

Solid Dispersion Techniques: A Review

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Abstract: Solid dispersions have attracted significant interest as an efficient means of improving the dissolution rate and hence the bioavailability of a range of poorly water-soluble drugs. To improve dissolution of poorly water-soluble drugs and thus enhancing their bioavailability, the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state is used. So this process is known as solid dispersion. The one of the mainly challenging aspects in formulation development is solubility behavior of a drug. The number of poor water soluble compounds has very increased. Compared to conventional formulations such as tablets or capsules, solid dispersions prepared by various methods can be used which have numerous benefits over the above conventional dosage form. For the preparation of solid dispersions, few of the aspects are to be considered such as; selection of carrier and methods of physicochemical characterization. In this review, an emphasis is put on solubility, various types of solid dispersions, BCS classification, carriers, solid dispersion techniques, mechanism to enhance dissolution in solid dispersion, characterization, advantages, disadvantages and the use of the solid dispersions.

Keywords: dissolution rate, solubility, bioavailability, solid dispersion, carrier.

1. Introduction

The enhancements of oral bioavailability of such weakly water-soluble drugs often demonstrate poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. Though, micronizing of drugs often leads to aggregation and agglomeration of particles, which results as poor wettability. Solid dispersions of poorly water-soluble drugs along with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The formation of solid dispersions as a practically viable method to improve bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt in nature, solubalization by co-solvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily be in the micronized state. A fraction of the drug might molecularly disperse in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The substantial improved surface area produces higher the dissolution rate and the bioavailability of poorly water-soluble

drugs. Adding up, in solid dispersions, a part of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitate as a very fine colloidal particles or oily globules of submicron size. solid dispersion technique was initially demonstrated by Sekiguchi and Obi. They proposed the more rapidly absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released in the fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. The likelihood of using solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced.

A solid dispersion technique has been used by different researchers who have reported encouraging results amid different drugs. The initial drug whose bioavailability was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Method for the preparation of solid dispersions, Lyophilization has been thought of as a molecular addition technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and afterward sublimed under vacuum to obtain a lyophilized molecular dispersion (Lin, 1980). [29]

The oral route is the effortless and easiest mode of administering drugs over other types of dosage forms. The oral dosage forms have a lot of advantages like accurate dosage, less bulk, greater stability and easy production is possible. At the present time, to the formulation scientists in the pharmaceutical industry one of the most key challenges is formulation of poorly soluble compounds for oral delivery. Almost 40% of well-known potential new drug by pharmaceutical industry are poorly water soluble. Deprived water soluble compounds a big dose is required to create desirable effect for the poor water soluble drug as they show decreased release rate and meager bioavailability. But high dose may leads to toxicity of the drug. So the most excellent option for increasing release rate is improvement of the solubility through formulation approaches. [12].

At what time aqueous solubility of a drug is less than 100µg/ml, Poor dissolution: Intrinsic dissolution rate <0.1mg/cm²/min, large molecular weight: (>500), Self-involvement and aggregation and high crystal energy (melting

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point >200°C is said to be poorly soluble [12].

Factor that Affecting the Drug Absorption: [30]

The Pharmaceutical factors:

It includes the physiological properties of the drug substances and formulation aspects.

The Physicochemical properties of drug substances.

- Drug solubility & dissolution rate
- Polymorphism
- Solvates & hydrates
- Particles size & effective surface area
- Ionization state
- Salt form of drug
- Drug pka & lipophilicity

The Formulation Factors:

- Disintegration time
 - Method of granulation
- Product age & storage conditions
- Manufacturing variables
 - Compression force
- Nature & type of dosage form
- Pharmaceutical ingredients

The Patient related factors (physiological factors):

Physiology of the Membrane:

- Nature of cell membrane
- Transport processes

The motility Gastro-Intestinal:

- Gastric emptying rate
- Intestinal motility
- Drug stability in GIT
- pH of GIT
- Surface area of GIT
- Intestinal transit
- Blood flow to GIT.
- Effect of food
- Solubility:

Solubility of the substance is the quantity that has passed into solution when equilibrium is attained among the solution and excess, i.e., undissolved substance, at a set temperature and pressure. The material to be dissolved is called as 'solute' and the dissolving liquid in which the solute is dissolved is called as 'solvent', which together form a 'solution'. Definition of different solubility terms is given in table.

Methods for Solubility improvement of Poorly Soluble Drug: [34]

The method that have commonly been used to beat drawbacks associated with poorly water- soluble drugs, in general includes [30].

The Chemical Modifications:

- Salt Formation
- Co-crystallization
- Co-solvency
- Hydrotropic
- Solubilizing agent
- Nanotechnology

The Physical Modifications:

- Particle size reduction
- Modification of the crystal habit
- Complexation
- Solubilization by surfactants
- Drug dispersion in carriers i.e., Solid dispersions

Some Others:

- Supercritical fluid method
- Spray freezing into liquid and Lyophilization
- Evaporative precipitation into aqueous solution
- Hot melt extrusion
- Electrostatic spinning method
- Direct capsule filling
- Polymeric Alteration
- High- Pressure Homogenization
- Inclusion Complexes

The Biopharmaceutical Classification System (BCS): The BCS was initial devised in 1995 by Amidon and his co-workers. According to the BCS, drug substances can be classified as given in table.

Table 2
Classification of drugs as per BCS system [12], [34]

Class	I	High	Solubility	High	Permeability
Class	II	Low	Solubility	High	Permeability
Class	III	High	Solubility	Low	Permeability
Class	IV	Low	Solubility	Low	Permeability

Raising the solubility and dissolution rate of the class II drug in the gastro-intestinal liquid the bioavailability may be enhanced. Mainly for drugs with low gastrointestinal solubility drug release is a critical and limiting step for oral drug bioavailability. It is probable to improve their bioavailability and decrease side effects, by improving the drug release profile

Table 1
Definition of different solubility terms [37]

Description of forms(solubility definition)	Parts of solvent required for one part of solute	Solubility range(mg/ml)	Solubility assigned(mg/ml)
Very soluble (VS)	Less than 1	More than 1000	1000
Freely soluble (FS)	1 to 10	100 -1000	100
Soluble	30-Oct	33-100	33
Sparingly soluble (SPS)	30-100	Oct-33	10
Slightly soluble (SS)	100-1000	10-Jan	1
Very slightly soluble (VSS)	1000-10000	0.1-1	0.1
Practically insoluble (PI)	More than 10000	Less than 0.1	0.01

of these drugs.

World Health Organization (WHO) list of Essential Medicines has assigned BCS classification on the base of data available in the public domain. Orally administered drugs out of 130 on the WHO list, 61 could be classified with certainty. 86% of these drugs belong to class I, 17% to class II, 40% to class III and 11% to class IV.

The class II & class IV compounds are highly needy on the bioavailability which ultimately depends on solubility. Therefore, a better understanding of dissolution and absorption behavior of drugs with low aqueous solubility is required to fruitfully formulate them into bioavailable drug products [24].

What is Solid Dispersion?

A process in which one or more active ingredients in an inert carrier or matrix at solid state are prepared by using different techniques for example the melting (fusion), solvent evaporation and melting-solvent method. In a solid diluent or diluents the dispersion of a drug or drugs by traditional mechanical mixing is not included in this category. The solid dispersions may also be called solid-state dispersions [7].

What are the Types of Solid Dispersions?

1. On the basis of carrier used [20]
2. On the basis of their molecular arrangement [4]

On the basis of carrier used:

On the base of carrier used solid dispersions can be classified into three generations:

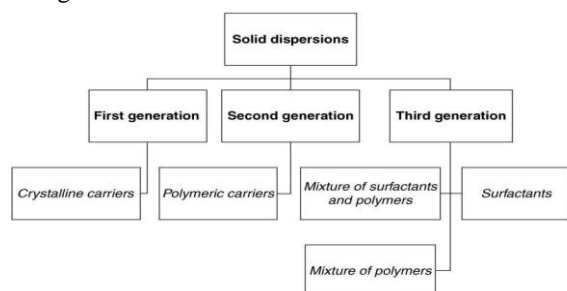


Fig. 1. Types of solid dispersions

First generation:

By crystalline carriers for example urea and sugars, first generation solid dispersions were prepared which were the first carriers to be engaged in solid dispersions. They have the demerits of forming crystalline solid dispersions and did not release the drug as quickly as amorphous ones. The first description of solid dispersions was from Sekiguchi and Obi in 1961. They noted that the formulation of eutectic mixtures improves the rate of drug release and consequently, the bioavailability of poorly water soluble drugs. Within the same decade, numerous solid dispersions were described using poorly water soluble drugs, such as sulfathiazole and chloramphenicol using urea as high water soluble carrier. These solid dispersions produced faster release and higher bioavailability than conventional formulations of the same drugs. The minute particle size and the better wettability of the drug were the major reasons for the observed improvements in bioavailability.

Later on, Levy and Kaning have developed solid dispersion systems, containing mannitol as carrier, by preparing solid solutions through molecular dispersions instead of using eutectic mixtures. The observed improvements were attributed to faster carrier dissolution, releasing microcrystals as 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 were the initial carriers to be used in solid dispersions. They have some disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones [35], [36], [25], [22].

Second generation:

The Second generation solid dispersions comprise amorphous carriers instead of crystalline carriers which are usually polymers. These polymers include synthetic polymers for example povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates as well as natural products base polymers such as hydroxypropylmethyl-cellulose (HPMC), ethyl cellulose, and hydroxypropylcellulose or starch derivatives like cyclodextrins. In the late sixties it was experiential that solid dispersions, where the drug was maintained in the crystalline state, might not be as effective as the amorphous, because the previous were more thermodynamically stable. Therefore, a second generation of solid dispersions appeared, containing amorphous carriers instead of crystalline. Certainly, the most common solid dispersions do not use crystalline carriers except amorphous. The drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers. Polymeric carriers have been the most successful for solid dispersions, as they are able to originate amorphous solid dispersions. They are separated into fully synthetic polymers and natural product-based polymers. Completely synthetic polymers include povidone (PVP) polyethyleneglycols (PEG) and polymethacrylates [14], [17], [21], [28], [32], [33], [39], [41].

The Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivatives, similar to cyclodextrins. Amorphous solid dispersions can be classified according to the molecular interaction of drug and carriers in solid solutions, solid suspensions or a mixture of together. Within amorphous solid solutions, drug and carrier are totally miscible and soluble, originating a uniform molecular interaction among them. The drug and carrier interface energy is extremely elevated, resulting in a really true solution.

Use of polymers in the formulation of a true solid solution creates an amorphous product in which the crystalline drug is dissolved. Such type of amorphous solid dispersion is uniform on a molecular level. So, only single phase is present. Amorphous solid suspensions occur when drug has narrow carrier solubility or a tremendously high melting point. Molecularly, obtained dispersion does not have a harmonized structure, but is composed of two phases. Small drug particles, when dispersed in polymeric carriers, are able to give an

amorphous final product. When a drug is both dissolved and suspended in the carrier, an assorted structure is obtained with mixed properties of amorphous solid solutions and amorphous solid suspensions. In second generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in the carrier. These systems are able to cut the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water soluble carrier, to provide better wettability and dispersibility of the drug by the carrier material, and to create amorphous forms of the drug and carriers. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile. [5], [8], [16], [40], [42], [43].

Third generation:

Newly, it has been exposed that the dissolution profile can be enhanced if the carrier has surface activity or self-emulsifying properties, then third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to attain the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as inulin, inutec SP1, compritol 888 ATO, gelucire 44/14 and poloxamer-407 as carriers was shown to be effective in originating high polymorphic purity and enhanced in vivo bioavailability. The association of amorphous polymers and surfactants has also been reported. For instance, the dissolution rate and bioavailability of LAB68, a poor water soluble drug, were improved after being dispersed in a mixture of PEG and polysorbate 80. The bioavailability of such solid dispersion was 10-fold higher compared to the dry blend of micronized drug. In addition, the solid dispersion system was physically and chemically steady for at least 16 months. HPMC was also associated with poloxamer and polyoxyethylene hydrogenated castor oil to prepare an amorphous felodipine solid dispersion. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles. [6], [9], [11], [44].

On the basis of their molecular arrangement:

Solid dispersions can be classified in following types:

The Eutectics Systems:

Such mixture consists of two compounds which in the fluid state are completely miscible except in the solid state only to a very partial extent. Through rapid solidification of the merged melt of two components these are formulated and that explain complete liquid miscibility and minor solid-solid solubility .31

Thermodynamically, such type of system is a closely blended physical mixture of two crystalline components. When the mixture of A and B with a fix composition is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. When a mixture having slightly soluble drug and carrier as an inert substance and highly water soluble is dissolved in an aqueous medium, the carrier will

dissolve rapidly, releasing extremely fine crystals of the drug [34].

Amorphous precipitation in a crystalline carrier:

In the crystalline carrier the drug may also precipitate in an amorphous form instead of simultaneous crystallization of the drug and the carrier (eutectic system). The amorphous solid state. The high energy condition of the drug in this system generally make much greater dissolution rates than the corresponding crystalline forms of the drug [34].

Glass solutions and suspensions:

These are the uniform glassy system in which solute is dissolved in glass carrier. Glass suspensions are blend in which precipitated particles are suspended in glass solvent. Lattice energy is much lower in glass solutions and suspensions. Melting points of glasses is not sharp while they soften increasingly on heating. Examples of carriers that form glass solutions and suspensions are citric acid, PVP, urea, PEG, sugars such as dextrose, sucrose, and galactose [31].

Solid Solutions:

In this system a uniform one phase system is shaped when the two components crystallize jointly. The particle size of the drug is reduced to its molecular size in the solid solution. Therefore, a quicker dissolution rate is achieved in a solid solution than the corresponding eutectic mixture. Solid solutions can be classified as continuous or discontinuous according to the degree of miscibility of the two components. In incessant solid solutions, the two components are miscible in the solid state in all proportions [23].

Continuous Solid Solutions:

The components are miscible in all proportions in a constant solid solution. Hypothetically, this means that stronger the bonding strength among the two components than the bonding strength connecting the molecules of each of the individual components .18

Discontinuous Solid Dispersions: [30]

Solubility of every of the components in the other component is partial in the case of discontinuous solid solutions. One of the solid components is totally dissolved in the other solid component in these regions. The joint solubilities of the two components start to reduce below a certain temperature. Goldberg reported that the term solid solution' should only be applied when the mutual solubility of the two components exceeds 5%.

The solid solutions are classified as substitution or interstitial according to the principle of molecular size of the two components.

Substitutional crystalline solid solutions:

A substitutional crystalline solid dispersion which the solute molecules substitute for the solvent molecules in the crystal lattice. Substitution is merely possible when the size of the solute molecules differs by less than 15% or so from to the

solvent molecules [30], [31].

Mechanism of enhanced dissolution in solid dispersion:
[12], [30]

A number of factors may influence or increase the dissolution rate for solid dispersion. These factors include the following:

Reduced Particle size or Reduced Agglomeration:

Both are related to reduction of particle size and increase in the exposed surface area of the drug. Size reduction has been considered to be result of eutectic or solid solution formation. It has also been optional that to the dissolution medium as physically separate units the presentation of particles may reduce aggregation. For solid dispersion many of the carriers used may have some wetting properties and may direct to cut agglomeration and increase surface area by improved wetting.

Increased solubility or Dissolution rate of the drug:

The solubility of the drug may increase by using many of the carriers. So carrier controlled the release of drug that is controlled by the carrier and is independent of drug properties. Secondly some system demonstrates release behaviour that is dependent on the properties of the drug rather than polymer.

*From crystalline to amorphous state transformation/
Formation of high Energy State:*

Amorphous drugs contain the higher energy state, least stability and can be considered as cooled liquids. The energy required to transfer a molecule from crystal is greater than mandatory for non-crystalline (amorphous) solid so they have greater aqueous solubility than crystalline forms. For example, the solubility of amorphous state of novobiocin is 10 times more than crystalline form.

Wetting:

The liquid forms a film over the surface of the solid while a strong affinity exists among a liquid and solid. When this affinity is non-existent or weak the liquid has difficulty dispensing the air and there be present an angle of contact among the liquid and the solid. This contact angle results from an equilibrium involving three interfacial tensions [3].

Interstitial Crystalline Solid Solution: [30], [31]

In interstitial solid solutions, dissolved molecules inhabit the interstitial spaces between the solvent in the crystal lattice. The solute molecules be supposed to have a molecular diameter that is no greater than 0.59 times than that of the solvent molecular diameter and the volume of the solute molecules should be less than 20% of the solvent.

Different Techniques for Solid Dispersions: [12]

Various methods of preparation solid dispersions are summarized as:

- Solvent evaporation
- Hot-melt extrusion
- Fusion method
- Solvent melt method

- Kneading technique
- Inclusion complexes
- Direct capsule filling
- Surface active carriers
- Particle size reduction
- Adsorption on insoluble carriers/fluidized bed system
- Solid deposition on super disintegrants
- Melt agglomeration method
- Dropping method

Solid Dispersion Advantages: [30], [34]

The solid dispersions technique offers the following pharmaceutical advantages.

- Solid dispersion method is useful to enhance solubility and bioavailability of poorly water soluble drugs.
- It is easier to create and is more applicable
- It leads to increase in extent and rate absorption of a drug, hence rapid dissolution rate occurs.
- Transformation of fluid form of drug into solid form.
- Control of various parameters like molecular weight, composition, particle porosity and wettability can enhance the bioavailability of poorly water soluble drugs.
- It is easier to create rapid disintegration oral tablets by solid dispersion.
- It is used to mask the bitter taste of drug.
- It is used to advance porosity of drug.

Solid Dispersion Disadvantage: [30], [34]

The disadvantages of solid dispersion are enlisted below:

- It direct to the poor scale-up for the purpose of manufacturing.
- The polymers used in solid dispersion can absorb moisture and cause phase-separation, crystal development and convert amorphous form into crystalline form. Thus result in decrease solubility and dissolution rate.
- It is laborious technique of preparation.
- It causes reproducibility of physicochemical characteristics.

Solid Dispersion Applications: [3], [18]

- The Solid dispersion systems were exposed to provide the bio available oral dosage forms for the anti-cancer drugs, which might be substituted for the standard injections to improve the patient compliance & comfort.
- Solid dispersion also proceeds as the functional carriers that offer the additional benefit of the targeting the release of the highly soluble forms of the poorly water soluble drugs for absorption to an optimum site.
- The solid dispersion systems were also established to decrease the food effects on the drug absorption, thus by increasing the convenience of the drug therapy as it is the need for a number of drugs to be taken with food was eliminated.
- The solid dispersion formulations were established to

accelerate the onset of action for the drugs such as NSAIDS [non-steroidal anti-inflammatory drugs] where immediate action is crucial in relieving acute pain and inflammation.

- The enhanced absorption efficiency was demonstrated for the solid dispersion systems that allows for the reduction in the content of the active agent per dose thus it decreases the cost associated with these drug therapies.
- The dry powder formulation consisting of the solid dispersion for use as inhalation is prepared in improving the immunosuppressive therapy in the lung transplant patients. Several problems can be avoided which includes use of local anesthesia & irritating solvents [38]

Solid Dispersions Limitations:

- Laborious and expensive methods of preparation.
- Reproducibility of physicochemical characteristics.
- Complexity in incorporating into formulation of dosage forms.
- Scale-up of manufacturing process.
- Constancy of the drug and vehicle [20]

A Carrier Selection:

A carrier should meet the following criteria to be suitable for increasing the dissolution speed of a drug.

- Liberally water-soluble with intrinsic rapid dissolution properties.
- Non-toxic and pharmacologically inert.
- Heat stable with a low melting point for the melt method.
- Soluble in a range of solvents.
- Able to preferably raise the aqueous solubility of the drug and
- Chemically compatible with the drug and not form a strongly bonded complex with the drug [13].

Generations of Carriers: [13], [34]

First generation carriers:

Example: Crystalline carriers: Urea, Sugars, Organic acids.

Second generation carriers:

As, fully synthetic polymers include povidone (PVP), polyethyleneglycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed by cellulose derivatives, such as hydroxypropylmethylcellulose (HPMC), ethylcellulose or hydroxypropylcellulose or starch derivatives, like cyclodextrins.

Third generation carriers:

As, Surface active self-emulsifying carriers: Poloxamer 408, Tween 80, and Gelucire 44/14 [34].

Solvents Selection: [13]

Solvent to be incorporated for the formulation of solid dispersion should have the following criteria:

- Both drug and carrier should be dissolved.
- Toxic solvents to be let alone due to the risk of residual levels after preparation e.g. chloroform and dichloromethane.
- Ethanol can be used as alternative as it is not as much of toxic.
- Water based systems are preferred.
- Surfactants are used to create carrier drug solutions but as they can reduce glass transition temperature, so care must be taken in to consideration.

Common solvents used are given in table.

Table 3
Different solvents used in the solid dispersions [13]

Solvent	Melting Point (°C)	Boiling Point (°C)	Vapour pressure at 25°C (pka)
Water	0	100	3.16
Methanol	-93.9	65	16.9
Ethanol	-117	78.5	5.79
Chloroform	-63	62	26.1
DMSO	19	189	0.08
Acetic acid	17	118	1.64

Characterization:

Solid dispersion is characterized by means of different techniques such as; Differential Scanning Calorimetry, Differential Thermal Analysis, Thermo-Microscopic Methods, X- ray Diffraction, Fourier Transform Infra-Red Spectroscopy (FT- IR), Scanning Electron Microscopy (SEM) and dissolution studies.

Different techniques are:

Differential Scanning Calorimetry (DSC):

DSC can be used to determine crystallinity by quantifying the temperature associated with melting (fusion) of the material. DSC is a well-known technique that measures heat flow into or out of a material as a function of time or temperature.

Differential Thermal Analysis (DTA):

In differential thermal analysis, the difference in heat among the sample and a thermally inert reference material is measured as a function of temperature. With a corresponding deviation of sample heat from that of the reference any transition that the sample undergoes outcome in liberation or absorption of energy by the sample. Whether the transition temperature is exothermic or endothermic is shown by plot of the degree of difference temperature versus the programmed temperature. In constructing phase diagram of high reproducibility; a higher temperature range is permitted, greater resolution obtained is the main advantage of this technique. A sample size of less than 1 mg can be used [7].

Thermo-Microscopic Methods:

In this method to learning the phase diagrams of binary systems hot stage microscope is used. The physical mixture or

dispersion (approx 1 mg) on a slide is heated at the rate of 1-5°C per minute. The melt and melting points are then recorded by visual observation. This method requires only a small amount of sample but it is limited to thermally stable compounds only. To characterize difflunisal-PEG solid dispersion this technique has been used [13].

X-ray Diffraction:

The X-Ray diffraction technique is a very significant and efficient tool in studying the physical nature of solid dispersions. Freshly, it was used to study binary eutectic systems. The diffraction method is also particularly valuable in detecting compound or complex formation since its spectra or lattice parameters are markedly diverse from those of pure components. The biggest drawback of using the diffraction method to study dispersion arrangement is its frequent inability to differentiate amorphous precipitation from molecular dispersion if the lattice parameter of the solvent component is not changed [1].

Dissolution Studies:

Dissolution study is carried out to establish the rate and extent of dissolution. The dissolution study of solid dispersion was performed on the USP- type II paddle apparatus at 37±0.20°C. Drug was dispersed in medium. Sample was taken time to time, filtered and analyzed for drug contents by measuring the absorbance at suitable wavelength using UV visible Spectrophotometer. [1], [27].

Fourier Transform Infra-Red Spectroscopy (FT-IR):

FT-IR spectroscopy can be used to find the possible interactions between the drug and the carrier in the solid state on FT-IR spectrophotometer by the conventional KBr pellet method [27].

Scanning Electron Microscopy (SEM):

SEM is useful in ascertaining the morphology, particle dimension of solid particles and sometimes polymorphism of drug. The fine dispersion of drug particles in the carrier matrix may be visualized. The application of the electron microscope method, though usually partial to chemicals with high resolution [15], [24].

2. Conclusion

The Solid dispersion systems have been realized as tremendously useful means in improving the dissolution properties of poorly water-soluble drugs. In the current years, a great deal of information has been accumulated concerning solid dispersion skill, but their commercial application is limited. A variety of process have been tried newly to beat the limitation and make the preparation almost feasible. The troubles involved in incorporating into formulation of dosage forms have been steadily resolved with the advent of alternative strategies. These comprise methods like spraying on sugar beads and direct capsule filling. Although there are some hurdles like scale up and manufacturing cost to beat, there lies a great promise that solid dispersion technology will hasten the

drug release profile of poorly water soluble drugs.

References

- [1] Aggarwal S, Gupta GD, Chaudhary S. Solid Dispersion as an Eminent Strategic Approach in Solubility Enhancement of poorly Soluble Compounds. *J Pharm Sci Res* 2010;1(8):1-14.
- [2] Argade PS, Magar DD, Saudagar RB. Solid Dispersion: Solubility Enhancement Technique for Poorly Water Soluble Drugs. *J Adv Pharm Edu Res* 2013;3(4):427-439.
- [3] Bhusnure OG, Kazi PA, Gholve SB, Ansari A, Kazi SN. Solid Dispersion: An Ever Green Method for Solubility Enhancement of Poorly Water Soluble Drugs *Int J Res Pharm chem* 2014;4(4):906-918.
- [4] Bhut VZ, Prajapati AB, Patel KN, Patel BA, Patel PA. Solid Dispersion as a Strategy to Enhance Solubility: A Review Article. *Int J Pharm Res Scholars* 2012;3(4):277-283.
- [5] Ceballos, A., et al. (2005). Influence of formulation and process variables on in vitro release of theophylline from directly-compressed Eudragit matrix tablets. *Fairmaco.*, 60: 913–918.
- [6] Chauhan, B., et al. (2005). Preparation and evaluation of glibenclamide polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur. J. Pharm. Sci.*, 26: 219–230.
- [7] Chiou WL, Riegelman S. Pharmaceutical Applications of Solid Dispersion Systems. *J Pharm Sci* 1971;60:1281–1302.
- [8] Chiou, W.L., and Riegelman, S., (1970). Oral absorption of griseofulvin in dogs: increased absorption via solid dispersion in polyethylene glycol 6000. *J. Pharm. Sci.*, 59: 937–942.
- [9] Cutler, L., et al. (2006). Development of a P- glycoprotein knockout model in rodents to define species differences in its functional effect at the blood-brain barrier. *J. Pharm. Sci.*, 95: 1944–1953.
- [10] Damian, F., et al. (2000). Physicochemical characterization of solid dispersions of the antiviral agent UC-781 with polyethylene glycol 6000 and Gelucire 44/14. *Eur. J. Pharm. Sci.*, 10: 311–322.
- [11] Dannenfels, R.M., et al. (2004). Development of clinical dosage forms for a poorly water soluble drug I: Application of polyethylene glycol-polysorbate 80 solid dispersion carrier system. *J. Pharm. Sci.*, 93: 1165–1175.
- [12] Dharna A, Neelam S, Singh S, Aroraint S. Solid dispersions: A review on drug delivery system and solubility enhancement. *J Pharm Sci Res* 2017;5(3):1-9.
- [13] Dixit AK, Singh RP, Stuti S. Solid Dispersion -A Strategy for Improving the Solubility of Poorly Soluble Drugs. *Int J Res Pharm Biomed Sci* 2012;3(2):90-964.
- [14] Drooge, J.V., et al. (2006). Characterization of the Mode of Incorporation of Lipophilic Compounds in Solid Dispersions at the Nanoscale Using Fluorescence Resonance Energy Transfer (FRET). *Macromol. Rapid Commun.*, 27: 1149–1155.
- [15] Gupta NB, Sharma P, Bhandari N, Singh K. To Enhance the Solubility of Poorly Water Soluble Drugs by Using Solid Dispersion: A Review. *Int Res J Pharm Appl Sci* 2013; 3(2):27-32.
- [16] Guyot, M., et al. (1995). Physicochemical characterization and dissolution of norfloxacin/cyclodextrin inclusion compounds and PEG solid dispersions. *Int. J. Pharm.*, 123: 53–63.
- [17] Hasegawa, S., et al. (2005). Effects of water content in physical mixture and heating temperature on crystallinity of troglitazone-PVP K30 solid dispersions prepared by closed melting method. *Int. J. Pharm.*, 302: 103–112.
- [18] Kadam V, Bharakhad VS, Jadhav SB, Kute A, Chintale AG. Role of Solid Dispersion In Improving Solubilty And Dissolution Rate: A Comprehensive Review *World J Pharm Res* 2014;3(1):1841-1860.
- [19] Kalia A, Poddar M. Solid Dispersions: An Approach Towards Enhancing Dissolution Rate *Int J Pharm Pharm Sci* 2011;3(4):9-19.
- [20] Kapoor B, Kaur R, Behl H, Kour S. Solid Dispersion: An Evolutionary Approach for Solubility Enhancement of Poorly Water Soluble Drugs. *Int J Recent Adv Pharm Res* 2012;2(2):1-16.
- [21] Karavas, E., et al. (2006). Application of PVP/HPMC miscible blends with enhanced mucoadhesive properties for adjusting drug release in predictable pulsatile chronotherapeutics. *Eur. J. Pharm. Biopharm.*, 64: 115–126.
- [22] Kaning, J.L., (1964). Properties of Fused Mannitol in Compressed Tablets. *J. Pharm. Sci.*, 53: 188–192.
- [23] Kim KT, Lee JY, Lee MY, Song CK, Choi J, Kim DD. Solid Dispersions as a Drug Delivery System. *J Pharm Investig* 2011;41(3):125-142.

- [24] Kumavat SD, Chaudhari YS, Badhe M, Borole P, Shenghani K. Physical Stability of Amorphous Solid Dispersion: A Review. *Int J Pharm Archive* 2013;2(5): 129-136.
- [25] Levy, G., (1963). Effect of particle size on dissolution and gastrointestinal absorption rates of pharmaceuticals. *Am. J. Pharm. Sci.*, 135: 78–92.
- [26] Li, F.Q., et al. (2006). In vitro controlled release of sodium ferulate from Compritol 888 ATO-based matrix tablets. *Int. J. Pharm.*, 324: 152–157.
- [27] Luhadiya A, Agrawal S, Jain P, Dubey PK. A Review on Solid Dispersion. *Int J Adv Res Pharm Biosci* 2012;1(2): 281-291.
- [28] Lloyd, G.R., et al. (1999). A calorimetric investigation into the interaction between paracetamol and polyethylene glycol 4000 in physical mixes and solid dispersions. *Eur. J. Pharm. Biopharm.*, 48: 59–65.
- [29] Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, *J. Am. Chem. Soc.*, 19: 930-934.
- [30] Patil AN, Shinkar DM, Saudagar RB. Review article: solubility Enhancement by solid dispersion. *Int J Curr Pharm Res* 2017;9(3):15-18.
- [31] Patil RM, Maniyar AH, Kale MT, Akarte AM, Baviskar DT. Solid Dispersion: Strategy to Enhance Solubility. *Int J Pharm Sci Rev Res* 2011;8(2):66-73.
- [32] Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. *J. Pharm. Sci.*, 58: 1505–1510.
- [33] Pokharkar, V.B., et al. (2006). Development, characterization and stabilization of amorphous form of a low T_g drug. *Powder Technol.*, 167: 20–25.
- [34] Rawat A, Verma S, Kaul M, Saini S. Solid Dispersion: A Strategy for Solubility Enhancement. *Int J Pharm Tech* 2011;3(2):1062-1099.
- [35] Sekiguchi, K., and Obi, N., (1964). Studies on Absorption of Eutectic Mixture. II. Absorption of Fused Conglomerates of Chloramphenicol and Urea in Rabbits. *Chem. Pharm. Bull.*, 12: 134–144.
- [36] Sekiguchi, K. and Obi, N., (1961) Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. *Chem. Pharm. Bull.*, 9: 866–872.
- [37] Stegemanna S, Leveillerb F, Franchic D, Jongd de H, Lindéne H. When Poor Solubility Becomes an Issue: From Early Stage to Proof of Concept. *Euro J Pharm Sci* 2007;3(1):249-261.
- [38] Upadhye SS, Kothali BK, Apte AK, Kulkarni AA, Khot VS. A Review on Solid Dispersion. *Adv J Pharm Life sci Res* 2015;3(4):33-45.
- [39] Urbanetz, N.A., (2006). Stabilization of solid dispersions of nimodipine and polyethylene glycol 2000. *Eur. J. Pharm. Sci.*, 28: 67–76.
- [40] Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. *Int. J. Pharm.*, 310: 220–229.
- [41] Vilhelmsen, T., et al. (2005). Effect of a melt agglomeration process on agglomerates containing solid dispersions. *Int. J. Pharm.*, 303: 132–142.
- [42] Yao, W.W., et al. (2005). Thermodynamic properties for the system of silybin and poly (ethylene glycol) 6000. *Thermochim. Acta.*, 437: 17–20.
- [43] Yoshihashi, Y., et al. (2006). Estimation of physical stability of amorphous solid dispersion using differential scanning calorimetry. *J. Therm. Anal. Calorim.*, 85: 689–692.
- [44] Yuksel, N., et al. (2003). Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: in vitro and in vivo evaluation. *Eur. J. Pharm. Biopharm.*, 56: 453–459.