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A mini review on solubility enhancement technique – Solid dispersion

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ABSTRACT

Many new drug substances have low aqueous solubility which can cause poor bioavailability after oral administration. Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. Generally, SDs can be defined as a dispersion of active ingredients in molecular, amorphous and/or microcrystalline forms into an inert carrier. The application of solid dispersions is a useful method to increase the dissolution rate of drugs. This article is indented to combine literature on solid dispersion technology for solubility enhancement with special emphasis on mechanism responsible for the same by solid dispersion, various preparation methods and evaluation parameters.

Key words: Bioavailability, dissolution rate, solid dispersion, poorly water-soluble drugs.

Introduction

Oral drug delivery is the simplest and easiest way of administered many drugs into the systemic circulation. Comparatively oral drug delivery system has other drug delivery system patient compliance, greater stability, accurate dosage and easy to produce. Therefore, most of the new chemical entities (NCEs) under research these days are intended to be used as a solid dosage form that invent an effective and reproducible *in vivo* plasma concentration after oral administration. In fact, most NCEs are poorly water soluble drugs, low absorption after oral administration, which can distract from the drug's inherent potency. Moreover, most promising NCEs, despite their high permeability are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window [1].

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Various factor limited the drug absorption from the gastrointestinal tract like nature of drug, physicochemical properties of drug, gastric empty time etc. When drug administrated orally, before it can reach to systemic circulation it must be dissolve in gastric and/or intestinal fluids. Hence, in pharmaceutical research focus on two domain enhancing the oral bioavailability of active agents include; improving solubility and dissolution rate of poorly water-soluble drugs, enhancing permeability of poorly water-soluble drugs. Lipid-based delivery systems are becoming increasingly popular as carriers of drugs because of their ability to bypass some of the more resistant chemical and physical barriers associated with poorly absorbed drugs [2].

Various approaches to beat the poor aqueous solubility of drug candidates have been investigated in drug research and development such as solid dispersion salt formation, prodrug formation, complexation, particle size reduction, microemulsions, micelles, liposomes, nanoparticles, nanoemulsions, nanosuspensions and solid-lipid nanoparticleetc. Solid dispersion is which review as one of the most effective strategies to enhanced the absorption of poor water soluble drugs[3].

Solubility

Solubility is the property of a solid, liquid or gaseous

chemical substance called solute to dissolve in solvent (solid, liquid or gaseous) to form a homogeneous solution of the solute in the solvent. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution[4-6].

Table 1: Solubility.

Definition	**Parts of solvent required** for one part of solute
Very soluble	<1
Freely soluble	1- 10
Soluble	10- 30
Sparingly soluble	30- 100
Slightly soluble	100- 1000
Very slightly soluble	1000- 10,000
Insoluble	>10,000

Mechanism of solubilization[7]

Drug solubility is the maximum concentration of the drug solute dissolved in the solvent under specific conditions of temperature, pH and pressure. The solubility of weak acids or weak bases varies considerably as a fraction of pH.

For weak acids the total solubility (C_s) is given by the expression;

$C_s = [HA] + [A^-]$

Where [HA] = intrinsic solubility of the non ionized acid , $[A^-]$ = the concentration of its anion

The anion concentration can be expressed in terms of dissociation constant K_a;

$C_s = C_o + K_a[C_o / H^+]$

[C_o = non- ionized acid concentration]

This equation indicates that the solubility of weak acid increases with the increasing pH. Solubility is higher optimal at higher pH.

Solubility for weak base is given by the expression;

$C_s = C_o + C_o [H^+ / K_a]$

This equation indicates that solubility of weak base decreases with increasing pH. Solubility is optimal at lower pH.

Techniques to enhance the solubility

Solubility improvement techniques can be categorized as under: [2, 8]

Table 2: Techniques to increase the solubility of drugs

<table>
<tr><td colspan="3">Physical modifications</td></tr>
<tr><td>a. Particle size reduction
1. Micrionization
2. Nanosuspension Homogenization Wet milling
3. Sonocrystallization
4.Supercritical fluid process
5. Spray drying</td><td>b. Modification of crystal habit
1. Polymorphs
2. Pseudopolymorph</td><td>c. Drug dispersion in carriers
1. Eutectic mixtures
2. Solid dispersions
3. Solid solutions
4. Cryogenic techniques</td></tr>
<tr><td colspan="3">Chemical modifications</td></tr>
<tr><td colspan="3">a. Change of pH
b. Use of buffers
c. Derivatization
d. Complexation
e. Salt formation</td></tr>
<tr><td colspan="3">Miscellaneous methods</td></tr>
<tr><td colspan="2">a. Supercritical fluid process</td><td>b. Use of adjuvants
(surfactants, solubilizers, cosolvency, hydrotrophy and novel excipients)</td></tr>
</table>

Solid dispersions: an approach for delivery of poorly soluble drugs

Effective method to improve the solubility and bioavailability of poorly water soluble drugs is solid dispersions. In 1961, Sekiguchi and Obi first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of such drugs [9-10]. Earlier studies show that solid dispersions systems increased the drug dissolution due to improved solubility, wet ability and dispersability using hydrophobic carriers[9]. The development of solid dispersion as a practically viable method and overcame the limitations of previous approaches such as a salt formation, solubilisation by co solvents and particle size reduction. The term solid dispersions refer to a group of at least two different components, generally a hydrophobic drug and hydrophillic matrix. The matrix can be either amorphous or crystalline. The drug can be dispersed molecularly, in crystalline particles based on their molecular arrangement or in amorphous particles (clusters) (11-12). Chieu and Riegelman defined term solid dispersions as, **"a dispersion involving formation of eutectic mixtures of drugs with water soluble carrier by melting of their physical mixtures"**[10, 13]. The dissolution is enhanced by dispersing a poorly soluble drug in a highly soluble solid hydrophillic matrix [14].

Mechanism of dissolution of solid dispersions

The currently accepted range of possible mechanisms for enhanced dissolution rate effectively stems from the seminal review of various authors. These mechanisms include:

- Surface area is increased.
- Wetting of drug is improved by direct contact of drug with hydrophillic polymers.
- The drug has higher energy in amorphous state than in the crystalline state through which the saturated concentration is increased.
- The saturated concentration around small particles is higher than around large particles.

Therefore, SD improves the bioavailability of poorly soluble drugs by increasing the drug dissolution rate and their saturated solubility in gastrointestinal fluids [15-17]

Classification of solid dispersions

1. On the basis of carrier used [1,18]

First generation solid dispersions: In 1961, Sekiguchi and Obi noticed that the formulation of eutectic mixtures improved the rate of drug release and, consequently, the bioavailability of poor water soluble drugs due to small particle size and better wettability. Later Levy and Kanig developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions. The observed improvements were attributed to a faster carrier dissolution, releasing microcrystals or particles of drug. These solid dispersions, which could be designed as first generation solid dispersions were prepared using crystalline carriers. Crystalline carriers include urea and sugars which was the first carrier to be employed in solid dispersions.

Second generation solid dispersions:A second generation of solid dispersions contained amorphous carriers instead of crystalline carriers. In amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a homogeneous molecular interaction between them. Polymeric carriers have been successful, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers (povidone, polyethyleneglycols, polymethacrylates) and natural product based polymer (hydroxy propyl methyl cellulose, ethylcellulose, hydroxypropyl cellulose, starch derivatives). In second generation solid dispersions, the drug is in a supersaturated state because of forced solubilization in the carrier.

Third generation solid dispersions: Third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The dissolution profile can be improved if the carrier has surface activity or self emulsifying properties. The use of surfactants such as inulin, inutec SPI, compritol 888 ATO, gelucire and poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhanced *in vivo* bioavailabillity.

2. On the basis of the molecular arrangement

The various types of solid dispersions can be distinguished on the basis of the molecular arrangement as follows:

Simple eutectic mixtures: The simple eutectic mixture is usually prepared from rapid solidification of fused liquid of two components which show complete liquid miscibility and negligible solid-solid solubility. Thermodynamically, such a system is regarded as an intimately blended physical mixture of its two crystalline components. When a eutectic composed of a poorly soluble drug is exposed to water or GI fluids, the carrier may be released into aqueous medium in fine crystalline form. The eutectic phase diagram is shown in figure 1 [10,19]

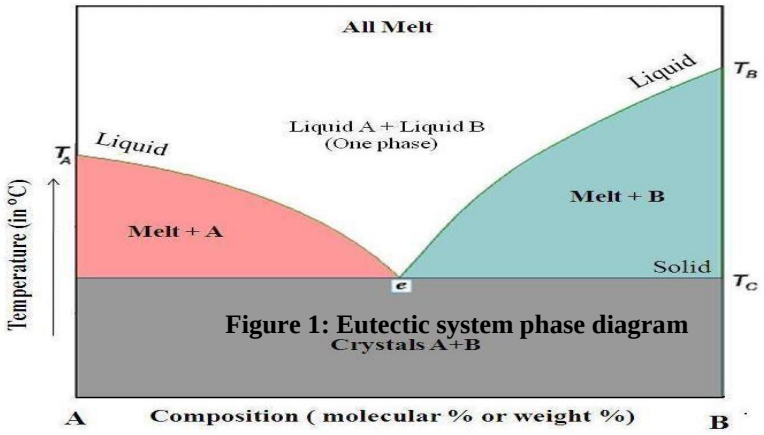

Figure 1: Eutectic system phase diagram

Fig 1:Eutectic system phase diagram

Solid solutions: In solid solutions, the two components crystallize together in homogeneous one-phase system. The particle size of drug in a solid solution is reduced is reduced to its molecular size. Thus, a solid solution can achieve a faster dissolution rate than corresponding eutectic mixtures[6]

These can be further classified according to miscibility as:

Continuous solid solutions: In this, method both the components are mixed to each other to obtain miscible solid state. The reason may be that the strength of bonding between the molecules of each of the individual components is weaker than the strength of bonding between two components. The soluble carrier present in the crystal lattice of the drug may result in faster dissolution rate as compared to pure compound[20,21]. Figure 2 illustrates continuous solid phase diagram [19]

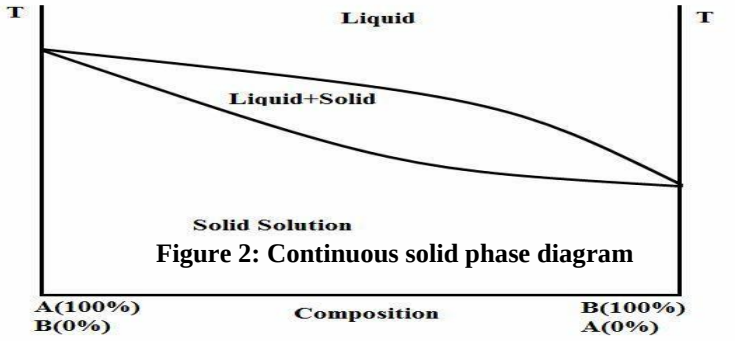

Figure 2: Continuous solid phase diagram

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Discontinuous solid solutions: In this case, the solubility of each of component is limited. One of the solid components is completely dissolved in the other solid component. Note that below a certain temperature, the mutual solubilities of two components start to decrease. Due to practical considerations it has been suggested by Goldberg (1964) that the term solid solution should only be applied when mutual solubility of two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form, strategy will depend not only on mutual solubility of two components but also on dose of drug component[12]

3. On the basis of distribution in solvendum

According to the way in which solvent molecules are distributed in solvendum:

Glass solutions: Chiou and Riegelman first proposed the idea of creating glassy solid solution as a method to increase solubility and absorption of a substance. Glassy state is seen as critical and decisive for durability and physical stability of incorporated lipophillic substance. Glassy solid solutions is a multi-

ingredient, glassy system, which consist of one phase only. At the molecular level it is homogeneous and uniform. The carrier in this system occurs in amorphous state, while the dissolved molecules are molecularly dispersed [22].

Amorphous solid solutions:

The drug with propensity to super cooling has more tendency to solidify as an amorphous form in presence of carrier [6].This method is similar to simple eutectic mixtures but the only difference is that the drug is precipitated in amorphous form [23,24].

Substitutional crystalline solid solutions: In this type of solid solution the solute molecules act as substitutes (in crystal lattice of solid solvent) for the solvent molecule continuous and discontinuous solid solutions can be prepared by this method. As possible the size of solute and solvent are of similar dimension ([20, 21].

Interstitial crystalline solid solutions: In this type of solid solution, the solute (guest) molecule occupies the interstitial space of solvent (host) lattice. It usually forms only a discontinuous solid state (10). The solute molecule should have a molecular diameter not more than 0.59 of the solvent molecule's molecular diameter. The volume of the solute molecules should be less than 20% of the solvent [25, 26]. The distribution of solute molecule in solvent in interstitial solvent system is shown in figure 3 [19].

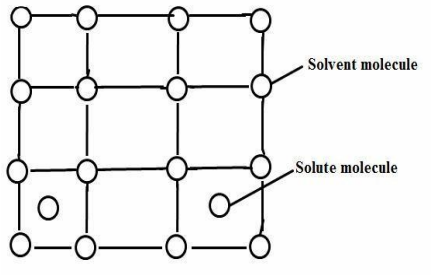

Fig 3: Interstitial solid solution

Amorphous precipitation in crystalline matrix: Instead of forming a simple eutectic mixture in which both the drug and the carrier crystallize simultaneously from a melting or a solvent method of preparation, the drug may also precipitate in precipitate out in an amorphous form in crystalline carrier. Since the amorphous form is the highest energy form of a pure drug, it should under almost all conditions, produce faster dissolution and absorption rates than the crystalline form whether the crystals are or are not dispersed in carrier [10]. Figure 4 shows the distribution in amorphous solutions [19].

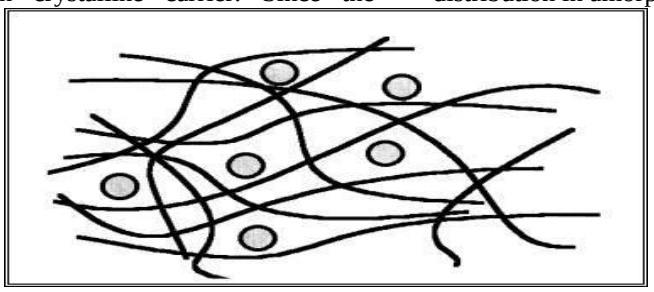

Fig 4: Amorphous solutions

Biopharmaceutical classification system

Biopharmaceutical Classification System (BCS) is a guiding tool for a strategy to improve the efficacy of drug development by proper selection of dosage form. The BCS, introduced by Amidon *et al* is a scientific framework for classifying a drug depending on *in vitro* solubility and *in vivo* permeability [27-30]. In the BCS, Class II drugs are those with high membrane permeability and low aqueous solubility, therefore, they are the ideal candidate for solid dispersion technologies for improving the solubility and bioavailability(Table 3)

Table 3: Biopharmaceutical classification system

Class	Permeability	Solubility	Salient Features	Examples	Reference
I	High	High	These compounds are well absorbed and their absorption rate is usually higher than excretion	No herbs are classified entirely as class I	29
II	High	Low	The bioavailability of these products is limited by solvation rate. A correlation between *in vivo* bioavailability and *in vitro* solvation can be found	*Zingiberofficinale, Curcumin longa*	29, 31
III	Low	High	The absorption is limited by permeation rate but the drug is solvated very fast	*Ginkgo bilabo, Allium sativum, Cassia senna,* Milk thistle	29
IV	Low	Low	These have poor bioavailability. They are not well absorbed over intestinal mucosa and high variability is expected	*Panax ginseng, Glycyrrhizaglabra*	29

Advantages of solid dispersions:

The solid dispersions provides the myriad spectrum of desired characteristics for effective delivery of phytoconstituents [30-32]

- Amorphous state of drug leads to enhancement in drug release.
- Improved wettability results in increased solubility.
- Presystemic metabolism is reduced due to increase in dissolution rate and absorption. Particles having higher porosity. Increase in porosity influence carrier properties and increase drug release profile.
- By changing water solubility drug bioavailability can be increased.
- Lower doses of the drugs are required due to rapid dissolution that results in increase in rate and extent of absorption.
- Liquid form of drug can be transferred in solid form.
- Particle size reduction in solid dispersion leads to increase surface area which causes increase in dissolution rate hence bioavailability is improved.
- Preferred by patients in comparison to liquid solubilisation products.

Limitations of solid dispersions

The limitations of solid dispersions technology have been a drawback for their commercialization [33-36]. These are enumerated in the following section:

- Expensive and laborious methods. .
- Tackiness property of solid dispersions make it difficult to handle.
- Large amount of carrier is required to achieve good dissolution.
- During storage of solid dispersions many problems encountered which are phase separation, conversion of amorphous to crystalline form and crystal growth due to which decrease in solubility, dissolution and bioavailability occurs.

Carriers used in solid dispersions [32,14]

The choice of carrier has a enormous impact on success rate of the solid dispersion strategy. The suitable characteristics of a carrier used are enlisted below:

- They should be non toxic
- High water solubility - improve wettability and enhance dissolution.
- Soluble in common solvent with drug - solvent evaporation.
- High glass transition point - improve stability.
- Relatively low melting point - melting process.
- Minimal water uptake.
- Low vapour pressure
- Capable of forming a solid solution with the drug - similar solubility parameter.

Table 4: Carriers used in solid dispersion [6, 37]

S. No.	Carriers	Nature
1.	Dextrose, Sorbitol, Mannitol, Lactose, Sucrose, Galactose, Maltose	Sugar
2.	Succinic acids, Citric acids	Acids
3.	Polyethylene Glycol, Povidone, Hydroxy Ethyl Cellulose, Hydroxyl Propyl Methyl Cellulose, Galactomannan, Pectine	Polymeric material
4.	Eudragit RS, Hydroxy Propyl Methyl Cellulose, Pthalate	Insoluble or Enteric Polymers

5.	Poloxamer 188, Spans, Polyoxyethylene Stearate, Renex, Texofor, Tweens, Deoxycholioc acid	Surfactants
6.	Sodium acetate, Ascorbic acid, Sodium-p-hydroxybenzoate,Sodium-o-hyroxy benzoate, Resorcinol, Sodium citrate	Hydrotropes
7.	Starburst, Polyamidoamine	Dendrimers
8.	Hydroxyalkylxanthines, Urea, Urethans	Miscellaneous

Solvent selection for solid dispersion system:

In order to prepare solid dispersion, solvents should be selected on the basis of following criteria: (32, 34).

- ❖ Dissolve both drug and carrier
- ❖ Water based systems preferable
- ❖ Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane
- ❖ Use of surfactants to create carrier drug solutions but care should be taken as they can reduce the glass transition point
- ❖ Ethanol is a less toxic alternative

Table 5: Solvents used in solid dispersion

Class	Solvents	Feature
Class I	Benzene Carbon tetrachloride 1,2- dichloroethane 1,1- dichloroethane 1,1,1- trichloroethane	Solvents to be avoided due to their deleterious environmental effect
Class II	Chloroform Ethylene glycol Methanol Pyridine Toluene	Should be limited in pharmaceutical products because of their inherent toxicity
Class III	Acetic acid,Acetone Formic acid Ethyl ether Propyl acetate	Less toxic and of lower risk to human health and should be limited by GMP or other quality based requirements
Class IV	Petroleum ether Isopropyl ether	Solvents for which no adequate toxicological data was found and are of interest to manufacturers of drug products

Manufacturing process: The subsequent section is a brief preface of the various techniques widely accepted to deal with the challenges of administering natural drugs, tackled by formulating solid dispersions.

- ❖ **Melting (fusion method)**

In this method, the mobility of carrier is high enough to change drug incorporation. In general, heating all components above their melting or glass transition temperatures, followed by mixing and cooling is 'melting method'. The uniformly mixed melted mass is allowed to cool at room temperature or under cool conditions. The cooling rate may have great impact on characteristics and stability of solid dispersions. For cooling and solidification process, ice bath agitation, solidification on petri dishes at room temperature inside a dessicator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in dessicator were used. The most important requirement of this method is that drug and carrier should be stable at room temperature.

The method is advantageous due to its simplicity and economy. 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.

The major disadvantage of this method is that the texture of solid dispersion after cooling is very hard. Therefore, size reduction is difficult [38-43].

- ❖ **Solvent method**

Solvent method was first applied to the preparation of solid dispersions by Tachibana and Nakamura [18].

This method aims to dissolve the drug and carrier simultaneously in a common solvent, followed by removal of solvent by evaporation. Solvent is allowed to evaporate by various processes including vacuum drying, heating on a hot plate, using rotary evaporator, a stream of nitrogen, spray drying, freeze drying and using supercritical fluids. To minimize the drug particle size in solid dispersion, the drug and matrix have to be dispersed in the solvent as fine as possible, preferably drug and matrix material are in dissolved state in one solution.

The main advantage of this method is that thermal decomposition of drugs or carrier can be prevented because of the low temperature required for the evaporation of organic solvents [10].

The major challenge in preparation of solid dispersion by solid evaporation method is selection of a common solvent to dissolve drug as well as carrier and to mix both the drug and the matrix in one solution, which is difficult when they differ significantly in polarity [44-48].

❖ **Melting solvent method**

The combination of melting method and solvent evaporation method is melting solvent method. It is performed by dissolving the drug in suitable solvent and mixing of this solution with the molten carrier followed by cooling, resulting in solidification [49]. Such a unique method possess the advantages of both the melting and solvent methods. Unfortunately, from a practical standpoint, it is only limited to drugs with low therapeutic dose, e.g. Below 50 mg [10].

❖ **Hot melt extrution method**

Hot melt extrution method is useful in preparation of solid dispersions in single step. It is a combination of melting and a mechanical process in which a drug, polymer and optionally plasticizer are mixed and melted under controlled condition of temperature and shear forces. The mass of co-melts is mixed with the help of transport screws and extruded through a die plate, yielding solid dispersions. The advantage of this method is that it has the potential of providing the shape to the heated drug-mixture into implants, ophthalmic inserts, or oral dosage forms. Metrex® process is a technology based on hot melt extrusions applied for development of a ritonavir - lopinavir combination tablet with improved dissolution. Another recently developed technology is Meltdose® for improved dissolution of fenofibrate [50-53]. Figure 5 is the schematic representation of components of a single screw melt extruder [19]

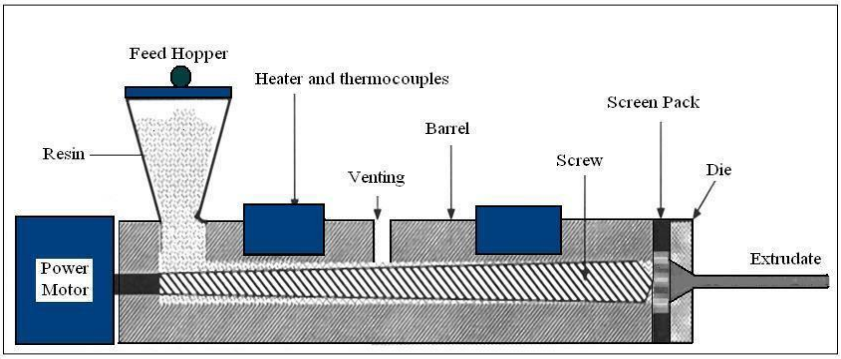

Fig 5 Schematic diagram showing components of a single screw melt extruder

Spray drying method

With tremendous development in spray drying process, it has emerged as a highly versatile technique operational in variety of industrial process such as food and dairy processing, ceramics, paints, fertilizers, detergents and pharmaceutical field. In this method drug and carrier are evaporated by spraying the solution as fine droplets into a chamber under controlled conditions of heat, humidity and air flow. It is cheap, fast and a one-step process and is widely used for processing solutions, emulsion, suspensions and manufacturing of solid dispersions. But the formulation of sticky product at outlet may occur, which adheres to the walls. This occurs due to high residual solvent which act as plasticizer and decrease glass transition temperature or the outlet temperature of the cyclone system [54-57].

❖ **Kneading method**

The physical mixture of drug and carrier is triturated to thick paste using small volume of solvent. The solvent used can be organic (alcohol, dichloromethane, acetone) or aqueous or mixture. The kneaded paste is dried in oven and the dried mass is pulverized and stored in desiccators. Kneading process is economical but residual solvent may be an issue [41].

❖ **Freeze drying**

Freeze drying consist of three successive steps: freezing, primary drying and secondary drying. A sample to be freeze dried consists of drug, excipients and one or more solvents. High freeze rates can be achieved by spray freezing on cryogenic liquid surface, or into cryogenic liquid, followed by freeze drying. In this method, the small frozen droplets are produced by spraying or atomizing drug-carrier solution or suspension into cryogenic liquid such as liquid nitrogen. The resulting frozen droplets are freeze dried in a conventional freeze dryer. It is advantageous for processing of thermolabile material but also has a disadvantage of being lengthy and expensive process (41, 61).

Detection of crystallinity in solid dispersions [58-60]

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions (Figure 1.7). 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 sample. It should be noted that through the assessment of crystallinity as method to determine the amount of amorphous drug it will not be revealed whether the drug is present as amorphous drug particles or as molecularly dispersed molecules e.g. solid dispersions of type II or III and V or VI.

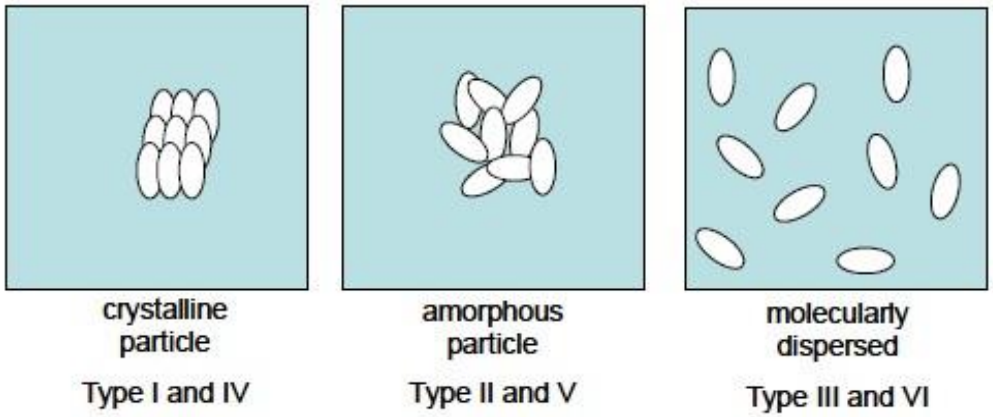

Fig 7: Schematic representation of three modes of incorporation of drug in a solid dispersion

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-quantative.
2. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared spectroscopy (FTIR) was used to accurately detect crystallinities ranging from 1 to 99 % in pure material. However in solid dispersions only qualitative detection was possible.
3. Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity of both completely crystalline and completely amorphous samples. In some studies, amorphous materials were plasticized by water sorption and crystallized during the experiment. However, crystallization can be accompanied by expel of water depending on the degree of hydration of crystalline material. In this case, the loss of water is used to calculate the amount of amorphous material.

   However, water vapour sorption in a binary mixture, e.g. solid dispersions, can be much more complicated than in pure materials, firstly because water sorption is not always proportional to the composition of a binary intimately mixed system. the second complication is that matrix or drug crystallization during water vapour sorption is often not complete within the experimental time scale due to sterical hindrance and proceeds to an unknown extent.
4. Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its T_g. However, this technique has

some limitations. First, 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 sample. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic. The dissolution energies of the two components in both crystalline and amorphous state should be determined in separate experiments in order to use this technique quantitatively. However, also drug-matrix interactions will contribute to the dissolution energy of the solid dispersion.
6. Macroscopic techniques that measure mechanical properties that are different for amorphous and crystalline material can be indicative for 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. The extent of supersaturation during dissolution experiments of solid dispersions are sometimes correlated to the mode of incorporation of drug. It is unmistakable that the mode of incorporation largely determines the dissolution behaviour, but knowledge about dissolution behavior is too poor to draw any conclusions from dissolution experiments, because it cannot be excluded that during dissolution crystallization of drug occurs.
8. A frequently used technique to detect the amount of crystalline material is Differential Scanning Colorimetry (DSC). In DSC, samples are heated with a constant heating rate and 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, recrystallization, melting or degradation. 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.

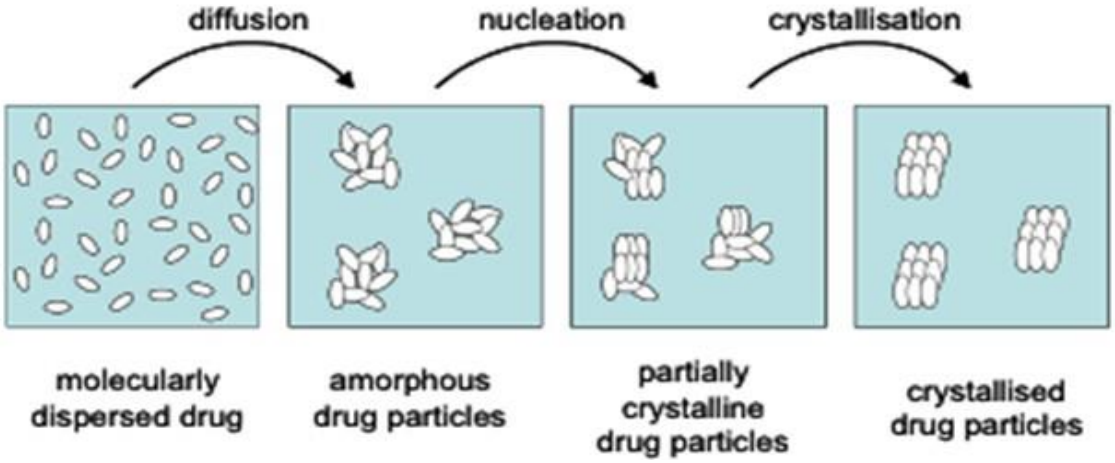

Fig 8: Physical changes in solid dispersions resulting in crystallization

Clearly many techniques can distinct between the crystalline and amorphous state for pure materials. However, in a mixture of two components, like in solid dispersion, it is always necessary to know the interaction between the individual components and the effect thereof on the physical property that is being quantified and from which crystallinity is to be derived [12, 36].

Table 6: List of drugs already used in the form of solid dispersions, along with type of polymers and methods employed [61-93]

S. No.	Drug	Polymer	Method
1.	*CefiximeTrihydrate*	Urea	Solvent evaporation method
2.	Gliclazide	PEG 8000 and PEG 6000	Fusion- Solvent Techniques
3.	Celecoxib	PEG 6000 and PVP K 30	Kneading and solvent evaporation method
4.	Glyburide	PEG 4000 and PEG 6000	Lyophilization techniques
5.	Allopurinol	Gelucire50/ 13	Physical mixing, solvent evaporation, kneading and closed melting method
6.	*Azithromycin Dihydrate*	Urea	Solvent evaporation method
7.	Itraconazole	PEG 6000 and polyvidonevinylacetate	Spray drying
8.	Meloxicam	Hydroxyethylcellulose, mannitol and PEG 4000	Solvent evaporation, melting and melting solvent method
9.	Lansoprazole	PEG 4000 and amphiphlic polymer Soluplus®	Solvent evaporation method
10.	Satranidazole	PVP K30 and PEG 4000	Solvent evaporation method
11	Nimodipine	HPMC	Spray drying method
12	indomethacin	Gelucire 50/13 and PEG4000	Hot melting method
13	Curcumin	HPMC 4000, HPMC 6 and PEO	Melting method
14	Carbamazepine	PVP K30, either Gelucire 44/14 or Vitamin E TPGS	Conventional solvent evaporation and supercritical methods
15	Carbamazepine	HPMC	Hot-melt extrusion
16	Carvedilol	Beta cyclodextrin and Hydroxypropyl-cyclodextrin	Solvent evaporation methods
17	Rofecoxib	Poloxamer 188	Melting method
18	Carvedilol	PEG 6000, poloxamer 407, HPMC and Na-starch Glycolate	Fusion and solvent evaporation method
19	Mefenamic acid	PVP K30, HPMC and PEG	Solvent evaporation method
20	Carvedilol	HPβCD and tartaric acid	Kneading technique
21	Itraconazole	PVPVA 64, PVP K25, PEG 6000 and HPMC 2910 E5	Spray drying
22	Glipizide	PEG 4000	Melt mixing method
23	Ibuprofen	PEG, Talc and PEG-Talc	Solvent evaporation method
24	Glipizide	Poloxamer 188 and Poloxamer 407	Kneading method
25	Furosemide	Microcrystalline cellulose	Cogrinding method
26	Curcumin	HPMC K 4M and HPMC K 15M.	Solvent change precipitation method
27	Valsartan	Poloxamer 188	Melting method
28	Nisoldipine	HPC and PVP K 29/32	Solvent method
29	Lacidipine	PEG 4000, PEG 6000, Hydroxy ethyl cellulose and Dextrin	Solvent evaporation method
30	Aceclofenac	Avicel 200 and Sylysia 350	Kneading method
31	Valsartan	Poloxamer 407	Melting method
32	Metformin HCl	Eudragit RLPO, Eudragit RSPO, HPMC K100 and compritol ATO 888	Solvent evaporation method

Conclusion

One of the most challenging problems in pharmaceutical field is to increase the bioavailability of orally administered poorly water soluble drug. The various techniques described above alone or in combination can be used to enhance the solubility of the drug, proper selection of solubility enhancement method is the key to ensure the goals oral bioavailability. Solid dispersion technology extremely helps in improving the dissolution property of poorly water soluble drugs. Various techniques described in this review are successfully used for the preparation of solid dispersions in the bench and lab scale and can be used as industrial scale also.

References

1. Costa P, Sarmento B, Vasconcelos T, Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs, Drug Discovery Today, 2007; 12(4):23-24.
2. Aggarwal S, Gupta GD, Chaudhary S, Solid dispersion as an eminent strategic approach in solubility enhancement of poorly soluble drugs, International Journal of Pharmaceutical Sciences and Research, 2010; 1(8):1-13.
3. Chau LNV, Chulhun P, Beom JL, Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs, European Journal of Pharmaceutics and Biopharmaceutics, 2013; 85(3):799-813.
4. Ketan TS, Anuradha KG, Jignasa KS, Drug solubility: importance and enhancement techniques, International Scholarly Research Network, 2012;1(1): 1-10.
5. Lachman L, Liberman HA, Theory and Practice of Industrial Pharmacy, 3rd edition. 1986, 462-464.
6. Sachan NK, Pushkar S, Solid dispersion: an industrially feasible alternative approach to formulate brick dust molecules, Bulletin of Pharmaceutical Research, 2011;1(1):75-80.
7. Theodore DS, Remington, The Science and Practice of Pharmacy, Edition 1995; 197-198.
8. Rathore DS, Thakur RR, Narwal S, Solid dispersion a new horizon in novel drug delivery system. Journal of Pharmacy Research, 2012; 5(2): 1007-1014.
9. Shinde SS, Patil SS, Mevekari FI, Satpute AS, An approach for solubility enhancement: solid dispersion, International Journal of Advances in Pharmaceutical Sciences, 2010; 1(3):299-308.
10. Chiou WL, Riegelman S, Pharmaceutical applications of solid dispersion system, Journal of Pharmaceutical Sciences, 1971; 60(9): 1281-1302.
11. Patidar K, Soni M, Sharma KD, Jain KS, Solid dispersion: approaches technology involved, unmet need and challenges, Drug Invention Today, 2010;2(7):349-357.
12. Kumar BP, Rao S, Murthy KVR, Sahu RK, Ramu B, Solid dispersion: a tool for enhancing bioavailability of poorly soluble drugs, Journal of Chemical and Pharmaceutical Sciences, 2011; 4(4): 170-179.
13. Sonpal RN, Lalwani AN, Darji V, Patel K, Solid dispersion: an efficient tool for increasing bioavailability of poorly soluble drugs, International Journal of Pharmaceutical Sciences Review and Research, 2011 ;89(1):37-52.
14. Kumar P, Arora V, Solid dispersion: a review, Journal of Pharmaceutical and Scientific Innovation, 2012;1(3):27-34.
15. Keck CM, Muller RH, Drug nanocrystals of poorly soluble drugs produced by high pressure homogenization, European Journal of Pharmaceutics Biopharmaceutics, 2006;62(1):3-16.
16. Junghanns JUAH, Muller RH, Nanocrystals technology, drug delivery and clinical applications, International Journal of Nano medicine, 2008;3(3): 295-309.
17. Hang Y, Roshab KS, Pushp RN, Yoon GK, Hoo KC. Enhancement of solubility and dissolution rate of cryptotanshinone, tanshinone and tanshinone II extracted from *Salvia miltiorrhiza*, Archives of Pharmacal Research, 2012; 35(8): 1457-1464.
18. Jun HP, Myung KC, Hoo C, Hoo KC, Solid dispersion as a strategy to improve drug bioavailability. Korean Society for Biotechnology and Bioengineering Journal, 2011;26;283-292.
19. Dhiman S, Kaur P, Arora S, Solid dispersion: opportunity in drug delivery system, Drug Invention Today, 2012;4(10):478-486.
20. Kumar S, Malviya R, Sharma PK, Solid Dispersion: Pharmaceutical technology for the improvement of various physical characteristics of active pharmaceutical ingredients, African Journal of Basic and Applied Sciences, 2011; 3(4):116-125.
21. Singh A, Sharma PK, Meher JG, Malviya R. Evaluation of enhancement of solubility of paracetamol by solid dispersion technique using different polymers concentration, African journal of Pharmaceutical and Clinical Research, 2011, 4(1):117-119.
22. Bozena K, Agata G, Sandra P, Artur O, Janusz P, Ewa ZP, Solid dispersion in pharmaceutical technology. Part I. Classification and methods to obtain solid dispersions, Polymers in Medicine, 2012;42(1): 17-27.
23. Gavali SM, Pacharane SS, Sankpal SV, Jadhav KR, Kadam VJ, Liquid solid compact: A new technology for enhancement of drug dissolution, International Journal of Research in Pharmacy and Chemistry,

2011; 1(3): 705-713.

24. Twile R, Giri TK, Tripathi DK, Jain V, Alexander A, An exhaustive review on solubility enhancement for hydrophobic compounds by possible application of novel techniques. Trends in Applied Sciences Research, 2012;7(8):596-619.

25. Robert E, Reed- Hill, Physical metallurgy principles, Van- Nostrand, Princetown, NJ, 1964.

26. Christian L, Jennifer D, Improving drug solubility for oral drug delivery using solid dispersions, European Journal of Pharmaceutics and Biopharmaceutics, 2000; 50(1):47-60.

27. Rohilla S, Rohilla A, Marwaha RK, Nanda A, Biopharmaceutics classification system: a strategic tool for classifying drug substances.International Research Journal of Pharmacy, 2011; 2(7): 53-59.

28. Amidon GL, Lennernas H, Shah VP, Crison JR, A theoretical basis for a biopharmaceutical drug classification: correlation of *in vitro* drug product dissolution and *in vivo* bioavailability, Pharmaceutical Research, 1995;12(3):413-420.

29. Waldmann S, Almukainzi M, Chacra NB, Amidon GL, Lee BJ, Feng J, Kanfer I, Zuo JZ, Wei H, Bolger MB, Lobenberg R, Provisional Biopharmaceutical Classification of Some Common Herbs Used in Western Medicine, Molecular Pharmaceutics, 2012;9(4): 815-822.

30. Giri TK, Alexander A, Tripathi DK, Physiochemical classification and formulation development of solid dispersion of poorly water soluble drugs: an updated review, International Journal of Pharmaceutical and Biological Archives, 2010;1(6):309-324.

31. Visser M.R., Baet L., Klooster G.V., Schueller L., Geldof M., Vanwelkenhuysen I., Kock H.D., Meyer S.D., Frijlink H.W., Rosier J, Hinrichs W.L.J. Inulin solid dispersion technology to improve the absorption of the BCS class IV drug TMC240.European Journal of Pharmaceutics and Biopharmaceutics, 2010; 74(2): 233-238.

32. Tiwari R., Tiwari G., Srivastava B., Rai A. Solid dispersions: an overview to modify bioavailability of poorly water soluble drugs.International Journal of PharmTech Research, 2009; 1(4): 1338-1349.

33. Das K.S., Roy S., Kalimuthu Y., Khanam J., Nanda A. Solid dispersions: an approach to enhance bioavailability of poorly water soluble drugs.International Journal of Pharmacology and Pharmaceutical Technology, 2011; 1(1): 37-46.

34. Verma S., Rawat A., Kaul M. and Saini S. Solid dispersion- a strategy for solubility enhancement.International Journal of Pharmacy and Technology, 2011; 3(2): 1062-1099.

35. KaliaA., Poddar M. Solid dispersions: an approach towards enhancing dissolution rate.International Journal of Pharmacy and Pharmaceutical Sciences, 2011; 3(4): 9-19.

36. Tyagi R., Dhillon V. Solid dispersions: a fruitful approach for improving the solubility and dissolution rate of poorly soluble drugs.Journal of Drug Delivery and Therapeutics, 2012; 2(4): 5-14.

37. Bowmik D., Harish G, Duraivel S., Kumar B.P., Raghuvanshi V., Sampath K.P. Solid dispersion- an approach to enhance the dissolution rate of poorly water soluble drugs.The Pharma Innovation Journal, 2012; 1(12): 24-38.

38. Sekiguchi K., Obi N. Studies on absorption of eutectic mixtures I; A comparison of behaviour of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chemical and Pharmaceutical Bulletin, 1961; 9(1): 866-872.

39. Van Drooge D. J., Hinrichs W.L.J, Visser M.R., Frijlink H.W. Characterization of the molecular dispersion of drugs in glassy solid dispersion at the nano meter scale, using differential scanning calorimetry and gravimetric water vapour sorption technique. International Journal of Pharmaceutics, 2006; 310(1-2): 220-229.

40. Janssens S., Mooter G.V.D. Physical chemistry of solid dispersions. Journal of Pharmacy and Pharmacology, 2009; 61(12): 1571-1586.

41. Alam M.A., Ali R., Al-Jenoobi F.I., Al-Mohizea A.M. Solid dispersion: a strategy for poorly aqueous soluble drugs and technology updates. Expert Opinion on Drug Delivery, 2012; 9(11): 1419-1440.

42. Sekiguchi K., Obi N. Studies on absorption of eutectic mixture II Absorption of fused conglomerates of chloramphenicol and urea in rabbits**.** Chemical and Pharmaceutical Bulletin, 1964; 12: 134-144.

43. PokharkarV.B., Mandpe L.P., Padamwar M.N., Ambike A.A., Mahadik K.R.,Paradkar A. Development and characterization and stabilization of amorphous form of a low T_g drug.Powder Technology, 2006; 167(1): 20-25.

44. Li F.Q., Jin H.H., Deng J.X., Hua S., Shu X., Liu J.Y. *In vitro* controlled release of sodium ferulate from compritol 888 ATO based matrix tablets. International Journal of Pharmaceutics, 2006; 324(2): 152-157.

45. Owusu A.G.Comparitive dissolution studies for mefenamic acid polyethylene glycol solid dispersion systems and tablets. Pharmaceutical Development and Technology, 1998; 3(3): 405-412.

46. Timko R.J., Lordi, N.G. Thermal characterization of citric acid solid dispersions with benzoic acid and phenobarbital. Journal of Pharmaceutical Sciences, 1979; 68(5): 601-605.

47. Yao W.W., Bai T.C., Sun J.P., Zhu C.W., Jie Hu., Zhang H.L. Thermodynamic properties for the system of silybin and polyethylene glycol 6000. ThermochimicaActa, 2005; 437(1-5): 17-20.

48. Vippagunta S.R., Zeren W., Stefanie H., Krill

S.L.Factors affecting the formulation of eutectic solid dispersions and their dissolution behaviour. Journal of Pharmaceutical Sciences, 2007; 96(2): 294-304.

49. Lin C.W., Cham T.M. Effect of particle size on available surface area of nifedipine fromnifedipine-polyethylene glycol 6000 solid dispersions. International Journal of Pharmaceutics, 1996; 127(2): 261-272.

50. Srinarong P., Waard H.D., Frijlink H.W., Hinrichs W.L. Improved dissolution behaviour of lipophilic drugs by solid dispersions: the production process as starting point for formulation consideration. Expert Opinion on Drug Delivery, 2011; 8(9): 1121-1140.

51. W. J. Moore, "Physical Chemistry," Prentice- Hall, Englewood Cliffs. N. J.; 1963.

52. Karavas E., Georgarakis E., Bikaris D. Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. European Journal of Pharmaceutics and Biopharmaceutics, 2006; 64(1): 115-126.

53. Wang X., Michoel A., Mooter G.V.D. Solid state characteristics of ternary solid dispersion composed of PVP VA64, Myrj 52 and itraconazole. International Journal of Pharmaceutics, 2005; 303(1-2): 54-61.

54. Desai J., Alexander K., Riga A. Characterization of polymeric dispersions of dimenhydrinate in ethyl cellulose for controlled release. International Journal of Pharmaceutics, 2006; 308(1-2): 115-123.

55. Ceballos A.M., Cirri F.M., Corti G., Mura P. Influence of formulation and process variables on *in vitro* release of theophylline from directly compressed Eudragit matrix tablets. IL Farmaco, 2005; 60(11-12): 913-918.

56. Prabhu S., Ortega M., Ma C. Novel lipid based formulations enhancing the *in vitro* dissolution and permeability characteristics of a poorly water soluble model drug, piroxicam. International Journal of Pharmaceutics, 2005; 301(1-2): 209-216.

57. Jung J.Y., Yoo S.D., Lee S.H., Kim K.H., Yoon D.S., Lee K.H. Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. International Journal of Pharmaceutics, 1999; 187(2): 209-218.

58. Mooter G.V.D., Weuts I., Rider T.D., Blaton N., Evaluation of Inutec SP1 as a new carrier in the formulation of solid dispersion of poorly water soluble drugs. International Journal of Pharmaceutics, 2006; 316(1-2): 1-6.

59. Won D.H. Improved physicochemical characteristics of felodipine solid dispersion particles by superficial anti solvent precipitation process. International Journal of Pharmaceutics, 301(1); 199-208.

60. Dhirendra K., Lewis S., Udupa N., Atin K. Solid dispersion: a review. Pakistan Journal of Pharmaceutical Sciences, 2009; 22(2): 234-246.

61. Hernandez J.I., Ghaly E.S., Malave A., Marti A. Controlled-release matrix of acetaminophen-ethyl cellulose solid dispersion. Drug Development and Industrial Pharmacy, 1994; 20(7): 1253-1265.

62. Giri T.K., Kumar K., Alexander A.A., Badwaik H., Dulal K.T. A novel and alternative approach to controlled release drug delivery system based on solid dispersion technique. Bulletin of Faculty of Pharmacy, Cairo University. 2012; 50(2): 147-159.

63. Srinarong P., Waard H.D., Frijlink H.W.,Hinrichs W.L. Improved dissolution behaviour of lipophilic drugs by solid dispersions: the production process as starting point for formulation consideration**.** Expert Opinion on Drug Delivery, 2011; 8(9): 1121-1140.

64. Paudel A., Worku Z.A., Meeus J., Guns S., MooterG.V.D. Manufacturing solid dispersions of poorly water soluble drugs by spray drying: Formulation and process consideration. International Journal of Pharmaceutics, 2013;453(1): 253-284.

65. Dimitrios N.B. Solid dispersion Part I: recent evaluation and future opportunities in manufacturing methods for dissolution rate enhancement of poorly water soluble drugs. Expert Opinion on Drug Delivery, 2011; 8(11): 1501-1519.

66. Karanth H., Shenoy V.S., Murthy R.R. Industrially feasible alternative approach in manufacture of solid dispersion: A technical report.AAPS PharmSciTech, 2006; 7(4): 31-38.

67. Vemavarapu C., Mollan M.J., Needham T.E. Coprecipitation of pharmaceutical actives and their structurally related additives by the RESS process. Powder Technology, 2009; 189(3): 444-453.

68. Cho E., Cho W., Cha K.H.Enhanced dissolution of megestrol acetate microcrystal prepared by antisolvent precipitation process using hydrophilic additives. International Journal of Pharmaceutics, 2010; 396(1-2): 91-98.

69. Wu K.L.J., Wang W., Winstead D.A. Formation and characterization of solid dispersions of piroxicam and PVP using spray drying and precipitation with compressed antisolvent.Journal of Pharmaceutical Sciences, 2009; 98(7): 2422-2431.

70. Dimitrios N.B. Solid dispersion, Part II: new strategies in manufacturing methods for dissolution rate enhancement of poorly water soluble drugs. Expert Opinion on Drug Delivery, 2011; 8(12): 1663-1680.

71. Dixit A.K., Singh R.P., Singh S. Solid dispersion: a strategy for improving the solubility of poorly soluble drugs. International journal of Research in Pharmaceutical and Biomedical sciences, 2012; 3(2): 960-966.

72. Boghra RJ, Kothawade PC, Belgamwar VS, Nerkar PP, Tekade AR and Surana SJ. Solubility, dissolution rate and bioavailability enhancement of irbesartan by

solid dispersion technique. Chemical and Pharmaceutical Bulletin, 2011; 59(4): 438-441.

73. El-Badry M, Fetih G and Fathy M. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in Gelucire 50/13 and PEG4000. Saudi Pharmaceutical Journal, 2009; 17: 217‑225.

74. Nguyen TN, Tran PH, Tran TV, Vo TV, Truong-DinhTranc T. Development of a modified-solid dispersion in an uncommon approach of melting method facilitating properties of a swellable polymer to enhance drug dissolution. International Journal of Pharmaceutics, 2015; 484: 228-234.

75. Sethia S and Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. International Journal of Pharmaceutics, 2004; 272 : 1-10.

76. Javeer SD and Amin PD. Solubility and dissolution enhancement of HPMC-based solid dispersions of Carbamazepine by hot‑melt extrusion technique. Asian Journal of Pharmaceutics, 2014:119-124.

77. Yuvaraja K and Jasmina Khanam J. Enhancement of carvedilol solubility by solid dispersion techniqueusing cyclodextrins, water soluble polymers and hydroxyl acid. Journal of Pharmaceutical and Biomedical Analysis, 2014; 96: 10-20.

78. Shah TJ, Amin AF, Parikh JR and Parikh RH. Process optimization and characterization of poloxamer solid dispersions of a poorly water-soluble drug. AAPS PharmSciTech 2007; 8 (2): E1-E7.

79. Dewan I, Hossain A and Islam SMA. Formulation and evaluation of solid dispersions of carvedilol, a poorly water soluble drug by using different polymers. International Journal of Research in Pharmacy and Chemistry, 2012; 2(3): 585-593.

80. Rao VP and Nagabhushanam MV. Enhancement of dissolution profile of mefenamic acid by solid dispersion technique. International Journal of Research in Pharmacy and Chemistry, 2011; 1(4): 1127-1134.

81. Yuvaraja K, Das SK and Khanam J. Process optimization and characterization of carvedilol solid dispersion with hydroxypropyl-β-cyclodextrin and tartaric acid. Korean J. Chem. Eng., 31: 1-9.

82. Janssens S, Armas HND, Roberts CJ, Mooter GVD. Characterization of ternary solid dispersions of itraconazole, PEG 6000, and HPMC 2910 E5. Journal of Pharmaceutical Sciences, 2008; 97(6): 2110-2120.

83. Isaac J, Kaity S, Ganguly S and Ghosh A. Microwave-induced solid dispersion technology to improve bioavailability of glipizide. Journal of Pharmacy and Pharmacology, 2012; 65: 219-229.

84. Khan GM and Jiabi Z. Preparation, characterization, and dissolution studies of ibuprofen solid dispersions using polyethylene glycol (PEG), talc, and PEG-talc as dispersion carriers. Drug Development and Industrial Pharmacy, 1998; 24(5): 455-462.

85. Choudhary D, Kumar S and Gupta GD. Enhancement of solubility and dissolution of glipizide by solid dispersion (kneading) technique. Asian Journal of Pharmaceutics, 2009: 245- 252.

86. Siahi-Shadbad MR, Ghanbarzadeh S, Barzegar-Jalali M, Valizadeh H, Taherpoor A, Mohammadi G, Barzegar-Jalali A and Adibkia K. Development and characterization of solid dispersion for dissolution improvement of furosemide by cogrinding method. Advanced Pharmaceutical Bulletin, 2014; 4(4): 391-399.

87. Waghmare P and Kadu P. Solubility enhancement of curcumin using HPMC K 4M and HPMC K 15M by solvent change precipitation method. World Journal of Pharmacy and Pharmaceutical Sciences, 2014; 3(11): 909-922.

88. Sharma A and Jain CP. Preparation and characterization of solid dispersions of valsartan with poloxamer 188. Der Pharmacia Lettre, 2010; 2(2): 54-63.

89. Khansili A and Bajpai M. Preparation and characterization of solid dispersions of nisoldipine. International Journal of Pharmaceutical, Chemical and Biological Sciences. 2015; 5(3): 604-611.

90. Prasanthi NL, Rao NR and Manikiran SS. Studies on dissolution enhancement of poorly water soluble drug using water soluble carriers. Asian Journal of Pharmaceutical and Clinical Research, 2010; 3 (2): 95-97.

91. Maulvi FA, Dalwadi SJ, Thakkar VT, Soni TG, Gohel MC and Gandhi TR. Improvement of dissolution rate of aceclofenac by solid dispersion technique. Powder Technology, 2011; 207: 47-54.

92. Ha NS, Tran TT, Tran PH, Park J and Lee B. Dissolution-enhancing mechanism of alkalizers in poloxamer-based solid dispersions and physical mixtures containing poorly water-soluble valsartan. Chemical and Pharmaceutical Bulletin, 2011; 59(7): 844-850.

93. Mannaa M, Bary AA,Assal ME and Abdullah F. Int J Pharm Sci Rev Res, 2016; 41(2): 154-160.

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