IJBPAS, July, 2021, 10(7): 2397-2417

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

DIFFERENT METHODS USED IN SOLID DISPERSION-A REVIEW

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Received 26th Aug. 2020; Revised 22nd Sept. 2020; Accepted 14th Oct. 2020; Available online 1st July 2021

https://doi.org/10.31032/IJBPAS/2021/10.7.5570

ABSTRACT

The solid dispersion system is improved the dissolution properties of poorly soluble drugs. Poor aqueous solubility leads to physical composition evolution failures. Due to poor aqueous solubility of drugs in aqueous and low dissolution profiles in water gastrointestinal track fluid frequently directs to inadequate bioavailability. In present, a large amount of knowledge has been assembled about solid dispersion technology. Fusion method, solvent method, fusion solvent method, and supercritical fluid method, kneading method, melt extrusion method, spray-drying method, and dropping method, melt agglomeration method, are used to prepared the solid dispersion. Solid dispersion techniques have received significant interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. The term solid dispersion is dealing with a group of solid products which is consisting of at least two different components, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. Classifications of biopharmaceutical system (BCS) class II drugs include those drugs which have low solubility and high permeability. In this class Solid dispersion is used for enhancing the bioavailability and oral absorption. In oral administration; some new chemical entities are not well-absorbed. There are various methods used to control the problems related to bioavailability issues and oral intake problems are lower bioavailability, high intra and inter-subject variability, dose proportionality, micro-capsulation, pro-drug formation, complexation, use of surfactants, salt formation, lipids, cyclodextrins, permeation enhancers, micronization, nano-particles, solid dispersions, and self-emulsifying etc. In this review article discusses the solid dispersion technology, limitations, classification and various preparation techniques with its advantages and disadvantages.

Keywords: **Solid dispersion; Solubility; Bioavailability; Biopharmaceutical classification system; Dissolution**

INTRODUCTION

Solubility is a major physical-chemical element that affects the immersion of drugs and their therapeutic benefits. Poor aqueous solubility leads to physical composition evolution failures. Due to poor aqueous solubility of drugs in aqueous and low dissolution profiles in water gastrointestinal track fluid frequently directs to inadequate bioavailability **[1]**. The huge amounts of drugs undergo poor water solubility and it influences the absorption of drugs from gastrointestinal **[2]**. For poorly soluble drugs, dissolution is the rate-limiting step for the gastrointestinal absorption from solid dosage forms. Increasing the water solubility can increase the bioavailability of drugs and this enhanced form the drug can also be used the preparation of controlled release dosage form **[3].**

The solid dispersion method of water-insoluble drugs was established by Chiou Reilgelman **[4]**. The most preferred route for the intake of a drug is an oral route. The oral route is mostly preferred because this route is easy for the intake of a drug without any pain. But, some drugs create difficulties in to intake of a drug orally because of their poor solubility **[5]**. Best therapeutic levels are provided by high oral solubility and high bioavailability. The salt formation, size reduction, utilization of lipid vesicles, solvency, complexation, utilization of prodrugs, surfactants, etc. It has been utilized to enhance solubility to profiles **[6]**.

First of all, Sekiguchi and Obi founded the idea of solid dispersion **[7]**. Solid dispersion is defined when more the two active ingredients in an inert carrier or matrix at solid-state to enhance bioavailability. Solid dispersion can be produced by two methods (a) melting method, (b) solvent method. The drug is dispersed into solid diluents with the help of traditional mechanical mixing. The solid dispersions are also called solid-state dispersions. The solid-state dispersion was firstly used by Mayersohn and Gibaldi **[8, 9]**.

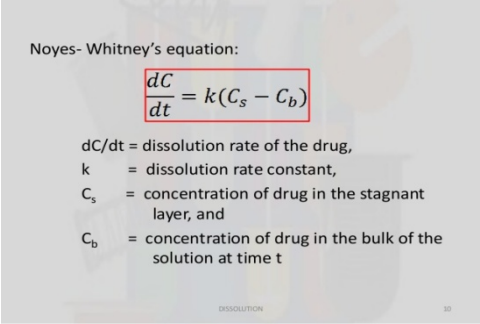
The solid-state dispersion process plays an important role in improving the dissolution properties of insoluble drugs **[10]**. The drug is rapidly dispersed in inert water-soluble carriers at solid-state in the solid dispersion method. Drug absorption can be restrained by various factors i.e. poor aqueous solubility and poor aqueous permeability from gastrointestinal tracts (GIT) **[11]**.

Solid dispersion is known as a group of solid products constituted of two components. These two components are: hydrophobic drug - The hydrophobic drug is distributed molecularly in amorphous particles (clusters) or crystalline particles. Hydrophilic matrix-the matrix is crystalline or amorphous **[12]**. Fusion method, solvent

method, fusion solvent method, and supercritical fluid method, kneading method, melt extrusion method, spray-drying method, dropping method, melt agglomeration method, are used to prepare the solid dispersion **[13]**.

The term solubility defined as the quantity of the drug that moves into the solution to set up the equilibrium at constant pressure and temperature and made a saturated solution is known as solubility. The Noyes-Whitney equation states that how the dissolution profile of very poorly soluble elements might be enhanced to decrease the barrier to oral availability **[2, 14]**.

Noyes-Whitney equation:



BIOPHARMACEUTICAL CLASSIFICATIONS:

a) Class I - high solubility, high permeability
b) Class II- low solubility, high permeability
c) Class III-high solubility, low permeability
d) Class IV-low solubility, low permeability **[15]**.

In the classifications of the biopharmaceutical system (BCS), class II drugs include those drugs which have low solubility and high permeability. In this class, Solid dispersion is used for enhancing bioavailability and oral absorption **[16]**. After intake of a drug orally, due to a solid dosage form arises productive and reproducible in vivo plasma absorption. The advantageous characteristics of the oral route are greater stability, easy manufacture, smaller bulk, accurate dosage. In oral administration; some new chemical entities are not well-absorbed. There are various methods used to control the problems related to bioavailability issues and oral intake problems are Lower bioavailability, high intra, and inter-subject variability, dose proportionality, micro-capsulation, pro-drug formation, complexation, use of surfactants, salt formation, lipids, cyclodextrins, permeation enhancers, micronization, nano-particles, solid dispersions, and self-emulsifying, etc **[17]**.

On the exposure of solid dispersion with aqueous media, it dissolves the carrier and drug released in fine colloidal particles. The release of fine colloidal particles increases surface area, dissolution rate, and enhances the bioavailability of poorly aqueous soluble drugs. A part of rapidly dissolved drug to saturate the GIT fluid in solid dispersions which enhance the drug

precipitation in the form of fine colloidal particles **[18]**.

CLASSIFICATIONS:

a) **First-generation solid dispersions**- by crystalline polymers prepared the 1st generation solid dispersions. Urea, Sugars, and Organic acids are the example of the crystalline polymer **[16]**. Crystalline polymers are more thermodynamically stable and they are not liberating the drug as rapidly as amorphous ones. This is the main disadvantage of forming crystalline solid dispersion **[19]**.

b) **Second generation solid dispersions**- Synthetic or natural product based polymers prepared the 2nd generation solid dispersions **[14]**. In the case of the second-generation solid dispersions, due to forced solubilization in the carrier, the drug remains in its supersaturated state **[19]**. These techniques are utilized to enhance wet-ability, and dispersibility of the drug by the carrier material, reduction in particle size to a molecular level, drug solubilization by the water-soluble carrier, to construct amorphous forms of the carriers and drug **[20]**. The natural polymers examples are polyethylene glycols, hydroxypropyl cellulose, polyvinyl pyrrolidones, and polymethacrylates, hydroxypropyl methylcellulose, ethyl cellulose, cyclodextrins, etc **[21]**.

c) **Third generation solid dispersions**- By surface-active self-emulsifying polymers prepared the 3rd generation solid dispersions. Some well-known examples of emulsifying polymers are Poloxamer 408, Tween80 and Gelucire 44/14, etc **[22]**. The solid dispersions of the third generation are used to find the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding the drug recrystallization **[23]**.

TYPES OF SOLID DISPERSION: [24]

Eutectic Mixtures – there are the two compounds which are utilized for the preparation of the eutectic mixture. They are entirely mixed in the liquid status but it has a limited area in the solid-state. These eutectic mixture techniques are mainly prepared by the fusion melt method. The quick solidification of fused melt of two components that show complete liquid miscibility is utilized for eutectic mixtures preparation **[25, 26] (Figure 1)**.

Amorphous Precipitation in Crystalline Matrix -The amorphous precipitation is quite the same as a eutectic mixture, but the only distinction is that the drug is precipitated out in an amorphous form

make it different from the eutectic mixture. In this form higher energy state of the drug produces maximum dissolution rates **[27]**.

Solid solutions -"A solid solution is a binary system comprising of a solid solute molecularly dispersed in a solid solvent" is called a solid solution. When two components crystallize together in a homogeneous one-phase system, the solid solution is also called molecular crystals dispersions **[28]**.

The solid solution divided into five parts -

Continuous solid solutions - The components are highly compatible and mixable in all parts. The bonding strength is stronger as compared to the single-component bonding is known as continuous solid solutions **[29] (Figure 2)**.

Discontinuous solid solutions- In discontinuous solid solutions, there is a limited solubility of each component with others **[30]**. It has two phases that can be used for drug to be molecularly dispersed is called discontinuous solid solution **[31] (Figure 3)**.

Substitutional crystalline solid solutions- Substitutional crystalline in the form of solid dispersion, having a crystalline structure, where solute molecules are the substitute for solvent molecules in the crystal lattice. The substitution takes place when the solute molecular size is less than 15% of the solvent molecule **[32] (Figure 4)**.

Interstitial crystalline solid solutions: In this type, the dissolved molecules occupied the space between the solvent molecules in the crystal lattice. The diameter of solute molecules should not more than 0.59 of solvent molecules **[29] (Figure 5)**.

Amorphous Crystalline Solid Solutions- In this type, the solute molecules are irregularly dispersed in the amorphous solvent are called amorphous crystalline solid solution **[33] (Figure 6)**.

Glass suspension – In this precipitated particles are suspended in glass solvent. The lattice energy is very lower in glass solution and suspension is called glass suspension **[27]**.

Glass solution – This is a homogenous mixture, in which a solute dissolves in a glassy solvent. Lattice energy is very lower in glass solution is called glass solution **[32] (Figure 7)**.

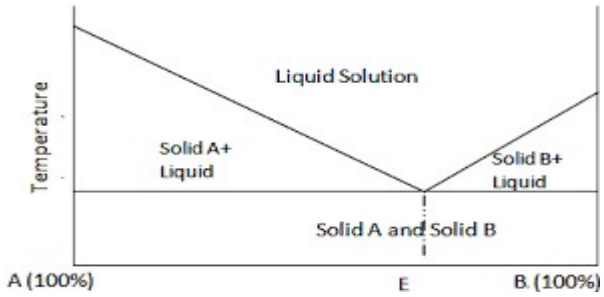


Figure 1: Phase diagram of the eutectic mixture with negligible solid

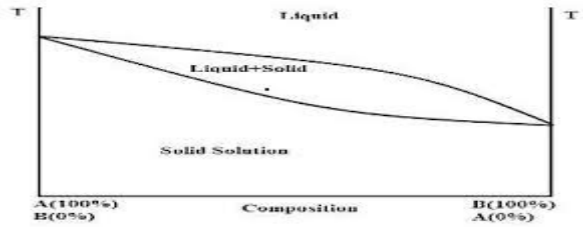


Figure 2: Phase diagram of a continuous solid solution

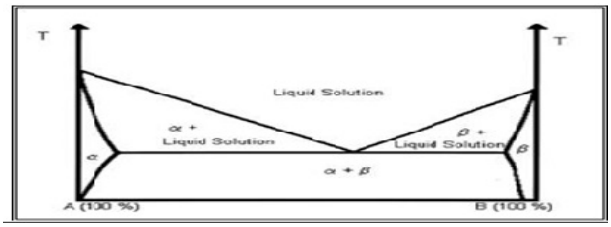


Figure 3: Phase diagram of discontinuous solid solution

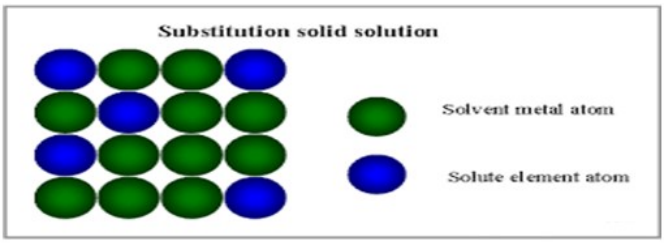


Figure 4: Phase diagram of substitution crystalline solid solutions

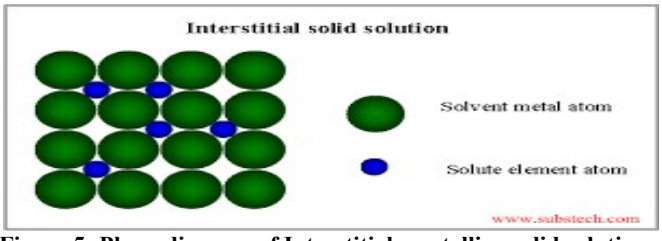


Figure 5: Phase diagram of Interstitial crystalline solid solutions

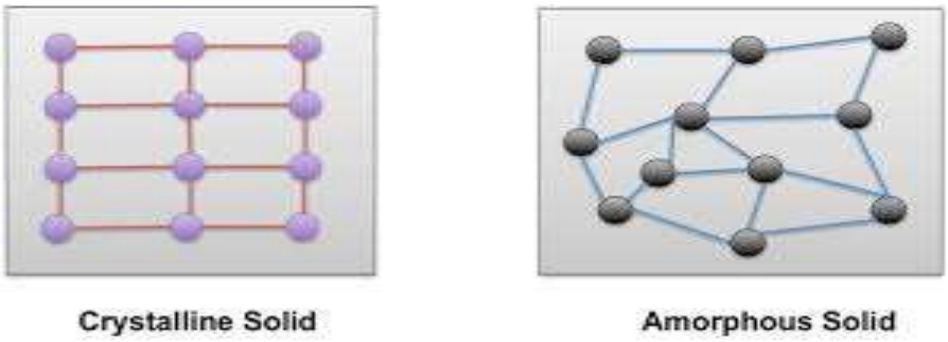


Figure 6: Phase diagram of amorphous crystalline solid solutions

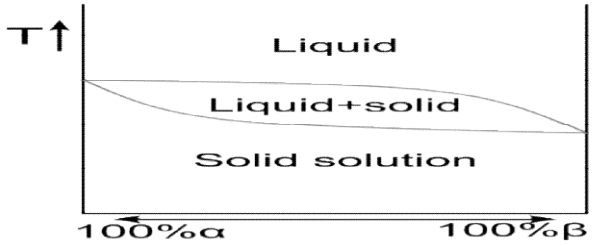


Figure 7: Phase diagram of glass suspension

ADVANTAGES OF SOLID DISPERSION:

- Rapid absorption and improved bioavailability and decrease collection when drugs interacting with hydrophilic carriers **[34]**.
- Reduction in particle size after drug dispersed in dissolution medium.
- Increased in dissolution rate, a high surface area also increased the bioavailability of the poorly water-soluble drugs **[35]**.
- Drug solubility increases as wet-ability increases.
- Use of carriers without surface activity.
- Carriers increase the drug dissolution rate by direct dissolution **[36]**.
- In solid dispersion, particles have a high degree of porosity.
- The absorbing of the solvent depends on the carrier properties to be used **[22]**.
- In crystalline state poor water solubility, in amorphous state higher solubility.
- In amorphous state enhancement of drug, release can usually be acquired using the drug moiety **[37]**.
- Decreased particle size, the increased surface area can increase the dissolution rate.
- Results improved bioavailability **[17]**.

DISADVANTAGES OF SOLID DISPERSION:

- Poor scale-up for the objective of manufacturing.
- The laborious and expensive process of preparation.
- The reproducibility of the physicochemical feature.
- The problem is incorporating into the formulation of dosage forms.
- The Stability of the drug and vehicle **[17, 38]**.

APPLICATIONS OF SOLID DISPERSION:

- To enhance, the solubility of poorly soluble drugs increases the rate of dissolution, absorption, and bioavailability.
- To decrease the side effect of various drugs.
- To reduce the smell and unpleasant taste of drugs.
- To improve the drug liberates from ointment creams and gels.
- To avoid unpleasant incompatibilities.
- To acquire an equal distribution of a small amount of drug in a solid-state.
- To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- To originate a rapid release primary dose in a sustained released dosage form.
- To originate sustained-release control of soluble drugs with poor soluble carriers.
- To reduce the use of drugs like morphine and progesterone **[39]**.

METHODS OF SOLID DISPERSION:

A. Solvent method- This solvent method was used to prepare solid dispersions of P-carotene-poly-vinylpyrrolidone **[42],** sulfathiazole-polyvinylpyrrolidone **[43],** griseofulvin-polyvinyl pyrrole-idone **[44],** reserpine-polyvinyl- pyrrolidone **[45],** and reserpine-deoxycholic acid **[46].** This method is used for the formation of mixed crystals of organic or inorganic compounds **[47].** The solvent method is formed by dissolving a physical mixture of two solid components in a common solvent, which has been followed by evaporation of the solvent [**42].** The first phase of the solvent methods includes a solution containing both matrix and material and drug. In the second phase of solid dispersion contains the removal of the solvent **[41].**

Advantages of solvent method-

- The lower temperature required for the evaporation of the organic solvents is the advantage of the solvent method, which leads to the

prevention of the thermal decomposition of carriers and drugs **[48]**.

Disadvantages of the solvent method-

- The cost of preparation is higher.
- The problem is completely removing the liquid solvent.
- The probable unfavorable effect of the supposed negligible amount of the solvent

on the chemical stability of the drug **[41]**.

B. Fusion Method- Sekiguchi and Obi was first who had suggested the fusion method melting method **[28].** The composition of a physical mixture of a drug and a water-soluble carrier obtained by heating in the fusion method. Fusion method followed by quick solidification in an ice-bath with vigorous mixing, when it direct melts. The total solid mass of the fusion method is pulverized, crushed, sieved. This fusion method is economic and very simple. This method is also called the melting method **[32]**.

Advantages of fusion method-

- This method is economic.
- This method solvent less procedure.
- Composition of solid dispersions by melting or fusion method **[49, 50]**.

Disadvantages of fusion method-

- The compatible drug and matrix are mixed well on heating **[40, 13]**.
- In the case of the fusion method, the high temperature in the drugs or carriers may decompose or evaporate. For example, succinic acid, used as a carrier for griseofulvin **[51]**, is quite volatile and also partially decomposes by dehydration near its melting point **[52]**.

C. Solvent evaporation method- In this method, the organic solvents evaporates on lower temperature by which the thermal decomposition of drugs or carriers can be stopped **[53]**. This method is made up of the solubilization of the drug. The carrier in a volatile solvent that is latter evaporated **[54, 55]**. When we dissolve the drug and the polymeric carrier in common solvents like ethanol, chloroform mixture of ethanol, and dichloromethane then it results in solvent evaporation solid dispersions **[56]**. Solid dispersion of furosemide with eudragit was

discovered by the solvent evaporation method **[57]**.

Advantages of solvent evaporated method-

- Thermal decomposition of drugs can be stopped by this method.
- Very low temperature is required for the evaporation process **[58]**.

Disadvantages of solvent evaporated method-

- There is a problem when drug and matrix mix together in a common solvent.
- The high cost of composition.
- It is a long procedure for the complete removal of the solvent from the final product.
- Phases can be separated during the drying procedure.
- The small amount of the solvent in the final product shows effects in chemical stability **[59]**.

D. Melting solvent method- In this method, the drug is dissolved in a suitable liquid solvent solution. Then dissolve into the melt of polyethylene glycol available below 700c without removing the liquid solvent. It has been representing that 510 % (w/w) of the liquid compound could be incorporated into polyethylene glycol 6000 without significant loss of its solid-state.

Advantages of melting solvent method-

- Have unique advantages for the fusion method and solvent evaporation methods.
- Very important for thermo labile drugs with a high melting point **[59]**.

Disadvantages of melting solvent method-

- Its adverse effect with the melting solvent method is limited for the drugs having a low therapeutic dose.
- The selected solvent or dissolved drug may be miscible with the melt of polyethylene glycol is not possible.

E. Kneading method-In the kneading method a mixture of drugs is accurately weighed and carrier in moistens with solvent and blended thoroughly in glass mortar **[31]**. In the kneading method, the carrier is penetrating the water and form a paste. The kneaded method is used for a specific time when the drug is included in it. The kneaded passed through the sieve when the mixture dried.

F. Melt extrusion method- This method is used for the production of diverse dosage forms in the

pharmaceutical industry e.g. sustained-release pellets **[60]**. In this method, the extruder is used for intense mixing of the components. Barrel, hopper, a kneading screw, heating jacket, and a die are components of the extruder. A mixture of both the carrier and drug is put into the hopper then moved through the screw and finally, it is extruded from the die.

Advantages of the melt extrusion method-

- The benefit of the melt extrusion process is that various shapes and configurations of the heated product matrix mixture are converted into ophthalmic patches, implants, or oral dosages.
- Production of solid dispersions on large-scale production can be achieved easily.
- Any shape can be produced by a melt extrusion method **[61, 62]**.

G. Spray drying method-Spray-drying is the most used method for solvent evaporation methods and is also used in the formulation of solid dispersions. In this method the drug is dissolved in a suitable solvent and carrier is dissolved in the water. These two solutions are mixed well until a clear solution is not obtained; sonication can use for the mixing. Then sprinkle it in a flux of heated air to eliminate the solvent. Because of its high specific surface area of the droplets, the solid dispersion is produced in seconds during solvent evaporates quickly, which can be easy enough to cease the phase separation **[65]**. The quantity of product content is dissolved in a suitable solvent and the amount of carrier needed is mixed in water. The sieving method is used to reduce in size of Solid dispersions **[60]**.

H. Dropping method solution- Ulrich et al. created the decay process in 1997 to promote the crystallization of different. The drop method is a novel process for the production of round particles from fused solid dispersions **[60]**. The dropping process does not use organic solvents so there is no solvent evaporation take place. It also avoids problems like pulverization and compressibility **[66]**.

I. Supercritical fluid method - The supercritical fluid methods are usually used with carbon dioxide. Carbon dioxide is used as a solvent, matrix, and substance are dissolved into an extensive vessel with lower pressure, and particulates are produced automatically, sprayed

across a nozzle. This process gives results in rapid refrigeration of the mixtures. Supercritical fluids approaches do not compulsorily allow organic solvents to be used and because carbon dioxide is considered environmentally sustainable, this technique is considered as "solvent-free". Supercritical fluid approaches are also classified as the quick expansion of the supercritical solution.

Advantages of Supercritical Fluid Method-

- The advantage of this approach is in which drug and matrix become saturated, precipitates, and form particles which is supercritical fluid method are anti-solvent quickly perforates in the form of droplets.

Disadvantages of Supercritical Fluid Method-

- It is a costly method; it is mostly used for dissolution for both drug and matrix i.e. organic solvents like dichloromethane or methanol **[67, 68]**.

J. Melt agglomeration method- In this method binder's act as carriers. solid dispersion is formulated by heating excipients and drugs together with a temperature above the melting point or by spraying a dispersion of drug in the molten binder on the heated excipients by utilizing a high shear mixer **[69]** or melt agglomeration method formulated by heating a mixture of the drug, carrier, and excipients to a temperature within or above the melting range of the carriers **[70]**. In the end, high homogenous distribution of drug agglomerate is achieved. The fine particles cause total adhesion while the large size of particles results in the densification of agglomerates. The mass is achieved to bowl shortly after melting attributed to the distribution of the fine particles **[67]**.

K. Electrospinning method- In the electrospinning method electric force is used to remove a small size fiber thread from the polymer. This a merging of solid dispersion with nano-technology utilize in the polymer industry. Stream of the Polymer solution is caused by electric force (5to 30kv). The electric force causes the body of the liquid to become charged. Electrostatic repulsion counteracts the surface tension. This is created by a strong cohesive force between the particle and droplets of a polymer which

forms a stream of fiber. The less-dense and stretching of fiber to small diameter is complete by utilizing a whipping procedure known as electrostatic repulsion. Electrostatic repulsion leads to the formation of uniform fiber in a small diameter. This procedure depends on the rate of feeding surface tension and electric force **[71, 72]**.

Advantages of Spinning Method-

- The composition of small fibers and controlling the release of biomedicine is used the electrospinning method.
- Simple and cheap process.
- In the future composition of solid dispersions can be utilized by the electrospinning method.

Disadvantages of Spinning Method-

- Less economical **[73, 74]**.

L. Lyophilization method- In the Lyophilization method has been thought of as a molecular mixing method. In a common solvent, the drug and carrier are co dissolved, Frozen, and sublimed to acquire a lyophilized molecular dispersion **[60].** The drug is used to minimize thermal stress during the development of the solid dispersion due to the lyophilization method, the solution is transformed into the glass or a glassy substance since the risk of phase separation is minimized. This is the advantage of lyophilization **[32]**.

M. Gel entrapment technique- In this technique, HPMC (hydroxyl propyl methyl cellulose) is diffused in an organic solvent and forms a clear and transparent gel. For example, dissolved in the gel by sonication for a few minutes. The organic solvent is vaporized under a vacuum. Mortar and sieved are used to decrease the solid dispersion in size **[60]**.

P. Co-precipitation method- In this method, a small amount of β-cyclodextrins drug is added to the solution of the carrier. This method is done in a dark place and under magnetic agitation. Vacuum filtration is used for the separation of the precipitates and dried at room temperature to avoid the depletion **[60]**.

Q. Co-grinding method-Weigh measured drug and carrier volumes and blend with 1 ml of water. Pass the acquired damp mass through a 44-mesh sieve; disperse the resulting granules in Petri dishes and dry under vacuum at 60 ° C until an unchanged weight is obtained. Store the granules in

dryers until further study is carried out **[71, 72]**.

LIMITATIONS:

- Drugs Chemical stability.
- Physical stability of vehicles.
- The method of composition.
- The reproducibility of its physicochemical properties.
- Solid dispersion production into dosage forms.
- The scale-up of manufacturing procedures **[75]**

MECHANISM OF SOLUBILITY ENHANCEMENT:

- **Reduced particle-sized particles**-The reduced particle-sized particles result in increased surface area and also helps to increase the rate of dissolution. The outcome is increased bioavailability **[38]**.
- **Particles with superior porosity**- The particles held in solid dispersions have a higher degree of porosity. On the carrier, properties increase porosity also determines; for instance, solid dispersions consisting linear polymers manufacture immense and enhanced.
- **Permeable particles**- they contain reticular polymers and, consequently, result in an increased dissolution rate. The porosity is increased by solid dispersion fine particles also hurtle the drug release rate **[76]**.
- **Drugs in the indefinite state**- The Poor water-soluble crystalline drugs tend to have greater solubility in the amorphous state. The drug in its amorphous state shows substantial liberation of drugs because without the requirement of energy to disintegrate the crystal lattice during the dissolution process. Drugs are presented as concentrated solutions after dissolution in the amorphous state, if precipitates are formed in drugs, then it is as a metastable polymorphic form with greater solubility than the most stable crystal form **[77, 78]**.
- **Particles with refined wettability**- wettability are upgraded during the formulation of solid dispersion. It has been shown in the study that the introduction of particles to the dissolution medium may decrease aggregation. Besides, several of the carriers utilized

for solid dispersions possess certain wetting properties; in consequence, enhanced wetting results in decreased aggregation and enlarged surface area **[79, 80]**.

CONCLUSION:

The solid dispersion technique is one the most effective technique to improve the solubility of poorly soluble drugs. In this technique study about physiochemical properties of drug and polymer. Solvent evaporation method is mainly used for the preparation of solid dispersion method. In present this technique is utilized for the preparation of fast dissolving tablets and orally disintegrating tablets. Solid dispersion increases the drug dissolution profile. In future enhancement of solid dispersion and this preparation figure out the problems which are related with the delivery of poorly soluble drugs.

ACKNOWLEDGMENT: Nil

CONFLICT OF INTEREST: The authors have no conflicts of interests

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