacol*; 1999; 51(2) 159-64
79. Samy EM, Hassan MA, Tous SS, Rhodes CT "Improvement of availability of Allopurinol from pharmaceutical dosage forms I – suppositories". *Eur J Pharm Biopharm*; 2000; 49(2) 119-27
80. Chiou WI and Riegelman S, "Pharmaceutical Applications Of Solid Dispersion Systems" *J Pharma Sci*; 1971; 60; 1281-302
81. Chalmers MJ, *Clinical and Exp. Hypertension (New York)*; 1999; 21(5-6)875-84.
82. Sica, Domenic A. Rationale for Fixed-Dose Combinations in the Treatment of Hypertension: *Drugs*; 2002; 62(3): 443-462.

