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VARIOUS APPROACHES TO IMPROVING THE AQUEOUS SOLUBILITY OF POORLY WATER-SOLUBLE DRUGS USING SOLID DISPERSION

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ABSTRACT:

Oral route administration is the most desirable and preferred method of delivering therapeutic agents due its systemic effects. Presently days, various hydrophobic drugs were coming into the market. Disadvantage of these drugs are its bioavailability issues because of poor gastric fluid dissolubility. In this way, it is important to improve its solubility and its penetrability in this manner improving the disintegration, absorption and bioavailability of these drugs. About 40% of orally administered drugs have formulation difficulties due to their insolubility in water. The dissolution rate, absorption, distribution and excretion of drugs depends on its solubility properties. Based on solubility, drugs are classified into the four classes of BCS classification. BCS class II and class IV drugs shows poor water solubility.

KEYWORDS:

Solid dispersion, Solubility enhancement, Solvent evaporation, Fusion method.

INTRODUCTION:

Oral route administration is the most desirable and preferred method of delivering therapeutic agents due its systemic effects. (Arunachalam et al., 2010) The advancement in treatment of sicknesses has been obvious with an upsurge in developed of new medications. An estimated 40% of these medications are poor water dissolvable. The majority of the medications have empowering experimental information gotten in vitro, the in vivo results have been frustrating. The attributes include:

1. Poor absorption, rapid breakdown and lamination (peptides and protein) resulting in insufficient concentration.
2. Distribution of drug to other tissue of the drug with high drug toxicity (Anti-cancer drug).
3. Poor solubility of drugs.
4. Plasma fluctuations due to unpredictable bioavailability.

Increasing the oral bioavailability of these poorly water-soluble drugs remains one of the most challenging aspects of drug development. (Karanth et al., 2006)

As per BCS classification drugs are classified in 4 classes i.e. class I, II, III, IV. Class II drugs are shows low solubility so, it is important to improve solubility through solid dispersion. (Joshi et al., 2012)

Solid dispersion is defined as dispersion of one or more active ingredient (hydrophobic) in an inactive carrier (hydrophilic) at a solid state prepared by melting (fusion), solvent, melting solvent method. (Kumar 2017)

Table 1: Biopharmaceutical Classification System

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

CLASSIFICATION OF SOLID DISPERSION (SD):

Based on physical state SD is classified as crystalline SD and amorphous SD. It is classified into first generation, second generation, third generation and fourth generation.

First generation SD:

In the first generation, carriers were generally used in SD are crystalline in nature. In the preparation of SD urea and sugar are considered as a crystalline carrier. Urea is the first crystalline carrier which is used in preparation of eutectic mixture with sulfathiazole (Sekiguchi and Obi). (Sekiguchi et al., 1961) Solubility of ofloxacin was improved by SD technique using urea and mannitol as a carrier. (Okonogi et al., 1997)

Second generation SD:

The second generation contains an amorphous carrier instead of a crystalline carrier. They have the ability to produce an amorphous SD in which drug and carrier are uniformly miscible and soluble to initiate homogeneous molecular interaction. (Vasconcelos et al., 2007) Povidone, Polyethylene Glycol (PEG) Polymethacrylate is a fully synthetic polymer and natural product-based polymers include cellulose derivatives such as Hydroxypropyl Methyl Cellulose (HPMC), Ethyl Cellulose (EC) or Hydroxypropyl Cellulose (HPC) or starch derivatives such as Cyclodextrin. (Kohri N et al,) Reported that the dissolution of all formulations of albendazole was improved using HPMC and hydroxypropyl methylcellulose phthalate (HPMCP). (kohri et al., 1999)

Third generation SD:

Recently, the dissolution profile can be improved if the substrate has surface activity or self-emulsifying properties, i.e. Third generation solid dispersions have appeared. They contain a surfactant as a carrier or mixture of amorphous polymers and surfactants as carriers. The third-generation solid dispersion aim to reach the maximum level Bioavailability for poorly soluble drugs and Stabilize solid dispersion, avoid drug recrystallization. (Singh et al., 2011) The solid dispersions are commonly made of a surfactant or a mixture of polymers. They achieve the highest bioavailability for poorly soluble active ingredients. In the preparation of third-generation solid dispersions the surfactant which is used are inulin, poloxamer 407, etc. (Kumar 2017)

Fourth generation SD:

Fourth generation media is inherently dual-purpose and has Solubilizing and surfactant properties. Because couriers are non-ionic, the solubility is independent of pH changes makes these carriers prime candidates for development solid dispersions. Soluplus is fourth-generation solid dispersion carrier has emerged as an important carrier for solid dispersion as it acts as a matrix polymer for solid solution and an active solubilizer through micelle formation in water. (Khan et al., 2015) The purpose of this study is to prepare matrix-type microparticles, comprising a solid dispersion of drug with an amino methacrylate copolymer and ethyl

cellulose binary blend, for use in the controlled release of a poorly water-soluble drug, nifedipine. (Huang et al., 2006)

MERITS OF SOLID DISPERSION:

1. Chemical approach to improve bioavailability without Modification of the active target can be achieved by salt formation or Incorporation of polar or ionizable groups into the parent drug structure resulting in a prodrug.
2. Solid dispersions appear to be a better approach to improve drug solubility compared to these techniques because they are easier to manufacture and more appropriate. For example, saltification can be used only for weakly acidic or basic drugs, not for neutral drugs. (Vasconcelos et al., 2007)
3. Increased disintegration rate and retention rate and less pre-engraving.
4. Changes the type of liquid medicine to a solid structure.
5. Constraints such as carrier mass and atomic arrangement, drug crystallinity, porosity, and wettability of molecules can improve bioavailability when effectively controlled, can deliver enhancements in bioavailability. (Roche et al., 2003)

DEMERITS OF SOLID DISPERSION:

1. Changes in crystallinity and decrease in dissolution rate with age. (Shah et al., 1995)
2. Humidity and temperature affect SD overwrite compared to actual combinations.
3. Some SDs may not lend themselves to easy customization due to their stickiness.
4. The disadvantage of SD is its helpless scaling in relation to the motivation behind the production. (Singh et al., 2011)

STANDARDS FOR CHOOSING CARRIERS:

- The carrier should be freely soluble in water with a high rate of dissolution.
- It should be non-toxic in nature.
- It should be pharmacologically inactive in nature.
- It should have heat soundness with a low liquifying point.
- It should have property to improve aqueous solubility of the drug.
- Economical. (Yoshihashi et al., 2006)

Table 2: Classification of carriers

Category	Examples of carriers
Sugars	Dextrose, sucrose, lactose, maltose, sorbitol, mannitol, galactose.
Acids	Citric acids, succinic acids.
Polymeric material	Povidone, polyethylene glycol, Hydroxyl propyl methyl cellulose, hydroxyl ethyl cellulose, pectin, galactomannan.
Enteric polymers	Hydroxypropyl methyl cellulose, phthalate, Eudragit RS.
Surfactants	Polyoxymethylene stearate, Poloxamer 188, deoxycholic acids, Tweens, spans miscellaneous urea, hydroxy alkyl xanthine, urethans.

IDEAL CANDIDATES FOR SD:

For the preparation of solid dispersion where drugs have the poor aqueous solubility and are permeable through biological membrane. Due to their poor aqueous solubility dissolution rate is decrease and thus absorption and bioavailability reduces. BCS class II drugs are the ideal drug candidate for the preparation of SD. Class II drugs have low solubility and high permeability. (Kumar 2017)

METHOD OF PREPARATION OF SD:

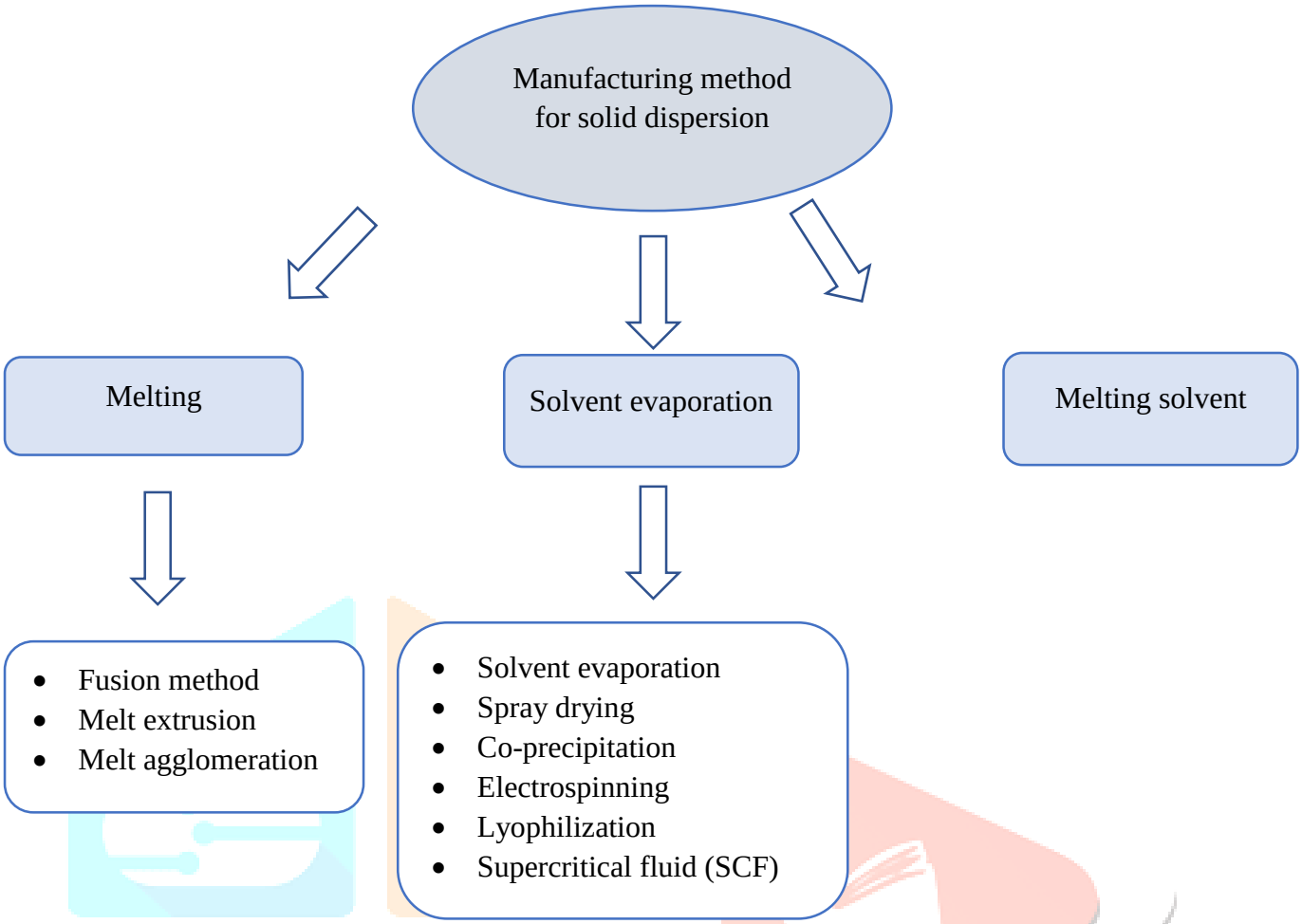

Fig 1. Manufacturing method for solid dispersion

A. Melting:

1. Fusion method:

The melting or fusion method, first proposed by Sekiguchi and Obi, in the preparation SD it involves heating directly to melt the physical mixture of a drug and a water-soluble carrier. The melted mixture is then rapidly solidified in an ice bath with vigorous stirring. The final solid mass is mashed, crumbled and shifted. This has therefore undergone a series of modifications, consisting in casting a homogeneous alloy in thin layer on a ferrite plate or a stainless-steel plate and cooling it by circulating air or water on the opposite side of the plate. Substances that are drugs or carrier, however, may deteriorate due to the high temperature during fusion interaction. A strategy to solve this problem could be to heat the suit in a solid or vacuum chamber or in the presence of dormant gases such as nitrogen. The advantage is its lightness and conservatism. The first SD was made using this technique for pharmaceutical applications. It was a combination of sulfathiazole and urea that were combined and then cooled to give the final dispersion. To obtain simultaneous crystallization of drug and matrix during cool down the eutectic mixture was used. (Singh et al., 2013; Narang et al., 2002; Saurabh et al., 2011)

2. Hot melt extrusion method:

This strategy uses the extruder for some serious mixing of parts. The segments of the extruder are the barrel, the hopper, the kneading screw, the insulating jacket and the feeder. (Ingle et al., 2011) Typically, the actual carrier and drug combination is fed into the hopper, at which point it passes through the screw and is finally discharged from the mould. The advantage of the strategy is to get different shapes and plans heated mixture of drug matrix in ophthalmic insert, implant or oral dosage form. (Rajmalle et al., 2014) Other advantages are conceivable, such as the uninterrupted production of the SD, which enables large series production without great effort. An object created with this strategy can be easily manipulated, as any shape can be created. (Allawadi et al., 2014) As with the

different strategies, the combination of drug and matrix is also an issue. (Liberman; Serajuddin et al., 1999)

3. **Melt agglomeration method:**

In this technique the binder acts as a carrier in the preparation of solid dispersion. SD are prepared by heat the binder, drug and excipient to a higher temperature melting of the binder or by spraying on the medicinal dispersion melted binder onto the heated excipient with a high-speed mixer.(Nikghalb et al., 2012) The rotary processor may be preferable to a refractory agglomerate because it is easy to control the heat and because a high binder content can be introduced into the agglomerates. (Argade et al., 2013; Seo et al., 2001)

B. Solvent evaporation method:

In this process, the drug and the polymer are dissolved in a common organic solvent and the solvent is evaporated at low temperature. At this point the following mixture is ground through sensitive screens. Some components are not suitable for this technique because only one solvent is used in this cycle. If the drug is a soluble in a solvent and the polymer decomposes by evaporation in another solvent, the solvents will evaporate according to the boiling point, then the drug or polymer will solidify immediately depending on the solvent used. This will display a message that polymorph editing was not completed. So, this ultimately leads to low solubility and low dissolution rate. Then, as it were, the drug and the polymer disintegrate in a solvent. The choice of polymer depends on the nature of the drug and the solubility of the drug in the organic solvent. Overall, ethanol, acetone, isopropyl alcohol and dichloromethane were used as solvents. (Hasegawa et al., 2005; Yoshihashi et al., 2006; Nikghalb et al., 2012)

1. **Spray drying method:**

The spray drying process is probably the best and most commonly used technique for dispersing solids. It's a solitary progression, a beneficial and easily repeatable cycle. The dominant principle of the spray drying process is the continuous change of the physical state of the material from a liquid to a solid state using a thermal drying chamber. In this interaction, the drug, polymer and sometimes surfactants are dissolved in a solvent and continuously sprayed into a heating chamber where the solvent disperses and turns into a solid state. (Chauhan et al., 2005) In this drying chamber, the solvent is atomized with atomizing air. The solvent is atomized into fine droplets by the atomization of air and into solid particles in the drying chamber. In this technique, the drug and inert carriers were completely dissolved in an appropriate solvent. The solvent used was a single solvent or a mixture of solvents depending on the solubility of the drug and the inert carriers. Due to the solubility of the drug and inert carriers, the drug molecules changed their crystalline nature to amorphous, improving solubility and bioavailability. (Seo et al., 2001; Nikghalb et al., 2012)

2. Co-precipitation method:

Coprecipitation is a proven technique to increase the dissolution of poorly water-soluble drugs to continuously improve bioavailability. In this technique, the nonsolvent is added dropwise to the drug and carrier solution with constant mixing. During solvent-free expansion, drug and carrier are accelerated together to form a framework for the microparticles. Finally, the resulting microparticle suspension is filtered and dried. The required amount of Polymer and drug were mixed, then the solvent was added to obtain a clear solution. The solution was first dried under vacuum at room temperature and stored in an incubator (37°C) for 12 hours. (Pouton et al., 2006; Nikghalb et al., 2012)

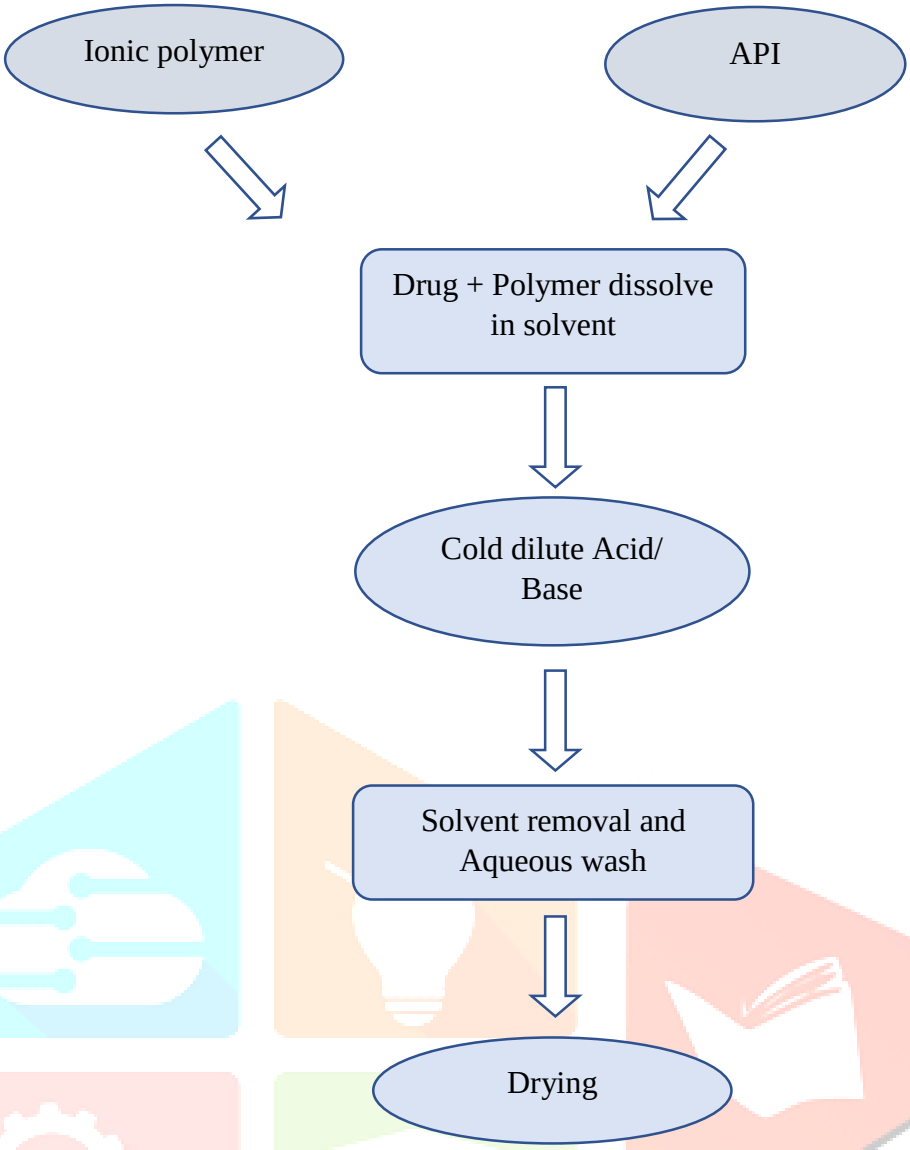

Fig 2. Co-precipitation process (Shah et al., 2013)

3. Electrospinning method:

Electrospinning is a process that produces strong fibers from a polymer stream of liquid solution or molten material, which is discharged through a millimetre-scale nozzle. (Zhang et al., 2007) The method involves applying a strong electrostatic field to a conductive capillary connected to a reservoir containing a solution or polymer melt and a conductive collector screen. After increasing the electrostatic field strength to, but not beyond, a critical value, the charged particles accumulated on the surface of the suspended droplet destabilize the conical hemispherical shape (commonly known as the Taylor cone). Above a critical value, a jet of charged polymer is ejected from the top of the cone (to discharge the charge accumulated on the surface of the hanging drop). The discharged charged jet is then transferred to the collector screen by electrostatic force. The Coulomb repulsion force is responsible for the dilution of the charged jet as it moves towards the collection screen. The dilution of the charged stream is limited by the increase in viscosity as the charged stream dries. This technique has great potential for obtaining nanofibers and controlling the release of biological drugs as it is the simplest and cheapest. this technique can be used in the future to make solid dispersions. (Singh et al., 2013; Dixit et al., 2014)

4. Lyophilization method:

The selected solid dispersions were dissolved in minimum amount of cyclohexanol. This solution quickly solidified by transferring small portions onto the inside surface of a cold Labconco bottle using a Pasteur pipette. Rotation in a methanol bath at -50°C. After some time, the thickness of the layer was obtained, the Labconco flask was placed under vacuum freezing adapter. The solvent was sublimated at 8-10°C mmHg and condensed in a condenser at -75°C. Once the solvent is completely removed up the powder residue was eliminated in the form of a porous, light and soft mass. the

lyophilized preparations were stored in a desiccator at room temperature. (Singh et al., 2011; Betageri et al., 1995; Singh et al., 2011)

5. **Supercritical fluid (SCF) technique:**

The general concept of using a supercritical fluid as an anti-solvent is relatively well established. Provides supercritical carbon dioxide several advantages over organic solvents, which are widely used in microencapsulation processes. Carbon dioxide is environmentally friendly acceptable, non-flammable, non-toxic, abundant, his critical coordinates are moderate, and he is Gas at ambient conditions under pressure and temperature. In anti-solvent techniques in supercritical fluids Carbon dioxide is used as an anti-solvent. (Taki et al., 2001) Using SCF-based processes produces particles with a narrow size range, low residual solvent content, and increased drug stability. The incorporation of drugs into the delivery system can be achieved through a variety of SCF-based methods, where the SCF can act as a solvent, anti-solvent, or simply as an adjunct during surgery. Also used an approach one solution of drug and carriers in this study in the common solvent and SCF are simultaneously introduced into the particle formation vessel. The solvent is rapidly extracted from the SCF, resulting in the formation and precipitation of SD particles on the walls and bottom of the vessel. (Tabbakhian et al., 2014; Dohrn et al., 2007)

C. **Melting solvent method:**

It consists the preparation of solid dispersions by dissolve the medication in a suitable liquid solvent and then Introducing the solution directly into the melt of polyethylene glycol (PEG) which is then solvent is evaporated. A clear, solvent-free film remains. The film is then dried to obtain constant weight. 5-10% (w/w) of liquid the compounds can be incorporated into the polyethylene Glycol 6000 without significant loss of solids. It is possible that the solvent or the dissolved drug should not mix with the melted drug polyethylene glycol. The liquid solvent used can also affect the polymorphic form of the drug, the precipitates as a solid dispersion. This technique has the unique advantages of fusion and Solvent Evaporation Methods. From practice the display is limited to drugs with a low concentration therapeutic dose for example 50 mg. (Singh et al., 2011; Singh et al., 2013)

CHARACTERIZATION OF SOLID DISPERSION: (Singh et al., 2013; Leuner et al., 2000; Patil et al.,2012)

- **Physical appearance**
- **Drug content**
- **Dissolution**
- **Fourier Transform Infra-red (FTIR) spectroscopy**
- **Differential Scanning Calorimetry (DSC)**
- **Scanning Electronic Microscopy (SEM)**

Physical Appearance:

It involves the visually observing the appearance of solid dispersion.

Drug content:

This is an analysis of the amount of drug present in a solid dispersion. In the test technique, the drug is taken and dissolved in appropriate solvents that ensure it is freely soluble in nature and diluted in an appropriate fixative. Finally, drug content was estimated by UV or high-performance liquid chromatography (HPLC) instrument.

Dissolution:

Dissolution estimates the dissolved component over a period of time. Percentage Drug release rate over a period of time estimated using basic UV spectroscopy or HPLC. The test is performed at a fixed volume and RPM at a temperature of 37 ± 0.5 °C. Commonly used dissolution apparatus is USP apparatus. Usually basket and paddle type of USP apparatus is used to checked the dissolution.

Fourier Transform Infra-red (FTIR) spectroscopy:

FTIR spectroscopy use for the determination of interaction between drug to drug and drug to excipients interactions. It estimates intensity over a narrow range of frequencies all at once.

Differential Scanning Calorimetry (DSC):

DSC is a thermoanalytical technique that estimates endothermic and exothermic reactions by gradually increasing the temperature. Endothermic reactions measure the melting and boiling limits. Exothermic reactions measure crystallization and polymerization.

Scanning Electronic Microscopy:

It is used to discover pattern images by scanning the surface of the material with a focused beam. Electron microscopy is useful to study the morphological structure of the material.

Application of Solid Dispersion: (Kumar 2017; Chiou et al., 1971)

- **It increases the solubility of poorly soluble drugs and thus increases the rate of dissolution, which increases the absorption and bioavailability of the drug.**
- **To stabilize unstable medicinal substances against various degradation processes such as hydrolysis, oxidation, etc.**
- **To reduce the side effects of some drugs.**
- **Masking the unwanted taste and smell of drugs.**
- **Avoid unwanted incompatibilities.**
- **Dispensing of liquids (up to 10%) or gaseous compounds in solid doses.**
- **Formulation of Sustained release dosage form like tablet etc.**

CONCLUSION:

Based on the above study, Solid Dispersion is one of the most effective technologies to overcome many poorly soluble drug bioavailability issues. However, there is some problem that can be overcome by applying novel and existing approach. This review focuses on current efforts to address the bioavailability issue and discusses various emerging technologies related to the development of SD.

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