Review Article
AMERICAN JOURNAL OF PHARMACY AND HEALTH RESEARCH
www.ajphr.com
2014, Volume 2, Issue 7
ISSN:2321–3647(online)

Solid Dispersion: An Effective Approach for Bioavailability Enhancement for Poorly Soluble Drugs

Pande SV.*, Biyani KR.
1.Dept. of Pharmaceutics, Anuradha College of Pharmacy, Anuradha Nagar, Sakegaon Road, Chikhli, 443201.

ABSTRACT

The simplest and easiest way of drug administration is oral route. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. The present review relates the solid dispersion technique for bioavailability enhancement of BCS class 4 drug. the dispersion classification in this review give detail idea about the mechanism of drug to be dispersed in the carrier for solubility enhancement with different mechanism of the solubility of drug in biofluids enhancement which helps further in bioavailability enhancement of the drug to minimize dosing frequency and dose. the review also gives detailed methods for solid dispersion preparation with their recent advancement techniques as well as their different evaluation techniques. the review concludes with the suggestion for the scope of the further research with practical limitation of the solid dispersion technique with further study like practical scale up technique and poor flow and compressibility.

Keywords: Solubility Enhancement, Solid Dispersion, Methods for Solubility Enhancement, Bioavailability Enhancement.

*Corresponding Author Email pande_swa@yahoo.com
Received 03 July 2014, Accepted 08 July 2014

Please cite this article in press as: Pande SV *et al.*, Solid Dispersion: An Effective Approach for Bioavailability Enhancement for Poorly Soluble Drugs. American Journal of Pharmacy & Health Research 2014.

INTRODUCTION

The simplest and easiest way of drug administration is oral route. The formulation of poorly soluble compounds for oral delivery at present is one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry. It is frequently reported that 40% of New Drug Molecule in pharmaceutical industry are poorly water soluble. especially those belonging to the Biopharmaceutics Classification System[1] (BCS) Class IV, dissolve slowly, poorly and irregularly, and hence poses serious drug delivery challenges like incomplete release from the dosage form, poor bioavailability leads to decreased release rate & poor bioavailability. So large dose is required for therapeutic activity but that may leads to toxicity of the drug. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response. The low dissolution rate and low solubility of drug substances in water in aqueous G.I.T fluid frequently leads to inadequate bioavailability. The solubility of a solute is the maximum quantity of solute that can dissolved in a certain quantity of solvent or quantity of solution at a specific temperature. In the other words the solubility can also define as the ability of one substance to form a solution with another substance. With the recent advent of high throughput screening of active pharmaceutical ingredient, the number of poorly soluble drug candidates has risen sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in the pharmaceutical industry So best option for increasing release rate is improvement of the solubility through formulation approaches[2]. One such formulation approach that has been shown to significantly enhance absorption of such drugs is to formulate solid dispersion.

Table 1: Solubility Definitions for Solvent required to solubilise one part of Solute

Definitions	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	1000-10000
Insoluble	>10000

Solid dispersion:

The solid dispersion review revealed the different views of different Scientists. Chiou and Riegelman defined the term solid dispersion can be defined as melting of the drug and

suitable carrier dispersed and forms their eutectic mixture[3]. Sekiguchi and Obi suggested that the drug present in a eutectic mixture in a microcrystalline state[4], after few years Goldberg et al. Proved drug in solid dispersion not necessarily microcrystalline state but some fraction might be in form of molecular dispersion in the matrix[5].

The term solid dispersion refers to the combination of at least two components, may be a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Therefore, based on their molecular arrangement the solid dispersion (SDs) can be classified.

TYPES OF SOLID DISPERSION[6]

First Generation Solid Dispersions

According to Sekiguchi and Obi in 1961 solid dispersions in which the concept of eutectic mixtures. Thus first generation solid dispersions were prepared using crystalline carriers. Eutectic mixtures are binary systems comprising of poorly water soluble drug and highly water soluble carrier and at eutectic point drug crystallizing out simultaneously only in the specific composition. When eutectic mixture is dissolved in aqueous medium, the carrier part will dissolve quickly and drug will be released in the form of fine crystals. The main disadvantage of first generation Solid dispersion is crystalline nature which leads to less solubility as compare to amorphous form, however, they possess good thermodynamic stability. First generation solid dispersion were generally prepared using crystalline carriers like urea, mannitol.

Second Generation Solid Dispersions

In second generation instead of crystalline carriers, amorphous carriers were used to disperse drugs which are generally polymers. Amorphous solid dispersions are further classified as solid solutions, solid suspension or mixture of both as per molecular interaction of drug and carrier. For eg. Polymeric carriers are synthetic origin like povidone, polyethylene glycols and polymethacrylates and natural origin polymers such as cellulose derivatives like hydroxypropylmethylcellulose, ethyl cellulose or starch derivatives, like cyclodextrins[6].

Third Generation Solid Dispersions

In the third generation solid dispersions surfactants are carrier or mixture of polymer are used as carrier. If carrier has surface active or self-emulsifying properties, the dissolution profile of poorly soluble drug can be improved and hence result in increased bioavailability. E.g surfactants as solid dispersion carriers are Sodium lauryl Sulphate, polaxamer 407, gelucire

44/14, compritol 888 ATO27, and inulin.

The particle solid state alteration at molecular or particle level of the involved a physical change in the drug which leads to improve drug solubility. The solid dispersion generally prepared using water-soluble carriers to improve the oral bioavailability of poorly water-soluble drugs[6].

Solid dispersion: Definition

Chiou and Reigelman first by defined solid dispersion in 1971 as "dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion, solvent or melting-solvent method". Modified Noyes-Whitney equation gives explanation about dissolution rate of very poorly soluble compounds improved to diminish the limitations to oral availability:

$$\frac{dC}{dt} = \frac{AD(Cs - C)}{h}$$

where dC/dt is the rate of dissolution, A is the surface area available for dissolution, D is the diffusion coefficient of the compound, Cs is the solubility of the compound in the dissolution medium, C is the concentration of drug in the medium at time t and h is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound concludes that as energy not necessary to break up crystal lattice in dissolution process hence higher drug release possible through dispersion[7].

Further based on molecular arrangement dispersion can be classified as[8],

Type1- Simple eutectic mixture

Type2-Amorphous precipitations in crystalline matrix.

Type3-Solid solutions

Type4-Glass suspension and solution

Simple Eutectic Mixture

In this system the two components are said to be Simple eutectic mixture when they were completely liquid miscibility after fusion but immiscible in solid state. Thermodynamically, these are systems physical mixture of two crystalline components. Thus the X-ray diffraction pattern gives additive composite of two components. E.g. Chloramphenicol - urea; Paracetamol - urea; Griseofulvin and Tolbutamide with PEG 2000[8].

Solid Solutions

The solid solution the two components are one phase system. The particle of Drug present in this system is molecularly in size and distributed in matrix. Thus, it have faster dissolution

rate than the eutectic mixture. The Solid Solution formed by complete diffusion of solidified melt of drug and carrier into homogenous phase. They classified as continuous or discontinuous system and second, substitution, interstitial or amorphous.

a) Continuous solid solutions:

In a continuous solid solution components are miscible in all proportions. This is theoretical solution having the bonding strength between two components is stronger than that of molecules of each of the individual components. Solid solutions of this type not reported uphill in the pharmaceutical world.

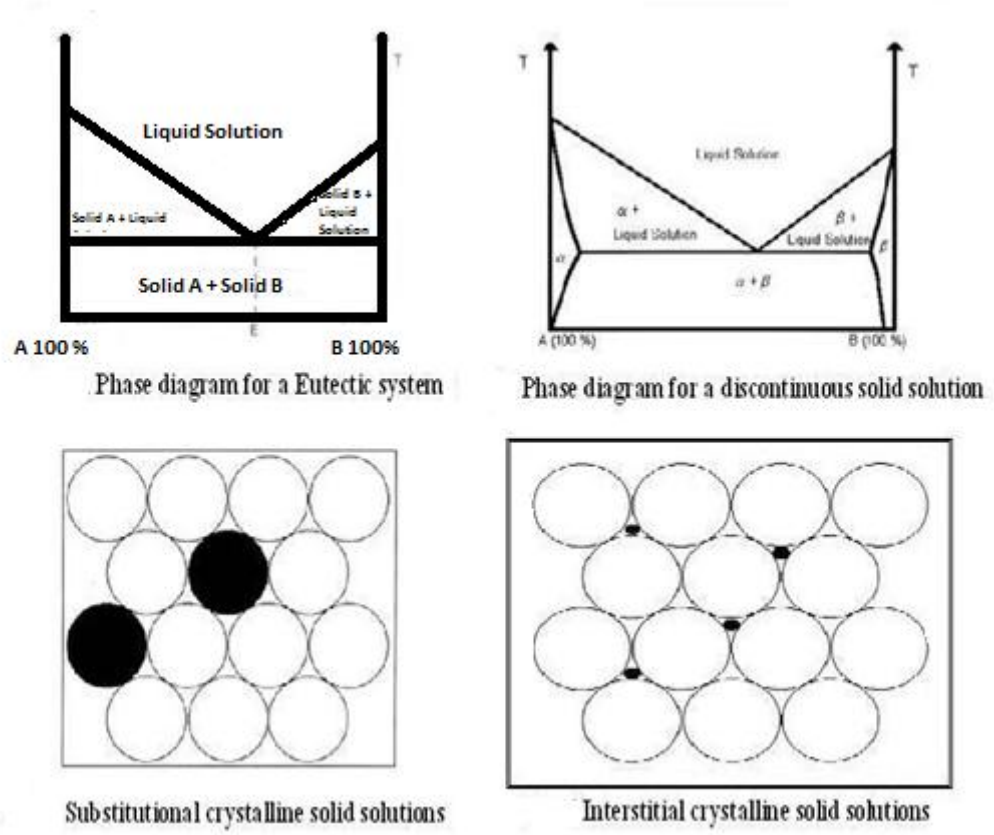

Figure 1: Phase Solubility Diagrams

b) Discontinuous solid solutions:

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Due to practical considerations it has been suggested by Goldberg et al. that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

c) Subsitutional solid dispersions:

Substitution is possible only when the size of the solute molecules differs by less than 15%

or so from that of the solvent molecules. Classical solid solutions have crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or fit into the intrsticies between the solvent molecules.

d) Interstitial solid solutions:

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. Solute molecule diameter should be less than 0.59 times than that of solvent molecular diameter.

- **Glass Solutions and Suspensions**

A glass solution is a homogeneous 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 glassy state is characterized by transparency and brittleness below the glass transition temperature. Glasses do not have sharp melting point; instead, they soften progressively on heating. The lattice energy, which represents a barrier to rapid dissolution, is much lower in glass solutions than in solid solutions.

- **Amorphous Precipitations in a Crystalline Carrier**

This is similar to simple eutectic mixtures but only difference is that drug is precipitated out in an amorphous form and the solute molecules are dispersed molecularly but irregularly within the amorphous solvent.

Compound or Complex formation

Drug and matrix strongly interact and form complexes in aqueous medium e.g. Cyclodextrins. The formation of soluble complex possibly takes place when low or intermediate fraction of carrier is employed in the preparation of solid dispersion.

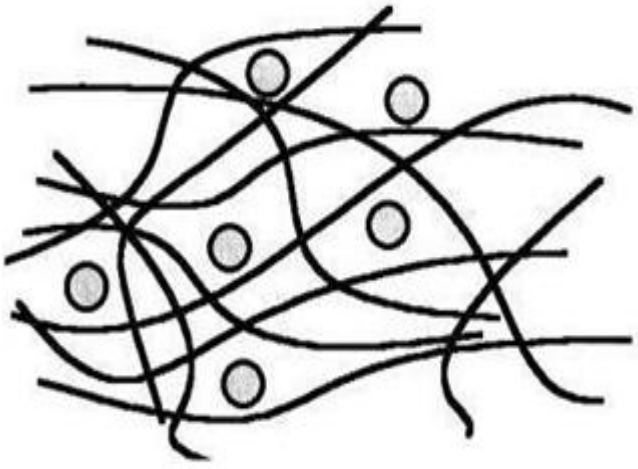

Figure. 2: Amorphous Solid Solutions.

Table 2 : Types of Solid Dispersion[8]

Sr.No	Solid Dispersion Type	Matrix*	Drug**	Remarks	phases
1.	Eutectics	C	C	The first type of solid dispersion prepared	2
2.	Amorphous precipitations in crystalline matrix	C	A	Rarely Encountered	2
3.	Solid solutions			Miscible at all composition,	
A.	Continuous Solid Solutions	C	M	Never prepared	1
C	Substitutional solid solutions	C	M	Molecular diameter of drug (solute) differs less than 5% from the 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	1or 2
4.	Glass suspension	A	C	Particle size of dispersed phase dependent on cooling/evaporation rate. Obtained after crystallization of drug in amorphous matrix	2
5.	Glass suspension	A	A	Particle size of dispersed phase dependent on cooling/evaporation rate many solid dispersions are of this type	2
6.	Glass solution	A	M	Requires miscibility OR solid solubility, complex formation or upon fast cooling OR evaporation during preparation, many (recent) examples especially with PVP	1

*A: matrix in the amorphous 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

METHODS FOR PREPARING SOLID SOLUTIONS[9]

Kneading Technique

In this method, carrier paste is formed with water and drug added in it and past kneaded for particular time with using suitable milling and slugging technique. The kneaded mixture is then dried and passed through sieve if necessary.

Solvent evaporation method

In this method, drug and carrier are dissolved in organic solvent. after entire dissolution The solution allows to evaporate at room temperature or at elevated temperature as per drug and excipient's nature. The solid mass remained sieved and dried. Ex. Solid dispersion of furosemide with eudragit was prepared by solvent evaporation method[10].

Co-precipitation method

In this method drug is added to the solution of carrier and system is kept under magnetic

agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the structure water from the inclusion complex[11].

Melting method

In this method firstly drug and carrier are mixed using mortar and pestle. The homogenous dispersion then is heated at or above the melting point of all the components. After heating it is cooled to form a congealed mass. Which is crushed and sieved. Ex. albendazole and urea solid dispersion was prepared by this method[12].

Co-grinding method

The physical mixture of drug and carrier is properly mixed with help of blender at a particular speed. This mixture is then undergoes for milling in vibration ball mill steel balls are added. The powder mixture is pulverized and at room temperature in a screw capped glass vial until use. Ex. chlordiazepoxide and mannitol solid dispersion was prepared by this method[13].

Gel entrapment technique

The polymers like Hydroxyl propyl methyl cellulose is dissolved in organic solvent to form a clear and transparent gel. Then drug for example is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and sieved[14].

Spray-Drying Method

The clear solution of drug and polymer obtained by dissolution of drug in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method, which is then spray dried using spray dryer[15].

Lyophilization Technique

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative method to solvent evaporation. Lyophilization has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion[16].

Electrospinning Method

In this procedure, a liquid stream of a drug/polymer solution is subjected to a potential difference between 5 and 30 kV. Which leads to formation of fibers of submicron size as electrical forces prevail over the surface tension of the drug/polymer solution at the air

interface. After solvent evaporation, the formed fibers can be collected on a screen of spinning mandrel[17].

Dropping method solution

The dropping method, developed by Ulrich *et al.* (1997) to facilitate for production of round particles from melted solid dispersions. A round drop of expected solid dispersion of a melted drug-carrier mixture is prepared by formation of drop with help of pipette and then dropped onto a plate, where it solidifies into round particles. The use of carriers that solidify at room temperature may aid the dropping process. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation.

Melt Extrusion Method

Solid dispersion by this method is composed of active ingredient and carrier, and prepare by hot-stage extrusion using a co-rotating twin-screw extruder. The concentration of drug in the dispersions is always 40% (w/w). Melt extrusion technique is used in the preparation of diverse dosage forms in the pharmaceutical industry e.g. sustained-release pellets[18].

Melt Agglomeration Process

This technique the binder itself acts as carrier. SD(s) are prepared either by heating the binder, drug and excipient to a temperature above the melting point of the binder or by spraying a dispersion of drug in molten binder on the heated excipient by using a high shear mixer[19].

Merits of Solid Dispersion[20]

The solid dispersion leads to the distribution of the drug homogenously in carrier molecularly, provided in solid dispersions various advantageous applications.

- Drug after solid dispersion increase patient compliance than solubilization product because solubilised product is in liquid dosage form and solid dispersion rises to solid oral dosage forms.
- It having simplicity of preparation, ease of optimization, and reproducibility
- The bioavailability enhances of the active agent to a desirable extent leads to less drug administration frequency.
- Transformation of drugs phase can be possible i.e. liquid form of the drug in to solid form is possible

Limitations of solid dispersion:

- Reproducibility of its physico-chemical properties

- Poor stability of dosage form
- Laborious and expensive method of preparation
- Aggregation, agglomeration and air adsorption during formulation
- Difficulty in pulverization and sifting because of their tacky and soft nature
- Changes in crystallinity and a dissolution rate decrease on ageing.
- Drug solubility alters by absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form.
- As most of the polymers used in solid dispersions can absorb moisture which leads to phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate.

MECHANISM OF BIOAVAILABILITY ENHANCEMENT[21]

The dissolution rate of the increase by solid dispersion formation varies higher upto 400 fold, relative to pure drug. The increase in dissolution rate is unpredictable as there can be possibility of many factors which leads to enhance drug dissolution hence can't say one is more important than the other factor. Solid dispersions increase the dissolution rate of poorly water soluble drugs by one of the following mechanisms.

- Reduction in particle size
- Improvement in wettability and dispensability
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles

TECHNIQUES OF SOLUBILITY ENHANCEMENT[22]

There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are.

1. Physical Modifications[6]

A. Particle size reduction

a. Micronization

The solubility of drug is related to drug particle size. By reducing the particle size the surface area of the drug increases which leads to improvement in the dissolution of the drug. Micronization of drugs done by milling techniques. Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.

b. Nanosuspension

Nanosuspensions are the sub-micron colloidal dispersion of pure drug with surfactants. The advantages are leads to increased dissolution rate is due to larger surface area exposed, while Ostwald ripening can not be hindered due to the uniform and narrow particle size range, which eliminates the concentration gradient.

B. Modification of the crystal habit

The crystal structure of the drug can occurred naturally or synthetically in one or more forms which called as polymorphs. Polymorphism is property of drugs in which the compound obtained in different crystalline form. They have different physicochemical properties including solubility, melting point, density, texture and stability.

The polymorphs can be classified as enantiotropes and monotropes based on thermodynamic properties.

In the case of an enantiotropic system, one polymorphic form can change reversibly into another at a definite transition temperature below the melting point, while no reversible transition is possible for monotropes. Metastable forms are associated with higher energy and thus higher solubility.

Similarly the amorphous form of drug is always more suited than crystalline form due to higher energy associated and increase surface area. Also same for the anhydrous form of a drug has greater solubility than the hydrates. This is because the hydrates are already in interaction with water. On the other hand, the organic solvates have greater solubility than the nonsolvates. Thus, the order for dissolution of different solid forms of drug is Amorphous >Metastable polymorph >Stable polymorph.

C. Drug dispersion in carriers

a. Solid dispersions

The term “solid dispersions” refers to the dispersion of one or more active ingredients in an inert carrier in a solid state with reduced particle size, frequently prepared by the melting method, solvent method, or fusion solvent-method.

D. Complexation

Complexation is the association between two or more molecules to form a nonbonded entity with a well defined stoichiometry. Complexation relies on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions.

a. Staching complexation

Staching complexes are formed by the overlap of the planar regions of aromatic molecules.

Nonpolar moieties tend to be squeezed out of water by the strong hydrogen bonding interactions of water. This causes some molecules to minimize the contact with water by aggregation of their hydrocarbon moieties. This aggregation is favored by large planar nonpolar regions in the molecule. E.g. Nicotinamide, Anthracene, Pyrene, Methylene blue, Benzoic acid, Salicylic acid, Ferulic acid, Gentisic acid, Purine, Theobromine, Caffeine, and Naphthalene.

b. Inclusion complexation

Inclusion complexes are insertion of the nonpolar molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The snug fit of the guest into the cavity of host molecule. So that the contact between the water and the nonpolar regions of the host and the guest is reduced.

E. Solubilization by surfactants

Surfactants are molecules with distinct polar and nonpolar regions. Most surfactants consist of a hydrocarbon segment connected to a polar group. The polar group can be anionic, cationic, zwitter ionic or non-ionic. When small apolar molecules are added they can accumulate in the hydrophobic core of the micelles. The presence of surfactants may lower the surface tension and increase the solubility of the drug within an organic solvent.

a. Microemulsion

In microemulsion surfactant should be soluble in the internal phase and co-surfactant should not. the internal or dispersed phase is having diameter < 0.1 μ. Advantages of microemulsion over coarse emulsion include its ease of preparation due to spontaneous formation, thermodynamic stability, transparent and elegant appearance, increased drug loading, enhanced penetration through the biological membranes, increased bioavailability, and less inter- and intra- individual variability in drug pharmacokinetics. Eg. Tweens and Labrafil with high hydrophilic - lipophilic balance.

2. Chemical Modification[6]

The solubility of an ionizable drug effected by pH of the solution. A drug that can be efficiently solubilized by pH control should be either weak acid with a low pKa or a weak base with a high pKa. Non-ionizable, hydrophobic substances can have improved solubility by changing the dielectric constant of the solvent by the use of co-solvents rather than the pH of the solvent.

3. Other Methods

a. Cocrystalization

A co-crystal are crystals in which two or more molecular species held together by non-covalent forces. Co-crystals are more stable. Co-crystals prepared by evaporation of a heteromeric solution or by grinding the components together and sublimation, growth from the melt, and slurry preparation.

b. cosolvency

It is commonly termed as solvent blending. Most cosolvents have hydrogen bond donor and/or acceptor groups as well as small hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, while their hydrophobic hydrocarbon regions interfere with waters hydrogen bonding network, reducing the overall intermolecular attraction of water.

g. Use of soluble prodrug

physico-chemical properties of the drug are improved by bio-reversible chemical alteration i.e. the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility.

h. Porous microparticle technology

In this technology, matrix having porous, water soluble, sponge like nature embed the poorly water soluble drug, so that after dissolution the matrix dissolves and wetting the drug and giving a suspension of rapidly dissolving drug particles.

i. Nanotechnology approaches

In Nanotechnology the materials study use at nanoscale level of approximately 100 nanometers (nm) or less. As small size leads to more surface area and small crystal lattice energy for dissolution which consider in more dissolution. But many new chemical entities of very low solubility, oral bioavailability enhancement by micronization is not sufficient because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution and the next step taken was Nanonisation

1. SELECTION OF CARRIER(S)[23]

The carrier properties have a main influence on the dissolution characteristics of the dispersed drug. A carrier should have the following properties suitable for increasing the dissolution rate of a drug. It should be

- Freely water soluble with rapid dissolution properties
- Nontoxic and pharmacologically inert
- Heat stable with a low melting point for the melt method

- Soluble in a variety of solvents
- Preferably enhancing the aqueous solubility of the drug
- Chemically compatible with the drug

Table 3 : Carriers used in the preparation of solid dispersion[25]

Chemical class	Examples
Acids	Citric acid, Tartaric acid, Succnic acid
Sugars	Dextrose, Sorbitol, Sucrose, Maltose, Galactose, Xylitol
Polymer material	Polyvinyl pyrolidone, PEG 4000, PEG 6000, Sodium alginate, Carboxy ethylcellulose, Guar gum, Xanthan gum, Methyl cellulose
Surfactant	Polyoxyethylene stearate, Polaxamer, Deoxycholic acid, Tweens and Spans, Gelucire 44/14, Vitamin E TPGS NF
Miscellaneous	Pentaerythritol, Urea, Urethane, Hydroxylakyl xanthenes.

SELECTION OF SOLVENT(S)[23]

The solvent properties have also influence on the dissolution characteristics of the dispersed drug. A solvent should have the following property for success in dispersion technology. It should be

- Both drug and carrier must be dissolved so form homogenous dispersion
- Toxic solvents to be avoided due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

Table 4 : List of Solvents Used In Solid Dispersion

S.no	Solvent	Melting point (°C)	Boiling point (°C)
1	Water	0	100
2	Methanol	-93.9	65
3	Chloroform	-63	62
4	DMSO	19	189

MECHANISM OF SOLID DISPERSION

There are two sets of observations with regard to the mechanism of drug release from solid dispersions.

1 Carrier-controlled Release[26]

According to Corrigan (1986) the dissolution rate of the drug is controlled by that of the inert carrier which supported by experiments of Dubois and Ford (1985) investigated that the dissolution rates of a range of drugs in a single carrier, prepared under comparable conditions, were identical in most cases. Consequently, the drug is molecularly dispersed within this concentrated layer.

2 Drug-controlled Release

The Sjokvist and Nystrom (1991) measured the particle size of the API and suggest dissolution rate enhancement proportional to size of the released particles. In support to this Sjokvist-Saers and Craig (1992) used a homologous series of drug. there was a linear relationship between the intrinsic dissolution rate of the model drugs in the dispersions and the drug solubility. It suggest that drug dissolution dominated by the properties (size, physical form, etc.) of the drug itself. This may still lead to considerable improvements in dissolution compared to conventional dosage forms due to the higher surface area associated the particles and the possibility of improved wetting and decreased agglomeration.

METHODS OF PREPARATION OF SOLID DISPERSION:

Various methods used for preparation of solid dispersion system. These methods are given bellow.

1.Melting method

2.Solvent methods

3.Melting solvent method (melt evaporation)

4.Melt extrusion methods

5.Lyophilization techniques

6.Melt agglomerations Process

7.The use of surfactant

8. Super Critical Fluid (Scf) technologies

1. Melting method[4, 27-28]:

First proposed by Sekiguchi and Obi, in this method the physical mixture of a drug and a water-soluble carrier prepared simply with mortar and pastel then it undergoes heat directly until it melted. The melted mixture is then solidified rapidly on an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved.

The super-saturation of a solute or drug in a system will form due to quenching the melt rapidly from a high temperature such that, the solute molecule arrested in the solvent matrix by the instantaneous solidification process. This technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Some adaptation are done in melting phase by suspending the active drug in a previously melted carrier, instead of using both drug and carrier in the melted state, therefore reducing, the process temperature. To cool and solidify the melted mixture, several processes such as ice bath agitation, stainless steel thin layer spreading followed by a cold draught,

solidification on petridish at room temperature, inside a dessicator, spreading on plates placed over dry ice, immersion in liquid nitrogen or stored in a dessicator were used.

Advantages

- It is convenient and economical method only for drugs stable at temperature below 1000°C
- it more easier method if the drug and carrier are miscible in the molten state
- It precludes the use an organic solvent thereby circumventing the enigmas of its removal from the dispersion
- Dissolution for dispersions obtained by melting technique are much faster than those prepared using solvent techniques

Disadvantages

- High melting carrier cannot be used
- Thermal degradation or instability may result at the melting point
- Decomposition may take place, often dependent upon composition, fusion time and rate of cooling
- Evaporation or sublimation and polymeric transformation of the dispersion component may take place
- Solidified miscibility between drug and carrier results in irregular crystallization that causes obvious problems during formulation

2. Solvent evaporation method[29,30]:

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight. 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 possible adverse effect of traces of the solvent on the chemical stability
- The difficulty of reproducing crystal form.

3. Melting solvent method (melt evaporation)[30]:

In this method drug is dissolved in a suitable liquid solvent and then this solution incorporated directly into the melt of polyethylene glycol, which evaporated to form a clear,

solvent free film. This film is further dried to constant weight.

Advantage:

- From a practical standpoint,
- This method gains the good possibility of obtain solid dispersion both the fusion and solvent evaporation methods.

Disadvantage:

- Solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion.
- It is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

4. Melt extrusion method[31-33]:

In this method 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.

Advantage

- Due to less time of heating (1 min), enables thermolabile drugs to be processed.

5. Melt Agglomeration Process[33]:

In this technique binder acts as a carrier. SD(s) 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). The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration.

The above parameters affect directly dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates.

6. Surfactant[8]:

Adsorption of surfactant on solid surface can modify hydrophilicity, surface charge, and other key properties that govern solubility process interfacially. 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.

7. Super Critical Fluid (SCF) Technology[34-35]:

This technology has been introduced in the late 1980s and early 1990s, pharmaceutical

applications has been studied intensively by a number of researcher groups CFs either as solvent: rapid expansion from supercritical solution (RESS) or antisolvent: gas antisolvent (GAS), supercritical antisolvent (SAS), solution enhanced dispersion by supercritical fluids (SEDS) and/or dispersing fluid: GAS, SEDS, particles from gas-saturated solution (PGSS). Conventional methods, i.e. Spray drying, solvent evaporation and hot melt method often result in low yield, high residual solvent content or thermal degradation of the active substance. At the critical point, densities of liquid and gas are equal and there is no phase boundary.

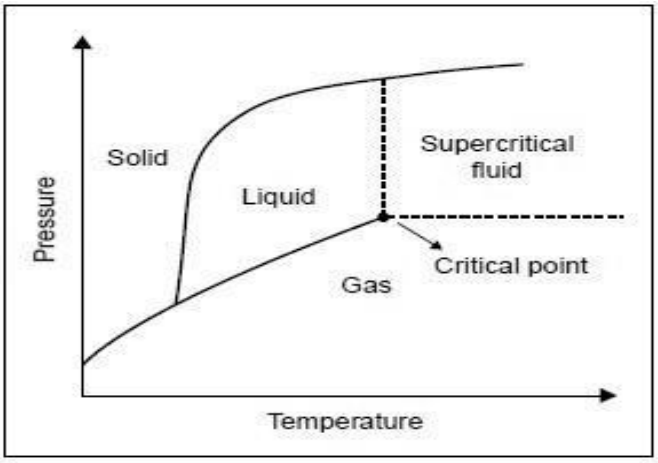

Figure 3 : Supercritical region of a hypothetical compound (Indicated by the dotted lines)

The supercritical fluid antisolvent techniques, carbon dioxide is used as an antisolvent for the solute but as a solvent with respect to the organic solvent. The SAS process involves the spraying of the solution composed of the solute and of the organic solvent into a continuous supercritical phase flowing cocurrently use of supercritical carbon dioxide is advantageous as it is much easier to remove from the polymeric materials when the process is complete, even though a small amount of carbon dioxide remains trapped inside the polymer; it poses no danger to the patient. In addition the ability of carbon dioxide to plasticize and swell polymers can also be exploited and the process can be carried out near room temperature Moreover, supercritical fluids are used to lower the temperature of melt dispersion process by reducing the melting temperature of dispersed active agent.

Advantages

- High melting carries can also be utilized
- Thermal decomposition of drug and carriers associated with the fusion method can be avoided

Disadvantages

- Larger volumes or organic solvent have to be used which makes the process slightly expensive
- Removal of the solvent is difficult
- Residual solvent can have possible adverse effect
- Difficulty of reproducing crystal forms
- Supersaturation of the solute cannot be attained unless the system goes through a highly viscous phase
- Selection of common solvent is difficult Drug particle size is affected by temperature and rate of evaporation

8. Lyophillization technique[21, 36]

Lyophillization is a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to get a lyophilized molecular dispersion. This is as an alternative technique to solvent evaporation.

Advantage

- The drug is subjected to minimal thermal stress during the formation of the solid dispersion.
- Risk of phase separation is minimized as soon as the solution is vitrified.
- The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. thereby decreasing the risk for phase separation to a minimum.
- Size of the particle so low to make them suitable for further processing or applications like pulmonary or nasal administration.
- Risk of phase separation is minimized as soon as the solution is vitrified.
- Offers the potential to customize the size of the particle to make them suitable for further processing.

Disadvantages

- The tablets are very fragile.
- The manufacturing process is very expensive.
- The technique is not suitable for all the products

9. Spray drying[37-38]

In this process the atomization of suspensions or solutions of drug and carrier of specific

concentration in requires solvent, into fine droplets followed by a drying the atomized droplet in heated air stream. The process allows production of fine, dust free powder of drug and carrier particles as well as agglomerated one to precise specifications. The operating conditions and dryer design depends upon the drying characteristics of the product.

The spray drying technique is a useful method to obtain spherical particle and narrow distribution.

Advantages

- Tremendous formulation flexibility from the wide variety of solvents, polymers and adjuvants that can be employed.
- Economical process as limited and reusable resources can be usually possible.
- **Disadvantages**
- Added costs associated with the use and consumption of the organic solvents.
- Requirement of unit operation for residual solvent removal

10. High- pressure homogenization[22]

The high pressure homogenization involves dispersing a drug powder in an aqueous surfactant solution and passing through a high-pressure homogenizer, subsequently Nano suspensions are obtained. The cavitation force experienced is sufficient to disintegrate drug from micro particles to nanoparticles. The particle size is dependent on the hardness of the drug substance, the processing pressure and the number of cycles applied. However, only brittle drug candidates might be broken up into nanoparticles by this technique.

11. Inclusion complexes[39]

1. Kneading technique

In this method drug and polymer mixed well with the small amount of the solvent i.e. water to form a thick paste by kneading and hence it is dried at 45°C in an oven. Pass the mass through the sieve no. 30 and store in the desiccator.

2. Co-precipitation

The specific amount of drug added into the solution of β- cyclodextrins. Keep the system under magnetic agitation with controlled process parameters and protect from the light. Separate the formed precipitate by vacuum filtration and then dry at room temperature in order to avoid the loss of the structure water from the inclusion complex.

3. Co-grinding

Weigh the calculated amounts of drug and carriers and mix together with one ml of water. Pass the damp mass obtained, through a 44-mesh sieve; disperse the resultant granules in Petri dishes and dried at 60°C under vacuum, until a constant weight is obtained. Store the granules in desiccators until used for further studies.

5. Spray-drying method

Dissolve drug in suitable solvent and the required stoichiometric amount of carrier material like β- Cyclodextrin in water. Mix the solutions by sonication or other suitable method to produce a clear solution. Dry it using spray dryer.

6. Microwave irradiation method

Drug and Cyclodextrin mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product.

11. Use of Block Co-Polymer as Dispersed Agent

In higher concentration block copolymer produce monomolecular micelles which are then associate form a different size of the aggregates in such a way that, hydrophobic chains blocked by hydrophilic chains. A. Aggregates of monomolecular micelles after association in such a way that Hydrophobic Chains blocked by hydrophilic chains B. Chain block co-polymer: a- Hydrophilic chain, b- Hydrophobic chain these aggregates have property to solubilize the drug. Thus the dissolution rate of drug gets increased. Also block co-polymer have properties to boost the stability of drug which is get solubilized in the monomolecular micelles. Thus the block co-polymer also play important task in preventing the problem in the stability of solid dispersion. Examples: Poly (propylene oxide)-poly (ethylene oxide) – poly (propylene oxide), Poly (beta-benzyl-L-aspartate), Bpoly (ethylene oxide) etc.

Applications of Solid Dispersions[40]:-

- To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo oxidation and other decomposition procedures.
- Masking of unpleasant taste and smell of drugs.
- Improvement of drug release from ointment creams and gels.
- To obtain a homogeneous distribution of a small amount of drug in solid state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

- To formulate a fast release primary dose in a sustained released dosage form.
- To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
- To reduce pre systemic inactivation of drugs like morphine and progesterone.

2. CHARACTERIZATION OF SOLID DISPERSION[41-52]

A number of techniques can be employed to identify the physical nature of the solid dispersions. No single method however, can furnish the complete information and hence a rational combination of the methods is preferred.

Thermal Analysis

a) Thermo-microscopic Methods

In this visually observe thaw and melting points of solids. The method is advantageous as small amount of sample is required and direct observation of the changes taking place in the sample through the thaw and melt stages. It gives information about the phase diagram of binary systems.

b) Differential thermal analysis (DTA)

This is an effective thermal method for studying the phase equilibrium of pure substance or solid mixture. Differential heat changes leads to physical and chemical changes which are function of temperature change at constant rate. Not only thawing, melting, polymorphic transition, evaporation, sublimation, desolvation but also changes such as decomposition of the sample detected. The method has been used routinely to identify different types of solid dispersion. The greatest advantage of using this technique is in constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution realest. A sample size of less than 1 mg can be used.

c) X-ray diffraction (XRD)

In this analytical tool, intensity of x-ray reflection is measured which is a function of diffraction process. The diffraction method is very important and efficient tool in studying the physical nature of solid dispersion which has been used in crystal structure studies in two different ways.

Single crystal x-ray crystallography dealing with the determination of bond angle and inter atomic distances. The detection of crystalline phases in mixed systems can be analyzed by powder X-ray diffraction.

As too much crystallinity causes brittleness. The crystallinity parts give sharp narrow

diffraction peaks and the amorphous component gives a very broad peak. The ratio between these intensities can be used to calculate the amount of crystallinity in the material.

The X-ray diffraction enables study of crystal lattice parameter, where the x-ray diffraction intensity from a sample is measured as a function of diffraction angles.

d) FT-IR Spectroscopy

FT-IR spectroscopy used to study the possibility of an interaction between drug and polymer in solid state. Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix.

e) Dissolution rate determination

The method involves comparing the in vitro dissolution rates of the solute component from a constant- surface tablet made from molecular dispersion (i.e., solid or glass solution) with a physical mixture of the same chemical composition. The technique is simple to perform. It tells whether the solid dispersion has improved the dissolution rate or not. The degree of crystallinity can also be studied if it is carried out under standard conditions.

f) Scanning Electron Microscopy

It usually gives primary information of system and tells about the amorphous or crystalline nature of solid dispersions. The application of the electron microscope technique, however, usually limited to chemicals with high resolution.

g) Thermodynamic methods

In this analysis, the phase diagrams of eutectic and solid solution systems give the value of heats of fusion, entropies and partial pressures at various compositions that helps to determine the solubility gap below the solid-liquid equilibrium temperature.

h) Differential scanning calorimetry (DSC)

DSC is a well-known technique that Crystallinity can be determined by quantifying the heat associated with melting (fusion) of the material. Glass transitions may occur as the temperature of an amorphous solid is increased. This is due to the sample undergoing a change in heat capacity; no formal phase change occurs. As the temperature increases, an amorphous solid will become less viscous. At specific point the molecules may obtain enough freedom of motion to spontaneously arrange themselves into a crystalline form. This is known as the crystallization temperature (Tc). This transition from amorphous solid to crystalline solid results in an exothermic peak in the DSC signal. As the temperature increases the sample eventually reaches its melting temperature (Tm). The melting process results in an endothermic peak in the DSC curve. The exact nature of the thermal transitions

has to be determined with complementary methods such as microscopic observations, thermogravimetry, X-ray diffraction or spectroscopic techniques to distinguish.

i) Hot stage microscopy

Hot stage microscopy is one of the oldest and most straightforward methods for studying phase transitions in crystals. Varying the temperature of a substance while viewing it under a microscope, often through crossed polarizers, provides a wealth of information about melting or recrystallization behavior as well as solid-state transformations. This technique also allows the detection of solvates by observing the evolution of a gas or liquid from a crystal. Novel polymorphs can be generated in this experiment either by high temperature transition of one form to another or by crystallization from the melt. Coupling hot stage microscopy with vibrational spectroscopy or DSC can further expand the utility of this method.

j) Nuclear magnetic resonance spectroscopy

Solid-state nuclear magnetic resonance (SS-NMR) spectroscopy can be used to investigate polymorphism by probing the environments of atoms in the solid state; non-equivalent nuclei will resonate at different frequencies and these changes in chemical shift can often be connected with changes in conformation or chemical environment of the compound.

SS-NMR is also useful because it is able to determine the number of crystallographically in equivalent sites in a unit cell. Unlike PXRD, SS-NMR spectroscopy is well-suited to studying amorphous forms of pharmaceuticals and solvates that are usually small to detect. Collecting spectra at various temperatures is a powerful tool in understanding polymorphic transformations and molecular motion in the solid.

PRACTICAL LIMITATIONS IN TECHNIQUE

Problem concerned with dosage form development

Poor Flow and Compressibility:-

It is usually found that, the solid dispersion show complexity in sieving and pulverization. Solid dispersion also shows poor compressibility and stability. generally during compression the solid dispersion stick to dies and punches. One of the new methods is, filling of drug-PEG melts in a hard gelatin capsule but care should be taken, while filling the temperature of drug- PEG melt should not exceed 70°C.

Problem concerned with Stability

In Methods like hot melt method, fraction of drug may not get dispersed in carrier which may leads to phase separation i.e. the crystalline and amorphous phase separated in or after

stipulated time period so additional stability study have to be performed.

CONCLUSION:

The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Drug dissolution i.e rate of drug release is the rate determining step for oral absorption of drugs, which further relates to the in vivo absorption of drug. Many drugs are poorly soluble in biofluids hence Because of solubility problem of many drugs the bioavailability of these gets affected and hence solubility enhancement of these drugs are necessary. Solid dispersions is one of the most effective process. However, the commercially problems such as cost effectiveness and instability of some of the drugs can be responsible for its wide unacceptability. Further research is required for the better implementation of solid dispersion technology on industrial scale as this is an excellent technique for the solubility enhancement of poorly soluble drugs.

REFERENCES:

1. Mundhe A, Fuloria NK, Pande SV, Biyani KR BCS Based Biowaivers and Their Current Regulatory Issues, Indo Am J Pharm Res ,3(6), 2013, 4617-4629.
2. Pande S. V., Biyani K. R. Formulation Methods of Oral Drug Delivery to Enhance Bioavailability of BCS Class 4 Drugs: A Review World J Pharm Pharma Sci 2(4), 1641-1657.
3. Chiou W.L., Riegelman S. “Pharmaceutical applications of solid dispersion systems.” J Pharm Sci. 1971, 60(9) 1281-1302.
4. Sekiguchi K., Obi N. Studies on Absorption of Eutectic Mixture. I. A comparison of the behaviour of eutectic mixture of sulfathiazole and that of ordinary sulfathiazole in man. Chem Pharm Bulletin 1961; 9,866-872.
5. Goldberg AH., Gibaldi M., 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.
6. Tomar R, Chittodiya P, Agrawal S, Bahrani P. Solubility Enhancement by Solid Dispersion - a Review, Int J Pharma Biological Archives 2013; vol-4, issue4, .: 623 – 631.
7. Patil M. R Maniyar A, Kale M. T, Akarte A., Baviskar DT Solid Dispersion: Strategy to Enhance Solubility, 8(2), 2011; 66-73.

8. Singh J, Manpreet M, Harikumar S. Solubility Enhancement by Solid Dispersion Method: A Review, J Drug Delivery & Therapeutics; 2013, 3(5), 148-15.
9. Nikghalb LA., Singh G, Singh G. and Kahkeshan K. Solid Dispersion: Methods and Polymers to increase the solubility of poorly soluble drugs, J Applied Pharma Sci 2012,2(10), 170-175.
10. Rasenack N, Hartenhauer H, Müller B. Microcrystals for dissolution rate enhancement of poorly water-soluble drugs. Int J Pharm. 2003, 254.
11. Moyano JR., Blanco MJ., Gines JM., Giordano F. Solid-state characterization and dissolution characteristics of gliclazide-betacyclodextrin inclusion complexes. Int J Pharm 1997, 148.
12. Kalaiselvan R, Mohanta GP, Manna PK, Manavalan R. Studies on Mechanism of Enhanced Dissolution of Albendazole Solid Dispersions with Crystalline Carriers. Indian J Pharm Sci 2006, 599-607.
13. Nokhodchi A, Javadzadeh Y, Siahi-Shadbad MR., Barzegar-Jalali M. The effect of type and concentration of vehicles on the dissolution rate of a poorly soluble drug (indomethacin) from liquisolid compacts. J Pharm Pharm Sci 2005;18-25.
14. Bhise S.B., Rajkumar M. Effect of HPMC on Solubility and Dissolution of Carbamazepine Form III in Simulated Gastrointestinal Fluids. Asian J Pharma2008, 2(1), 38-42.
15. Bakatselou V., Oppenheim R.C., Dressman J.B. Solubilization and wetting effects of bile salts on the dissolution of steroids. Pharm Res,1991;8, 1461-1469.
16. Betageri G.V., Makarla K.R.. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int. J. Pharm, 1995; 124, . :155-160.
17. Deitzel J.M., Kleinmeyer J., Harris D., Beck T. The effect of processing variables on the morphology of electrospun nanofibers and textiles. Polymers 2001; 42, 261-272.
18. Karanth H., Shenoy V.S., Murthy R. Industrially feasible alternative approaches in the manufacture in the the solid dispersion: A technical report. AAPS PharmSciTech, 2006; 7(4), 87.
19. Tsinontides SC, Rajniak P, Hunke W, Placek J. Freeze drying principles and practice for successful scale-up to manufacturing. Int. J. Pharm 2004, 280(1),1-16.
20. Das S. K., Roy S., Kalimuthu Y., Khanam J., Nanda A. Solid Dispersions : An Approach to Enhance the Bioavailability of Poorly Water-Soluble Drugs, International Journal of Pharmacology and Pharmaceutical Technology, I(1), 37-46.

21. Kapoor B, Kaur A, Kour S, Behl H., Kour S. Solid dispersion: an evolutionary approach for solubility enhancement of poorly water soluble drugs. Int J Recent Advances in Pharmaceutical Research,2012;2(2), 1-16.
22. Argade PS, Magar D, Saudagar RB. Solid Dispersion: Solubility Enhancement Eechnique for Poorly Water soluble drugs, Journal of Advanced Pharmacy Education & Research,2013, 3(4), 427-439.
23. Shah JC., Chen JR., Chow D., Preformulation study of etoposide. Increased solubility and dissolution rate by solid-solid dispersions, Int J Pharm, 1995, 31, 103-111.
24. Perng CY., Kearney AS., Patel K., Palepu NR., Zuber G., Investigation of formulation approaches to improve the dissolution of SB- 210661, a poorly water soluble 5-lipoxygenase inhibitor, Int J Pharm, 1998, 17, 31-38
25. Dhirendra K., Solid Dispersions: A Review, Pakistan Journal of Pharma. Sci.,2002 22(2), 234-246.
26. Corrigan O. And Stanley C., Mechanism of Drug Dissolution Rate Enhancement From β-Cyclodextrin-Drug Systems, Journal of Pharmacy and Pharmacology, 1982, 34(10),. 621–626.
27. Greenhalgh DJ, Williams AC, Timmins P, York P. Solubility Parameters as Predictors of Miscibility in Solid Dispersions. Journal of Pharm Sci., 1999; 88, 1182-1190.
28. Timko RJ., Lordi NG. Thermal analysis studies of glass dispersion systems. Drug Dev Ind Pharm.1984; 10, .425-451.
29. Butler, MJ, Method of producing a solid dispersion of a poorly water-soluble drug. US Patent No. 5 1999; Referene : 326.
30. Kim EJ., et al. Preparation of solid dispersion of felodipine using a solvent wetting method. European Journal of Pharmaceutics and Biopharmaceutics,2006; 64, 200-205.
31. Lakshman JP., Cao Y., Kowalski J., Serajuddin A.T. Application of melt extrusion in the development of a physically and chemically stable high-energy amorphous solid dispersion of a poorly water-soluble drug. Mol Pharm. 2008; 5, 994-1002.
32. El-Egakey MA., Soliva M., Speise P. Hot extruded dosage forms, Pharm Acta Helv. 1971;46,:31-52.
33. Breitenbach J. Melt extrusion: from process to drug delivery technology. Eur J Pharm Biopharm. 2002; 54, :107-117.
34. Subramanian B., Rajewski RA., Snavely K. Pharmaceutical Processing with Supercritical Carbon Dioxide. Journal of Pharmaeutical Sciences, 1997; 86, . 885– 890.

35. Palakodaty S, York P. Phase behavioural effects on particle formation process using supercritical fluids. Pharm Res. 1999; 16, .976–985.
36. Takayama K., Nambu N., Nakai T. Factor affecting the dissolution of ketoprofen from solid disoersion in various water soluble polymers. Chem Pharm Bull. 1982; 30, .673-677.
37. Sharma D.K., Joshi S.B. Solubility enhancement strategies for poorly water soluble drug in solid dispersion: A Review. Asian Journal of Pharmaceutics. 2007;Vol 1, ..:9-19.
38. Ambike A.A., Mahadik K.R., Paradkar A. Spraydried amorphous solid dispersions of simvastatin, a low Tg drug: *In vitro* and *in vivo* evaluations. Pharm Res. 2005; 22, 990–998.
39. Minhaz MA., Rahman MM., QamrulAhsan M., HabiburRahman, Chowdhury R.. Enhancement of solubility and dissolution properties of clonazepam by solid dispersions. Int. J. of Pharm. & Life Sci.,2012; 3(3), 1510-1518.
40. Rohini P, KiranKadali SDVS, BhagvanRaju M., Pavankumar K. Studies on Dissolution Enhancement of Itraconazole Using Water-Soluble Carriers. Inventi Rapid: Pharm Tech, 1(1).
41. Tantishaiyakul V., Kaenopparat N., Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. Int J Pharm. 181, 143-151.
42. Rodriguez-Espinosa C., Martinez-Oharriz M.C., Martin C., Goni MM., Velaz I., Sanchez M. Dissolution kinetics for coprecipitates of diflunisal with PVP K30. Eur J Drug Meta Pharmac. 1998; 23, .:109-112.
43. Dawei C., Xing L., Wenyan F. Studies on preparation and dissolution of solid dispersions of nifedipine-polyvinylpyrrolidone. Zhongguo Yaoxue Zazh., 2000; Vol 35;598-600.
44. Mao-quan C., Song L., Hong-chen G., Guo-jie L. Study on solid dispersions of tanshinone. Huadong Ligong Daxue Xuebao. 2001; 27, .191-194.
45. Xue K, Qineng P., Aiming S. Formation and solubilization of cefuroxime axetil solid dispersion. Zhongguo Yaoxue Zazhi. 2001; 36, 106-108.
46. Marin M., Teresa Margarit M., Salcedo V., Gloria E. Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone. II Farmaco. 2002; 57, 723-727.
47. Li G, Shengrong G, Fengsheng Z. Effect of PVP K30 on solubility of daidzein. Zhongguo Yiyao Gongye Zazhi. 2003; 34, 273-275.

48. Gang H, Jianfeng Z, Hailiang C. Manufacture of solid dispersion tablets of nitrendipine and its dissolution in vitro. Huaxi Yaoxue Zazhi. 2003; 18, .28-29.
49. Ruxing W, Dawei C, Haiyang H, Kexin L. Preparation and dissolution of the solid dispersions of ketoprofen- polyvinylpyrrolidone. Shenyang Yaoke Daxue Xuebao. 2006; 23, .:201-204.
50. Fuzheng R, Qiufang J, Yanhui T, Yongjia S, Jialei C, Feng G, Jingbin C. Characteristics of bicalutamide solid dispersions and improvement of the dissolution. Drug Dev Ind Pharm. 2006; 32,.:967-972.
51. Jing Z. Zhao- Gang Y., Xiao-Mei C., Jia-Bei S., Gulistan A., Xuan Z., Qiang Z. Preparation and physicochemical Characterization of Solid Dispersion of Quercetin and Polyvinylpyrrolidone, Journal Chinese Pharma. Sci. 2007, 16, .51-56.
52. Mamatha T, Venkateswara RJ, Mallik B, Shagufta A, Shanthi M. Studies to enhance dissolution of Lansoprazole. Indian Pharmacist. 2008; 7, :65-70.