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Review Article

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REVIEW - SOLID DISPERSION: PROMISING WAY OF BOOSTING THE DRUG'S SOLUBILITY AND BIOAVAILABILITY

Mali Kamlesh D.*, Bhansali Saurabh V., Bagad Rutuja B., Bhave Rucha M., Bag Monali R. and Barhate Kunal R.

R.C.P. Institute of Pharmaceutical Education and Research Shirpur, Dist.- Dhule, Maharastra, 425405.

***Corresponding Author: Mali Kamlesh D.**

R.C.P. Institute of Pharmaceutical Education and Research Shirpur, Dist.- Dhule, Maharastra, 425405.

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ABSTRACT

Formulation scientists facing a challenges in case of Improving oral bioavailability of drugs those given as solid dosage forms due to solubility problems. Many techniques have been exercised to improves solubility and oral bioavailability of drugs. Among several methods, Solid dispersion is a solubilization technology emphasizing basically on drug-polymer two component systems in which drug dispersion and its stabilization is the key for formulation development. Different formulation strategies have been taken to prepare solid dispersions. It is evident that solid dispersions improve solubility of drug particles thus enhancing dissolution characteristics of drugs they increase the oral bioavailability. This review paper will focus on solubility and its mechanism, factor affecting solubility, approaches of solubility enhancement, different aspects of solid dispersion preparation; their classification, preparation method, and characterization technique.

KEYWORDS: Bioavailability, Solubility, Biopharmaceutical classification, solid dispersions, solid dispersions method, characterization.

INTRODUCTION

Solubility of a substance in a solvent at given temperature and pressure is the amount of substance that has passed into solution when equilibrium is attained between the solution and the undissolved substance and the solution is known as saturated solution. Substance that gets dissolved known as solute and in which it dissolves or disperse known as solvent. Solubility is generally expressed as the number of grams of solute in one liter of saturated solution [1]. The process of solubility is depending on the bonding between the solute and solvent molecule. The bonds in solubilization is mainly dipole interaction, London forces, hydrogen bonding, Ionic bonding etc. mechanism of solubility shown in figure 1.

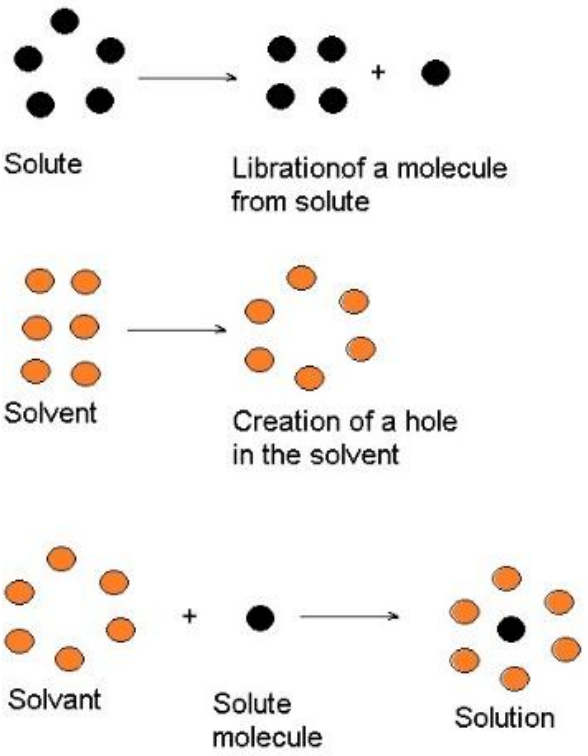

Figure 1: Mechanism of solubility.

When an attraction of solute-solvent molecule is more than the solute-solute molecule, at that time solvent-solute bond formed and solubilisation occur. e.g. the sugar molecular solid, dissolves in water, the weak bonds between the individual sucrose molecules are broken, and molecule are release into solution and solubilise it takes energy to break the molecules.[2] Intrinsic Solubility is defined as the maximum concentration to which a solution can be prepared with a specific solute and solvent. Solubility depends on the solute and solvent as well as temperature, pressure and Ph.[3] The aqueous solubility of a drug is an important molecular property that mainly influences the extent of its oral bioavailability. Due to their poor aqueous solubility many drug candidates become unsuccessful to reach in the market in spite of exhibiting potential pharmacodynamics properties. Therefore, it is very useful to find appropriate formulation approach to improve aqueous solubility and thus bioavailability of poorly soluble drug. Solid drugs administered orally for systemic activity must dissolve in the gastrointestinal fluids prior to their absorption. Thus, the rate of dissolution of drugs in gastrointestinal fluids could influence the rate and extent of their absorption. The rate of dissolution of a solid is a function of its solubility in the dissolution medium, that influence absorption of relatively insoluble drugs.[4] Solubility and permeability of drug as per BCS affect the formulation development and bioavailability of oral drug delivery. The biopharmaceutics classification system (BCS) has been developed to provide a scientific approach to allow for the prediction of in vivo pharmacokinetics of oral immediate release (IR) drug products by classifying drug compounds based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form. **See figure.1** With the trend of increasing insoluble drugs, many companies are now re-evaluating their strategy. They know that there are many available tools, methods and technologies to measure, predict and improve solubility and several new techniques emerging. So, investigation of solubility behaviour and approaches to solubility enhancement are an essential part of preclinical development and formulation of oral dosage form.[5]

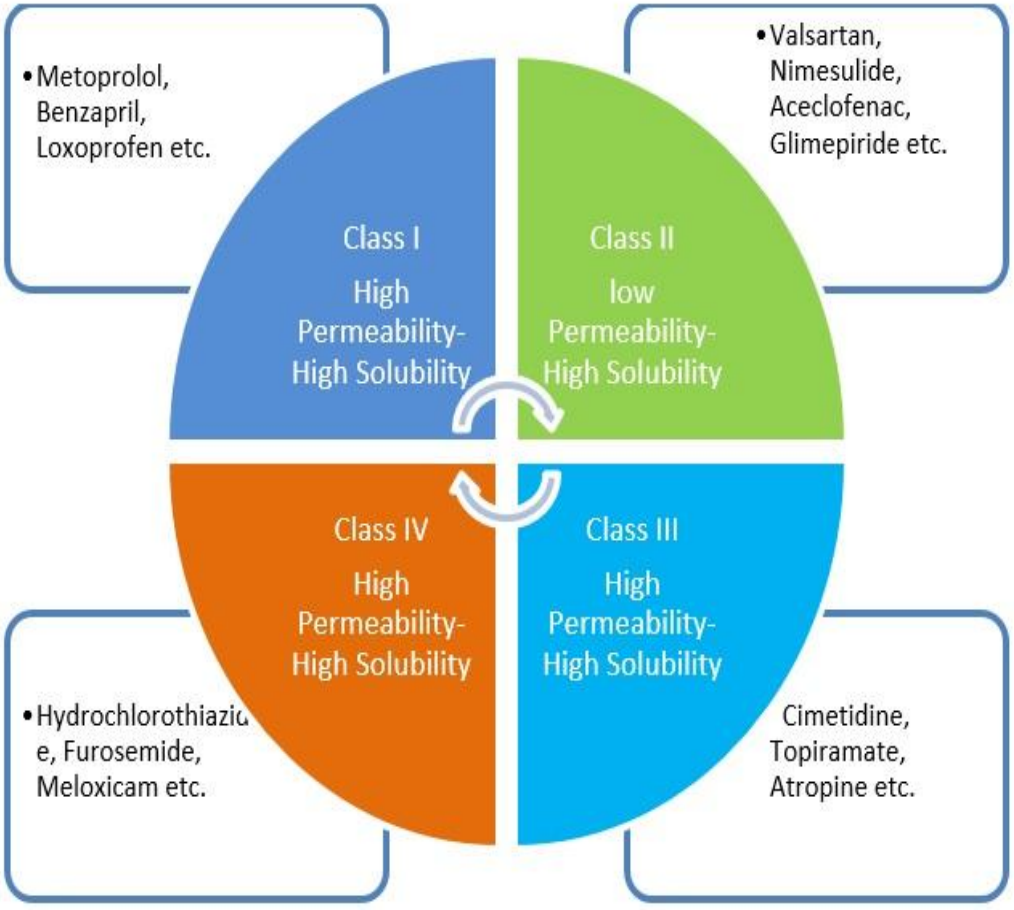

FIG. 1: Biopharmaceutics Classification System.

2. FACTORS AFFECTING SOLUBILITY

Various factor affecting the solubility of substance given in following figure 2

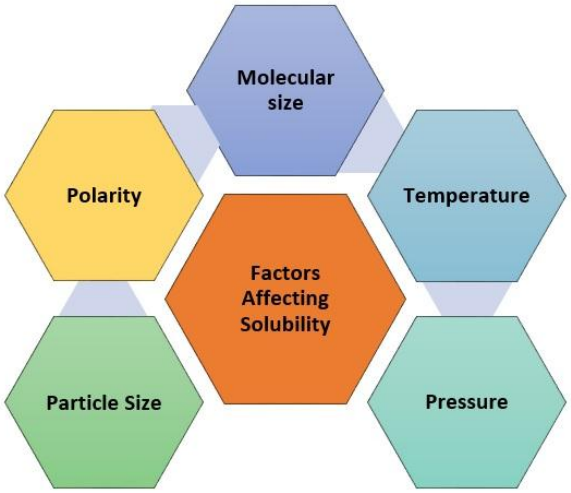

FIG. 2: Factors Affecting Solubility.

2.1 Molecular size: Molecular size will affect the solubility of drug. The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance.[6]

2.2 Temperature: Temperature will affect solubility. If the solution process absorbs energy, then the temperature is increased as the solubility will be increased. If the solution process releases energy, then the solubility will decrease with increasing temperature.[7] Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.[8]

2.3 Pressure: For solids and liquid solutes, changes in pressure have practically no effect on solubility. For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. A soda bottle is an example of where CO2 is bottled under high pressure.[9]

2.4 Particle Size: The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent so solubility increase.[10]

2.5 Polarity: Polarity of the solute and solvent molecules will affect the solubility. Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is a polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction. All molecules also have a type of intermolecular force much weaker than the other forces called London Dispersion forces where the positive nuclei of the atoms of the solute molecule will attract the negative electrons of the atoms of a solvent molecule. This gives the non-polar solvent a chance to solvate the solute molecules.[11]

3. APPROACHES TO ENHANCE THE SOLUBILITY

Poor aqueous solubility leads to poor dissolution and ultimately poor oral bioavailability. The enhancement of solubility of poorly water-soluble drugs remains one of the most challenging aspects of drug development. Although, salt formation, solubilization and particle size reduction have commonly been used to increase solubility, dissolution rate and thereby oral absorption and bioavailability of such drugs. Different techniques have been developed. The methods employed to enhance the drug solubility can be summarizing as follows:

1) Micronization

It involves reducing the size of the solid drug particles to 1 to 10 microns commonly by spray drying or by use of air attrition methods (fluid energy mill). Smaller the particle size increases the surface area and therefore, greater are the rate of absorption. Examples of drugs whose solubility have been increased by micronization include Danazol, Griseofulvin and several steroidal and sulfa drugs.[12]

2) Polymorphs.

A polymorph is a solid crystalline form of a given compound resulting from at least two possible molecular arrangements of the compound in solid state. Two different polymorphs of the same drug show differences in appearance, solubility, melting point, density, dissolution, etc, properties which affect the bioavailability, stability, and even safety and efficacy of the drug. . A metastable polymorph is more soluble than the stable polymorph of a drug that exhibits polymorphism. For example, the B form of Chloramphenicol palmitate is more water soluble than the A and the C forms.[13]

3) Use of surfactant

Surfactants can lower surface tension and improve the dissolution of lipophilic drugs in aqueous medium. Commonly used non-ionic surfactants include polysorbates, polyoxy ethylated castor oil, polyoxyethylated glycerides, lauryl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols.[14]

4) Co-solvency

In this approach, the solubility of poorly water soluble drugs is enhanced by adding water miscible solvent in which drug is soluble and the solvent used in combination to increase the solubility of solute. E.g. propylene glycol, ethanol, glycerin, and polyethylene glycol.[15]

5) Hydrotrophy

Hydrotropy is the term originally put forward by Neuberg to describe the increase in the solubility of a solute by the addition of fairly high concentrations of alkali metal salts of various organic acids. Hydrotropes are amphiphilic substances composed of both a hydrophilic and a hydrophobic functional group. E.g. sodium hydroxide, urea, mannitol, toluene, sodium benzoate, etc.[16]

6) Complexation

Complexation process is the association between two or more molecules to form a non-bonded entity with a well-defined stoichiometric. Complexation depends on relatively weak forces such as London forces, hydrogen bonding and hydrophobic interactions. Examples of complexing agents are; chelates-EDTA, EGTA, molecular complexes-polymers, and inclusion complexes with cyclodextrin.[17]

7) pH modification

pH is helpful in enhancing the solubility for drug behave as either weak acid or weak base, by salt formation or by adding of buffers to formulation. E.g. buffered aspirin tablet.[18]

8) Use of salt form

Salt Formation is the most common and effective method of increasing solubility and dissolution rates of acidic and basic drugs. Acidic or basic drug converted into salt having more solubility than respective drug. Ex. Aspirin, Theophylline, Barbiturates.[19]

9) Spray freezing into liquid and lyophilisation

This technique involves atomizing an aqueous, organic, aqueous-organic co-solvent solution, aqueous organic emulsion or suspension containing a drug and pharmaceutical excipients directly into a compressed gas (i.e. CO_2, helium, propane, ethane), or the cryogenic liquids (i.e. nitrogen, argon or hydrofluroethers). The frozen particles are then lyophilized to obtain dry and free-flowing micronized powders use of acetonitrile as the solvent increases drug loading and decreases the drying time for lyophilisation.[20]

10) Supercritical fluid recrystallization

Supercritical fluids (e.g. CO_2) are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Pc), allowing it to combine the properties of both the liquid and a gas. At near critical temperatures, SCFs are highly compressible, allowing modest changes in pressure that greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power. Once the drugs are solubilised within SCF, they may undergo recrystallization at greatly reduced particle size.[21]

4. SOLID DISPERSION

The term solid dispersions refer to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. A dispersion of one or more active ingredients in an inert carrier or matrix at solid state.[22] Alternatively, solid dispersions can be used to increase the dissolution rate of poorly soluble drugs, and they have proven to increase the amount of dissolved drug at the absorption site sometimes to supersaturated concentrations and consequently improve the bioavailability.[23] Solid dispersions are investigated in many studies because they are highly versatile in their application. They can form the basis of products applied for various routes of administration and for various dosage forms, including the most popular dosage form.

4.1 Classification of solid dispersion[24]

On the basis of recent advancement in solid dispersion, they can be classified as:

1. First generation solid dispersions

The solid dispersions that can be made with crystalline carriers are referred to as first generation solid dispersions. Urea and sugars are two examples of crystalline carriers. This technique produces a thermodynamically stable crystalline solid dispersion that slowly releases the medication. When compared to crystalline solid dispersions, the dissolving rate of amorphous solid dispersions (ASDs) is faster.

2. Second generation Solid dispersion

Second generation Solid dispersion made up of Amorphous carriers such as PVP, PEG, cellulose derivatives etc. Because of their thermodynamic stability, second generation solid dispersions (SD) were shown to be more effective than first generation solid dispersions (SD). According to the physical state of drug, ASDs can be classified as amorphous solid suspensions and amorphous solid solutions [glass solutions]. Because of the forced solubilization of the drug in the carrier, the drug is supersaturated in second generation solid dispersions. Polymers' aqueous solubility decreases as their chain lengths or molecular weights grow, but their viscosity rises which lead to delay the drug release. High viscosity polymers can be used to prevent drug recrystallization throughout the manufacture and storage. The disadvantage of second generation solid dispersion is drug precipitation and recrystallization which affect the drug release profile.

3. Third generation solid dispersion

Third-generation solid dispersions, which contain carriers with surface activity or emulsifying activities, can improve the dissolving profile of API. Precipitation and recrystallization problems can be prevented by using a unique type of carrier in the formulation of solid dispersions. Surfactants and emulsifiers improve the drug's physical and chemical stability in solid dispersion while also improving its dissolving profile. example, Inulin, Gelucire, and poloxamer.

4. Fourth generation solid dispersion

Fourth generation solid dispersion also known as Controlled release solid dispersions (CRSD). It contains a medication that is poorly soluble in water and has a short biological half-life. Water soluble or insoluble carriers are used. The two goals of CRSD are to improve drug solubility and extend drug release in a regulated manner. Ethyl cellulose, Eudragit, HPC, and other water soluble carriers are utilized in CRSD.

6. POSSIBLE MECHANISM OF INCREASED DISSOLUTION RATE BY SOLID DISPERSION[25]

The increased dissolution rate for solid dispersions can be attributed to a number of factors like- Reduction in Particle Size, Solubilization Effect, Wettability and Dispersibility, formation of Metastable form etc. see the possible mechanism of increased dissolution rate by solid dispersion is given in following figure 3.

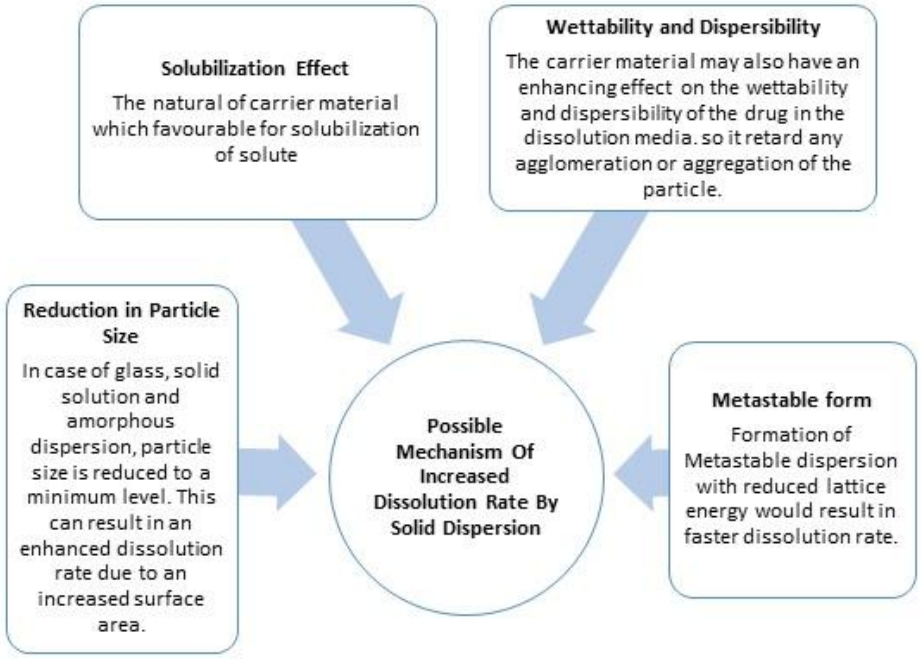

Fig. 3: Possible Mechanism Of Increased Dissolution Rate By Solid Dispersion.

7. METHODS FOR PREPARATION OF SOLID DISPERSION

7.1 Melting or Fusion Method

A physical mixture of a Drug and a water- soluble carrier is heated until it is melted. The melt is solidified rapidly in an ice bath under vigorous stirring, pulverizing and then sieving. Rapid congealing is desirable because it results in supersaturation of the drug as a result of entrapment of solute molecules in the solvent matrix by instantaneous solidification. See figure 4.

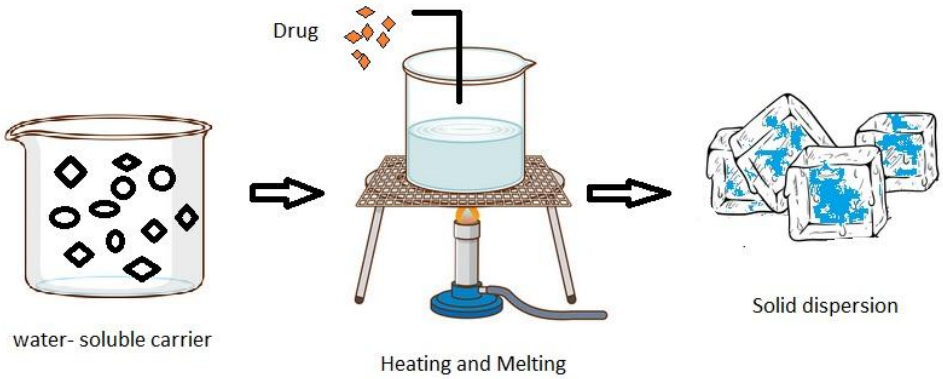

FIG. 4: Melting or Fusion Method.

Melting method is simple and economical because solvent is not used in this method. But this method may not be suitable if the drug or the carrier is unstable at the fusion temperature or evaporate at high temperature. One more disadvantage of this method is the tacky and intractable nature of the resulting solidified melt and irregular crystallization owing to the presence of a miscibility gap on the phase diagram for a given drug carrier system.[26]

7.2 Solvent evaporation Method

This method has been used for the preparation of solid solutions or mixed crystals of organic or inorganic compound. They are prepared by dissolving a physical mixture of two solid components in a common solvent, followed by evaporation of the solvent. e.g. solid dispersions of β-carotene and polyvinyl pyrrolidone, Solid dispersions of sulfathiazole and polyvinyl pyrrolidone. See figure 5.

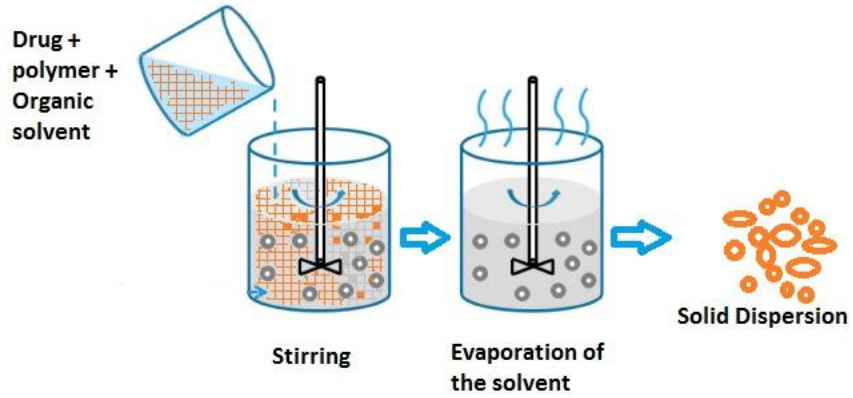

FIG. 5: Solvent Evaporation Method.

Thermal decomposition of drug or carrier can be prevented because of low temperature required for the evaporation of organic solvent which is major advantage of this method. However, there are some disadvantages like higher cost of preparation, difficulty in complete removal of solvent, possible adverse effects of residual solvent, selection of a common volatile solvent, difficulty in reproducing crystal form, inability to attain a super saturation of the solute in the solid system unless the system goes through the highly viscous phase.[27]

7.3 **Melting Solvent Method**

In this method the drug is first dissolved in a suitable liquid solvent and then the solution is incorporated into the melt of carrier without removing the liquid solvent.[28]

7.4 Co-grinding method

A physical mixture of drug and carrier is blended at a specific speed for a period of time. Steel balls are then put to the mixture in the chamber of ball mill. Then Pulverize the powder mixture. The sample is then collected and stored in a screw-capped glass vial at room temperature until needed. This approach was used to make solid dispersions of chlordiazepoxide and mannitol.[29]

7.5 Supercritical Fluid Process

Super critical fluid process can be used for solid dispersion formulation. Supercritical CO_2 is a good solvent for water insoluble as well as water soluble compounds under suitable conditions of temperature and pressure. The critical point is the temperature and pressure at which the substance is in equilibrium as a vapour and a liquid. SCF is employed in this process to create a solid dispersion of insoluble polymer with the drug, resulting in an increase in dissolving property. It surpasses traditional techniques (spray drying, hot melt, etc.). In this process, SCF carbon dioxide is primarily used, resulting in very quick solid mixture precipitation, with no time for drug and polymer separation during solid dispersion preparation. It forms small, stable particles with a larger surface area for better flow and low organic solvent residual [30]. See figure 6.

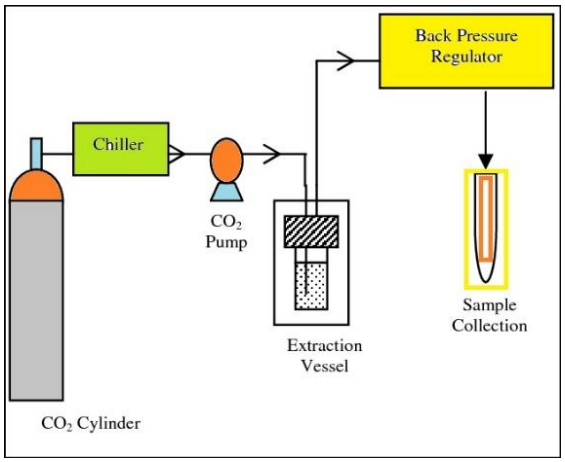

Fig. 6: Supercritical Fluid Process.

7.6 Kneading method for solid dispersions

Mixture of the drug and polymer wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was then dried under vacuum for 24 h. Dried powder to be passed through 60# sieve and stored in a desiccator until further evaluation.[31]

7.7 Modified Solvent Method

Drug is dissolved in solvent at its saturation solubility with continuous stirring up to 30 minutes. Polymer is suspended in sufficient amount of water. The drug solution is poured at once into polymer suspension. The entire solvent is evaluated under reduced pressure at 60°C with rota evaporator with solvent recovery.[32]

7.8 Solvent Wetting Method

Drug is dissolved into the appropriate amount of solvent. Amount of solvent used varied depending on the weight of drug and polymer. After complete dissolution of drug, the solution is dropped on to the polymer. After that the solvent is removed at room temperature.[33]

7.9 Spray Drying Method

In this method the drug and polymer are dissolved in common solvent. Then the solvent is evaporated by spray drier. The operating parameters depend on physicochemical characteristics of the drug and polymer.[34] See figure 7.

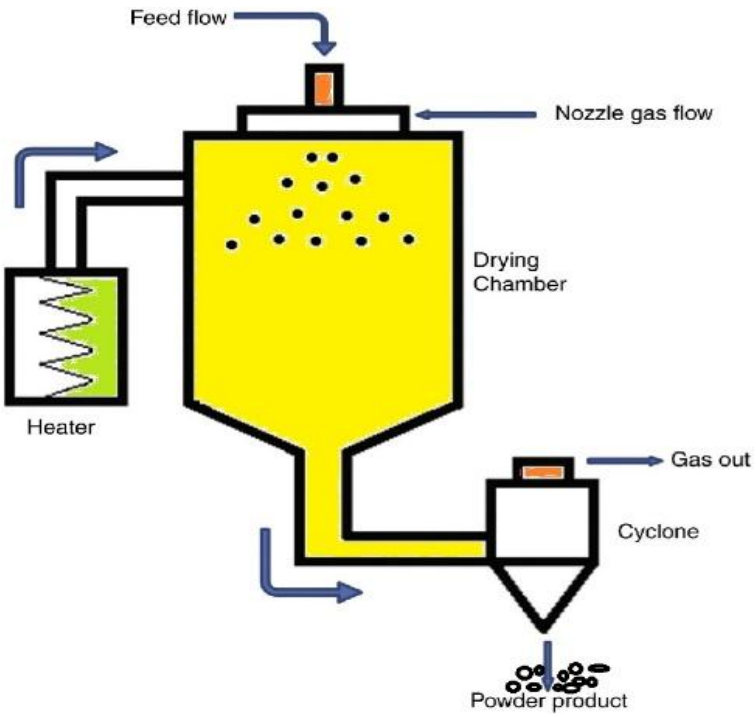

Fig. 7: Spray Drying Method.

7.10. Melt extrusion methods

Solid dispersions can be prepared by hot stage extrusion using a co-rotating twin screw extruder. An extruder consists of 2 distinct parts: a conveyer system that transports the material and sometimes imparts a degree of distributive mixing and a dye system that forms the materials into the required shape. The drug carrier mix is filled in the hopper and is conveyed, mixed, and melted by the extruder. The die then shapes the melt in the required form such as granules, pellets, films, or powder that can be further processed into conventional tablets or capsules. See figure 8.

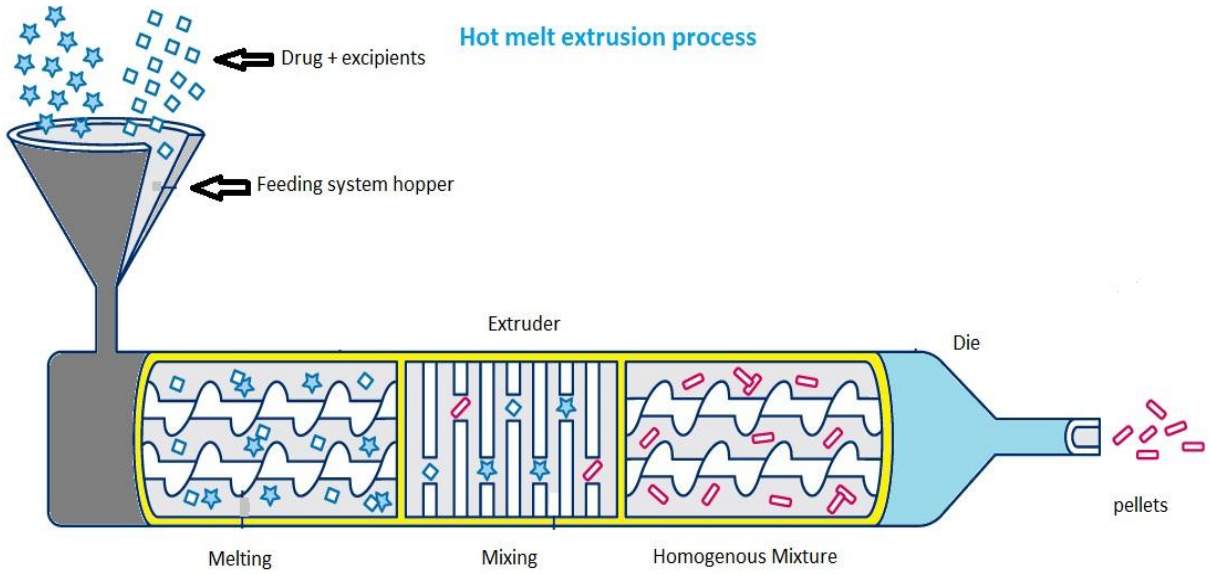

Fig. 8: Melt Extrusion Methods.

The advantages of hot-melt extrusion include lower temperature and shorter residence time of the drug carrier mix, absence of organic solvents, continuous operation, minimum product wastage, good control of operating parameters, and possibility to scale up. Oxygen and moisture may be excluded almost completely for substances prone to oxidation and hydrolysis. The disadvantages are few and mainly relate to negative effects of shear force. The advantage of this method is that the mixture is only subjected to an elevated temperature for about one minute which is good for thermolabile drugs. The drug-carrier mixture is typically processed with a twin screw extruder. This mixture is melted and homogenized simultaneously and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder, the intermediates can then be further processed into conventional tablets.[35]

7. 11 Crystallo- Co- Agglomeration

The agglomerates are prepared using the crystallization vessel, Drug and lipophilic polymers are dissolved into the organic solvent. Then aqueous phase containing hydrophilic polymers are mixed with the organic phase and continuously stir the content by constant speed stirrer. The stirring is continued to obtain agglomerates, which is then filtered and dried overnight at room temperature.[36]

7. 12 Microwave method

In this method the drug and polymer or physical mixture are exposed to the microwave oven for Preparation of solid dispersion. In microwave oven the drug: polymer systems are exposed for different predetermined time interval at predetermined power. After that the solid dispersion are solidified at room temperature and stored for further evaluations. Microwave method is simple and economical because solvent is not used in this method as well as this method could be most potential method for preparation of solid dispersions as it is economical, less time consuming and can be suitable for scale up.[37] See figure 9.

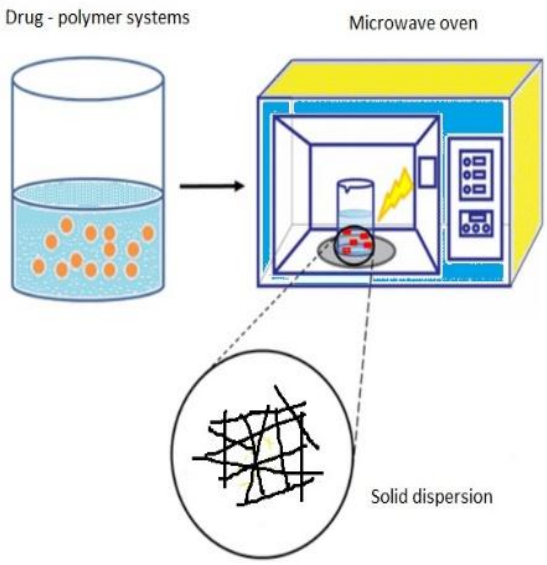

FIG. 9: Microwave Method.

7.13 Electrospinning method

A nano-sized fibre thread is pulled from a polymer sol/polymer melt using electric force in this process. it is a combination of solid dispersion and nanotechnology. Electric force (5 to 30kv) is applied to a stream of polymer solution/melt, causing the liquid's body to become charged and electrostatic repulsion to neutralize surface tension. This created a strong cohesive force between the polymer particle or droplets and the fibre stream. Then, using a whipping process known as electrostatic repulsion, the fibre is thinned and stretched to nano diameter, resulting in the development of uniform nano diameter fibre. This procedure is entirely dependent on the rate of feeding surface tension and the amount of electric force applied.[38]

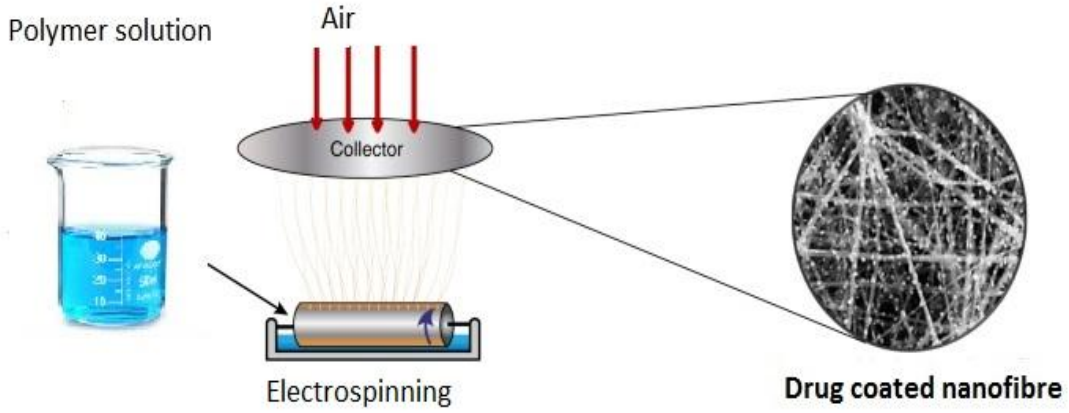

Fig. 10: Electrospinning Method.

8. CHARACTERIZATION OF SOLID DISPERSION[39,40]

Characterization of solid dispersion can be done by various method given in below figure

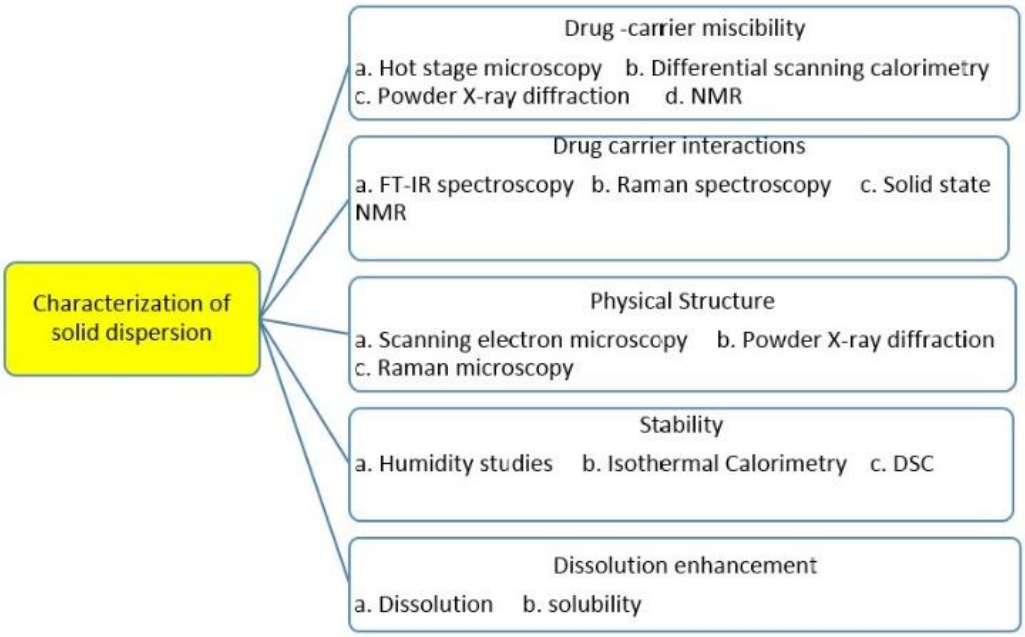

Fig. 11: Melting or Fusion Method.

Powder X-ray diffraction can be used to qualitatively to detect the presence of crystalline forms in solid dispersion and factors affecting recrystallization during storage for stability studies. Sharper diffraction peaks in diffractogram indicate more crystalline material.

In Infrared spectroscopy (IR) you can detect the variation in the energy distribution of interactions between drug and polymer. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect **drug excipient interaction** in between material.

Macroscopic techniques like Optical microscopy, electron microscopy use to measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. They also use to detect surface morphology of formulation, drug, polymer etc.

In Differential Scanning Calorimetry (DSC) samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline, drug excipient interaction, melting point, purity of substance etc.

The energy of dissolution is measured using calorimetry, which is dependent on the crystallinity of the sample. Amorphous material dissolves exothermically, whereas crystalline material dissolves endothermically. Solubility can be evaluating by phase solubility or saturation method. Dissolution rate determine by various dissolution apparatus according to dosage form. Drug dissolution testing is commonly used in the pharmaceutical industry to give essential in vitro drug release information for both quality control and drug development objectives, such as determining batch-to-batch consistency of solid oral dosage forms such as tablets.

9. CONCLUSION

10. REFERENCES

1. Dressman J. Drug solubility: how to measure it, how to improve it. Adv.Drug Delivery Reviews, 2007; 1-2.
2. Bard B, Martel S, Carrupt P. High throughput UV method for the estimation ofthermodynamic solubility and the determination of the solubility in biorelevant media. Eur J. pharma science, 2008; 33: 230–240.
3. Bernard F, Peter E, Bernard F. Computational approaches to determine drug solubility. Adv. Drug Delivery Reviews, 2007; 1-13.
4. John E, Comerb K. Study of equilibrium solubility measurement by saturation shake-flask method using hydrochlorothiazide as model compound. J. Pharma Biomed Analysis, 2008; 46: 335–341.
5. Christel A, Bergström A, Kristina L, Artursson P .Accuracy of calculated pH-dependent aqueous drug solubility. Eur J Pharm Sciences, 2004; 22: 387–398.
6. Christian L, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Biopharma, 2000; 50: 47-60.
7. Duncan Q, Craig M. The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharma., 2002; 231: 131–144.

8. Patidar K, Kshrisagar M, Saini V, Joshi P, Soni M. Solid Dispersion Technology: A Boon for Poor Water Soluble Drugs. Ind J. Novel Drug delivery, 2011; 3(2): 83-90.
9. Lindenberg M, Kopp S, Dressman J. Classification of orally administered drugs on the WHO model list of essential medicines according to biopharmaceutical classification system. Eur J Pharm Biopharm, 2004; 58: 265-278.
10. Blagden N, Matas M, Gavan, P,York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates, Adv Drug Delivery Rev., 2007; 21: 1-15.
11. Keck C, Muller R, Drug nanocrystals of poorly soluble drugs produced by high pressure homogenisation. Eur J Pharm Biopharm, 2006; 6: 3-16.
12. Yohei K, Koichi W, Manabu N, Shizuo Y, Satomi O. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: Basic approaches and practical applications. Int J Pharma., 2011; 1-10.
13. United states pharmacopoeia. U.S.P., convention, Rockville, 2009; 32(2): 2607-2644.
14. Gary G, liversidge K, Cundy C.Particle size reduction for improvement of oral bioavailability of hydrophobic drug. Int J Pharma., 1995; 125: 91-97.
15. Juan J. García-Rodriguez et. al Changed crystallinity of mebendazole solid dispersion: Improved anthelmintic. Act Int J Pharma., 2011; 403: 23–28.
16. Noushin B, Farrin S, Simin D. The Effect of Various Surfactants on Release Behavior of Procainamide HCl from Ethylcellulose Based Matrices. Ira J Pharma Research., 2005; 1: 13-19.
17. Jachowicz R, Nu¨rnberg E, Pieszczek B, Kluczykowska B. Maciejewska Solid dispersion of ketoprofen in pellets. Int J Pharma., 2000; 206: 13–21.
18. Sandrien J, Hector Novoa de A, Jean P. Guy M. The use of a new hydrophilic polymer, Kollicoat IR®, in the formulation of solid dispersions of Itraconazole. Eur J pharma sciences, 2007; 30: 288–294.
19. Jose R et. al. Thermal stability of solid dispersions of naphthalene derivatives with cyclodextrin and cyclodextrin polymers. Thermochimica Acta, 2006; 444: 57–64.
20. John E, Comerb K, Tak´acs-Nov´ak. Study of equilibrium solubility measurement by saturation shake-flask method using hydrochlorothiazide as model compound. J Pharma Biomed Analysis, 2008; 46: 335–341.
21. Abu T, Serajuddin Y. Salt formation to improve drug solubility Adv Drug Delivery Reviews, 2007; 1-14.
22. Jae-Young Jung et. al .Enhanced solubility and dissolution rate of itraconazole by a solid dispersion technique. Int J Pharma., 1999; 187: 209–218.
23. Blagden N, de Matas M, Gavan P, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates Advanced Drug Delivery Reviews, 2007; 1-14.
24. Sharma KS, Sahoo J, Agrawal S, et al. Solid dispersions: a technology for improving bioavailability. J Anal Pharm Res., 2019; 8(4): 127–133. DOI: 10.15406/japlr.2019.08.00326
25. Ilse Weuts et al. Phase behaviour analysis of solid dispersions of loperamide and two structurally related compounds with the polymers PVP-K30 and PVP-VA64. Eur J Pharma, 2004; 22: 375–385.
26. Jonathan B, Miller M, Dahan. A. Accounting for the solubility–permeability interplay in oral formulation development for poor water solubility drugs: The effect of PEG-400 on carbamazepine absorption. Eur J. Biopharma., 2012; 1-6.
27. F. Fawaz et.al .Bioavailability of norfloxacin from PEG 6000 solid dispersion and cyclodextrin inclusion complexs in rabbits. Int J Pharma, 1996; 132: 271–275.
28. Moesa J, Koolena S. Pharmaceutical development and preliminary clinical testing of an oral solid dispersion formulation of docetaxel (ModraDoc001) Int J Pharma., 2011; 420: 244–250.
29. Sharma C, Jain P. Preparation and characterization of solid dispersions of carvedilol with PVP K30. Res Pharm Sci., 2010; 5(1): 49–56.
30. Elisabeth R et al. A three step supercritical process to improve the dissolution rate of Eflucimibe. Eur J Pharma., 2005; 26: 184–193.
31. Ahuja N, Katare O, Singh B .Studies on dissolution enhancement and mathematical modeling of drug release of a poorly water-soluble drug using water-soluble carriers. Eur J Biopharma, 2007; 65: 26–38.
32. Han Gon Choi et.al Preparation, characterization and in vivo evaluation of ibuprofen binary solid dispersions with poloxamer 188 Intl J Pharm., 2007; 343: 228–237.
33. Eun-Jung Kim et al Preparation of a solid dispersion of felodipine using a solvent wetting method. Eur J Biopharma, 2006; 64: 200–205.
34. Sff.
35. Fukuda M, Miller D, Peppas N, James W. Influence of sulfobutyl ether _-cyclodextrin (Captisol®) on the dissolution properties of a poorly soluble drug from extrudates prepared by hot-melt extrusion. Int J Pharma., 2008; 350: 188–196.
36. Rane Y, Mashru R, Sankalia M, Sankalia J. Effect of Hydrophilic Swellable Polymers on Dissolution Enhancement of Carbamazepine Solid Dispersions Studied Using Response Surface Methodology . AAPS PharmSciTech, 2007; 8(2): 1-11.
37. Moneghinia M, Bellicha B, Pietro B, Francesco P. Microwave generated solid dispersions containing Ibuprofen. Int J Pharma., 2008; 361: 125–130
38. Xue, Jiajia et al. "Electrospinning and Electrospun Nanofibers: Methods, Materials, and Applications." Chemical reviews, 2019; 119,8: 5298-5415. doi:10.1021/acs.chemrev.8b00593
39. Xin W, Armand M, Mooter G.Solid state characteristics of ternary solid dispersions composed

of PVP VA64, Myrj 52 and itraconazole. Int J Pharma., 2000; 303: 54–61.
40. Hisham O, Peng K, Steve B, Graham B. Characterization and stability of ternary solid dispersions with PVP and PHPMA. Int J Pharma, 2011; 419: 20– 27.