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Solubility Enhancement Techniques: An Overview

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Abstract

Solubility, the phenomenon of dissolution of solute in a solvent in a specified condition to give a homogenous system, is the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. the primary aim of this review was to improve the solubility of BCS Class-II drugs because of their low solubility and dissolution rate. Therefore, the enhancement of solubility of practically insoluble drug was the most challenging aspect of drug development pharmaceutically active molecules with low solubility convey a higher risk of failure for drug innovation and development. pharmacokinetics, pharmacodynamics, and some other parameters, such as drug absorption, drug distribution, protein binding, etc. are majorly affected by their solubility. among all pharmaceutical dosage forms, oral dosage forms cover more than 50%, and the drug molecule should be water-soluble. for maintaining good therapeutic activity by the drug molecule on the target site, solubility and bioavailability are the major factors. hence with the advancement of chemical science, the need of development of pharmaceutical technologies to improve patient compliance for medication. This article aims is to describe the different solubility enhancement techniques to improve the solubility of the drug by different approaches such as traditional and Novel methods like pH adjustment, Micronization, homogenization, Salt formation, Lyophilization, hot melt Extrusion, Solvent evaporation, melt son crystallization, prodrug approach, etc. for the acquirement of the effective absorption and improved bioavailability.

Keywords: Solubility Enhancement, Dissolution, Bioavailability, Solid dispersion, BCS Classification, lipophilicity.

Introduction

The Important Phenomenon and as a maximum of time discussed but not a completely resolved issue, "Solubility or dissolution enhancement technique is a most challengeable field for the researchers in the formulation design and developmental process of Solubility and the dissolution. These are the main concepts of any physical as well as chemical science including their biopharmaceutical and pharmacokinetic considerations in the treatment with any medicine. As a result, recently more than 40% of new chemical compounds are fails before enter into a drug developmental process because of their non-optimal biopharmaceutical properties. These properties such as rate of absorption, the rate of distribution etc. Therefore, correspondingly to the IUPAC, The solubility defined is as an analytical composition of saturated solution in terms of the proportion of a solute in the amount of solvent with temperature is the solubility of that solute."[1]Due to this important purpose Solubility enhancement is one of the essential parameters which ought to be taken into consideration in system improvement of orally administered drug with terrible aqueous solubility. Solubility is the function bodily belongings regarding the capacity of a given substance, the solute, to dissolve in a solvent. "The solubility is defined as the amount of solute molecules which dissolve in a solvent or solutions at a specified temperature". [2]

Solubility equilibrium occurs when there are two processes proceed with a constant rate. Under at the conditions of equilibrium solubility may be exceeded to give also-called supersaturated solution, which is metastable, Solubility is not to be confused with the ability to dissolve or a substance, since these processes may occur not only because of dissolution but also because of a chemical reaction. For example, zinc is insoluble in HCL, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in HCL is solution but also because of a chemical reaction.[3]This article provides an overview on some of the current approaches and some of the advanced approaches for the formulation of drugs. These comprise formulation in lipid based colloidal drug delivery systems and experimental as well as computational approaches towards the identification of the most suitable carrier systems. For much less lipophilic materials the education of drug nanoparticles with the aid of using milling and precipitation is investigated, for instance, via Microsystem-primarily based totally production techniques. Some of the techniques to formulate poorly water-soluble drug materials provide exciting alternatives for the improvement of patient-individualized Dosage bureaucracy as exemplified in section[4]The pharmacopoeia listing in phrases of variety of the milliliters of solvent required to effects 1 gm of solute. The Indian pharmacopoeia affords standard phrases to explain a given variety that's primarily based totally on the quantity of drug dissolved in solvent mention in theTable-1.[5]

Descriptive terms	Approximate volume of solvent in milliliters per gram of solute
Very Soluble	Less than 1
Freely Soluble	From 1-10
Soluble	From 10-30
Sparingly Soluble	From 30-100
Slightly Soluble	From 100-1000
Very Slightly Soluble	From 1000-10000
Insoluble	Greater than 10000

Table No 1: USP and BP Expression for Approximate solubility:

Extensive use of solubility from different angles has brought about solubility being expressed in various manners. It is commonly expressed as a concentration with the aid by using mass (g of solute in step with kg of solvent, g per dL (100 mL) of solvents), molarity, molality, mole fraction, or different comparable description of concentration. [3]

Biopharmaceutical Classification system (BCS)

The Idea of permeability and solubility traits had been useful to categories the drug in 4 class Biopharmaceutics Classification System (BCS). the negative solubility and dissolution of poorly water drugs within the aqueous gastrointestinal fluids frequently reason inadequate bioavailability. [6]BCS was brought with the aid of using the United States Food and Drug Administration (FDA) and it classifies the drug into 4 in step with permeability and solubility. Solubility obstacle is confronted with inside the Class II and Class IV of the dissolution. The BCS is mentioned in Table No. 2. [7]

Table No 2: The Biopharmaceutics Classification System for drugs:

Class	Solubility	Permeability	Absorption pattern	Rate limiting step in the absorption	Example
I	High	High	Well absorbed	Well absorbed	Diltiazem
II	Low	High	Variable	Dissolution	Nifedipine
III	High	Low	Variable	Permeability	Insulin
IV	Low	Low	Poorly absorbed	Case by case	Taxol

Poorly soluble drugs are frequently a hard the front for formulators with inside the industry. Conventional methods like, use of surfactants, Micronization, salt formation, pH regulation, solvency, hot melt extrusion, complexation, etc. for augmentation of solubility have constrained applicability. [8]

Importance of Solubility Enhancement

Oral ingestion is the maximum useful and typically hired direction of drug transport because of its ease of management, excessive affected person compliance, Cost-effectiveness, least sterility constraints and versatility with inside the layout of dosage shape. As end result, some of the usual drug agencies are willing greater to supply bioequivalent oral drug products. Solubility is one of the crucial parameters to acquire desired quality of drug in systemic stream for accomplishing required pharmacological reaction Hydrophobic pills regularly require excessive doses. Water is the solvent of remarkable for liquid pharmaceutical formulations. Most of the medication like weakly acidic or weakly primary having terrible aqueous solubility Poorly water-soluble drugs having sluggish drug absorption results in inadequate and gastrointestinal mucosal toxicity and variable bioavailability. For this reason, the hassle of solubility is one of the important demanding situations for components chemists.[9]

Factors Affecting Solubility

The solubility relies upon at the bodily shape of the stable, the character and composition of solvent medium, particle length, temperature, strain, nature of the solute and solvent, molecular length polarity, polymorphs, the rate of solution.[10]

1.Particle size:

Particle length impacts on solubility. As particle length decreases, the surface area with quantity ratio will increase. As thesurface area of particle will increase it reasons more interplay with solvent. [11]

2.Temperature:

Solubility is change with change in the temperature. If the method of solution absorbs the energy the solubility gets improve with enhancing the temperature. however, in instances wherein solution method releases the energy while there's a temperature is increases and the solubility can be reduced.

4. Nature of solute and solvent:

In this term their natures, the solubility of greater compounds varies greatly. the nature of solute and solvent relies upon on awareness of solute in particular amount of solvent at particular temperature.

5.Pressure:

For gaseous solutes, the growth in strain will increase solubility and a lower in strain lower the solubility. For solids and liquid solutes, modifications in strain don't have any impact on solubility.

6.Polarity:

Polarity of each solute and solvent molecules impacts the solubility. Generally polar solute molecules will dissolve in polar solvents and non-polar solute molecules will dissolve in non-polar solvents.

7.Polymorphs:

The capacity of a substance to crystallize in multiple crystalline shape is polymorphism. Polymorph is an agent having capacity to crystallize in multiple crystalline shape. It Polymorphs can range in melting factor.

8. Common Ion Effect

When a compound this is soluble possesses the equal ion because the precipitate this is blended right into a solution and reasons the solubility of the ionic precipitate to lower, it's far referred to as the not unusual place ion impact.

CONVENTIONAL SOLUBILITY ENCHANCEMENT TECHNIQUES:

1) PH ADJUSTMENT

soluble drugs with molecule that can be protonated (base) or deprotonated (acid) is potentially be dissolved in water by a pH change method. pH adjustment is the main principle in which it is used for various oral and parenteral administration. upon intravenous administration the poorly soluble drug may be remains because blood is a fix buffer with pH between 7.2 –7.4. to evaluate this approach, the buffer capacity and tolerability of the selected pH are most important to consider. In the pH of the stomach is around 1 -2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also like as the drug is passes through the intestines. some Ionizable compounds that are stable and soluble after the suitable pH adjustment the compound are may be acids or bases or zwitterionic. solubilized excipients that increase environmental pH with a suitable dosage form, such as a tablet or capsule, of a range higher than Pak of weakly-acidic drugs increases the solubility, those excipients which act as an alkalizing agents may enhance the solubility of weakly basic drugs. pH adjustment is also be combined with co-solvents is normal increase the solubility of the poorly soluble drug. if the precipitation upon dilution is amorphous, bioavailability can be increased due to an increased concentration gradient and increase the surface area for dissolution. if the precipitation upon dilution is pleasant or amorphous, bioavailability may be extended because of an extended gradient and more advantageous floor location for dissolution. this approach is used majorly in study as pre-clinically pH adjustment is the most important technique for the evaluation of efficacy of hydrophobic drugs due to its universality and its relative simplicity.

Advantages:

• Simple to formulate and analyze.

• Simple to supply and speedy track.

Disadvantages:

• Risk for precipitation in dilution with aq. media having a pH of compound is much less soluble.

• Tolerability and toxicity associated with the usage of a non-physiological pH and severe pH.[12]

2) COMPLEXATION:

In complexation extraordinarily at the risk forces inclusive of London forces, hydrogen bonding and hydrophobic interactions concerned.[1] frequently enough drug solubilization may be received with the aid of using which include most effective complexing agent in aq.form, or a strong drug product, however occasionally complex of greater than the complexing agent is wanted to acquire favored solubility[14]

A) Stacking complexes

It is expanding with the aid of using affiliation site of non-polar of drug and complexes agent these effects in exclusion of the non-polar site from touch with water, thereby decreasing overall full energy of the

gadget. stacking may be homogeneous or mixed, however effects in clean solution.[13] the Stacked association is one wherein the revelation of the hydrophobic areas to water is reduced. the riding pressure for this process is regularly passive.[15]

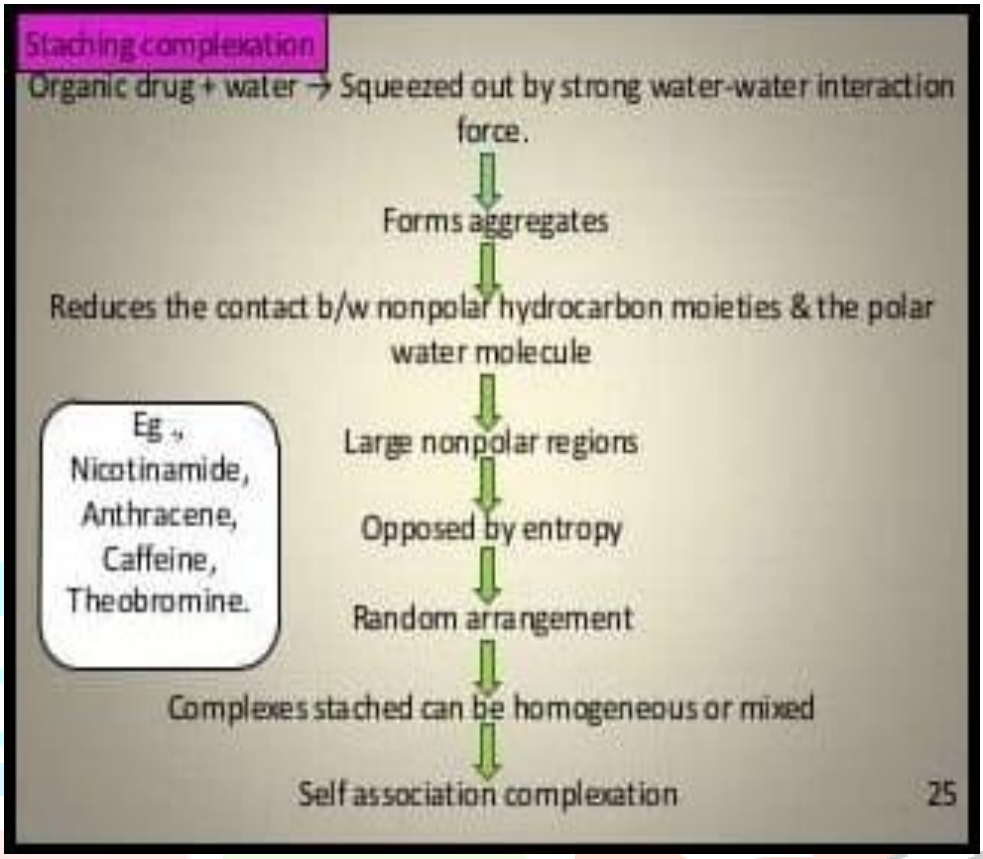


Figure1:system of stacking complexation.[16]

Inclusion complexes:

It is shaped with the aid of using the adding the nonpolar molecule or the nonpolar location of 1 molecule into the hollow space of some other molecule or institution of molecules, the 3 essential cyclodextrins α, ß, and γ-CD. Cyclodextrins have a hydrophilic outside and a hydrophobic inner hollow space. Cyclodextrin and their derivatives generally use in complexation. They shape complicated with drug and enhance the solubility and bioavailability of poorly soluble drug.[13] The Permeation of insoluble pills via diverse organic Membranes also can be more advantageous with the aid of using making ready drug- CD Inclusion compounds.[17]

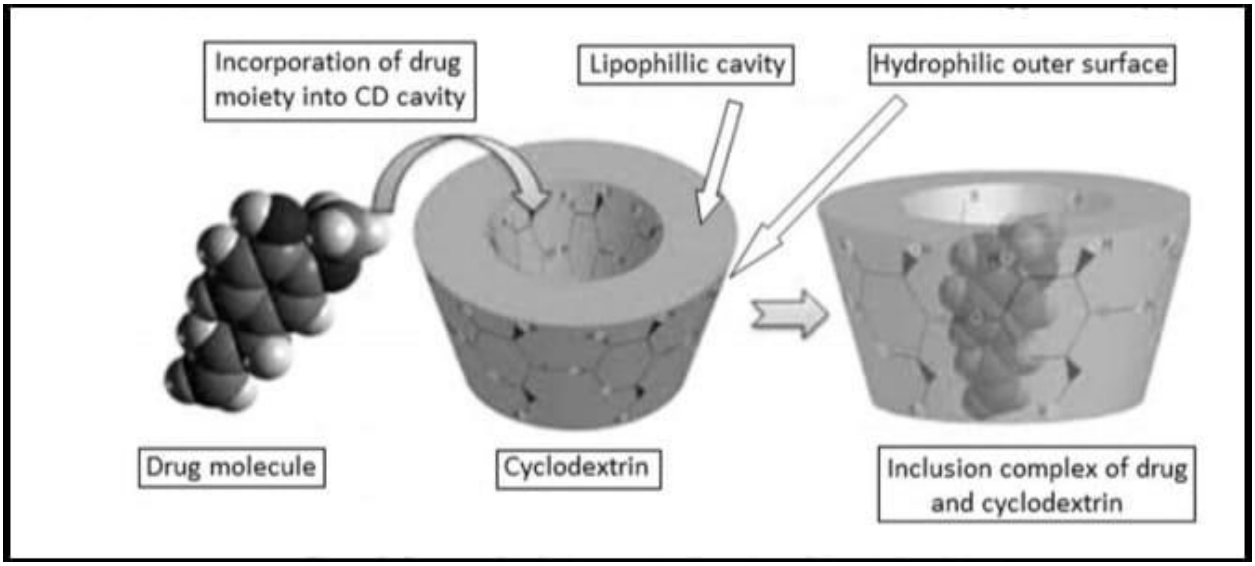


Figure 2: Process of inclusion complicated formation of drug and cyclodextrins [18]

3) HOT MELT EXTRUSION:

Hot-soften extrusion (HME) is one such approach that has been broadly used the industry. It is single-step continual manufacturing, success in enhancing the solubility of poorly soluble drugs. It additionally describes diverse hydrophilic and hydrophobic providers applied in HME[19] Hot soften extrusion is largely similar to the fusion approach besides that extreme blending of the additives is precipitated via way of means of the extruder. Just like the conventional fusion process, miscibility of drug and matrix may be a hassle. Furthermore, the product is less complicated to deal with due to the fact at the opening of the extruder the form may be adjusted to the following processing step without grinding.[13].

Extruders encompass 4 types of sections:

1. **Feeding**: This is a gap in which fabric enters the extruder. Either a hopper is connected to the outlet for passive feeding, or the fabric(s) can be constantly pumped into the extruder via way of means of one or extra outside feeder(s).

2. Conveying/Mixing: Consisting of the barrel and screw(s), this part of the extruder introduces warmness and shear pressure to the fabric(s), melting the feedstock and mixing the substances right into a homogeneous aggregate as they flow via the extruder.

3. Extrusion: A die is connected to the terminal of the extruder, making an allowance for the substances to be extruded right into a huge variety of shape factors, along with rods, tubes, films, and sheets.

4. Post-Processing: After extrusion, the fabric may be processed in addition to gather a favored shape. Some not unusual place procedures consist of palletization to create effortlessly processed feedstock, milling to supply fabric for tableting, or injection molding to create a very last dosage shape.[20]

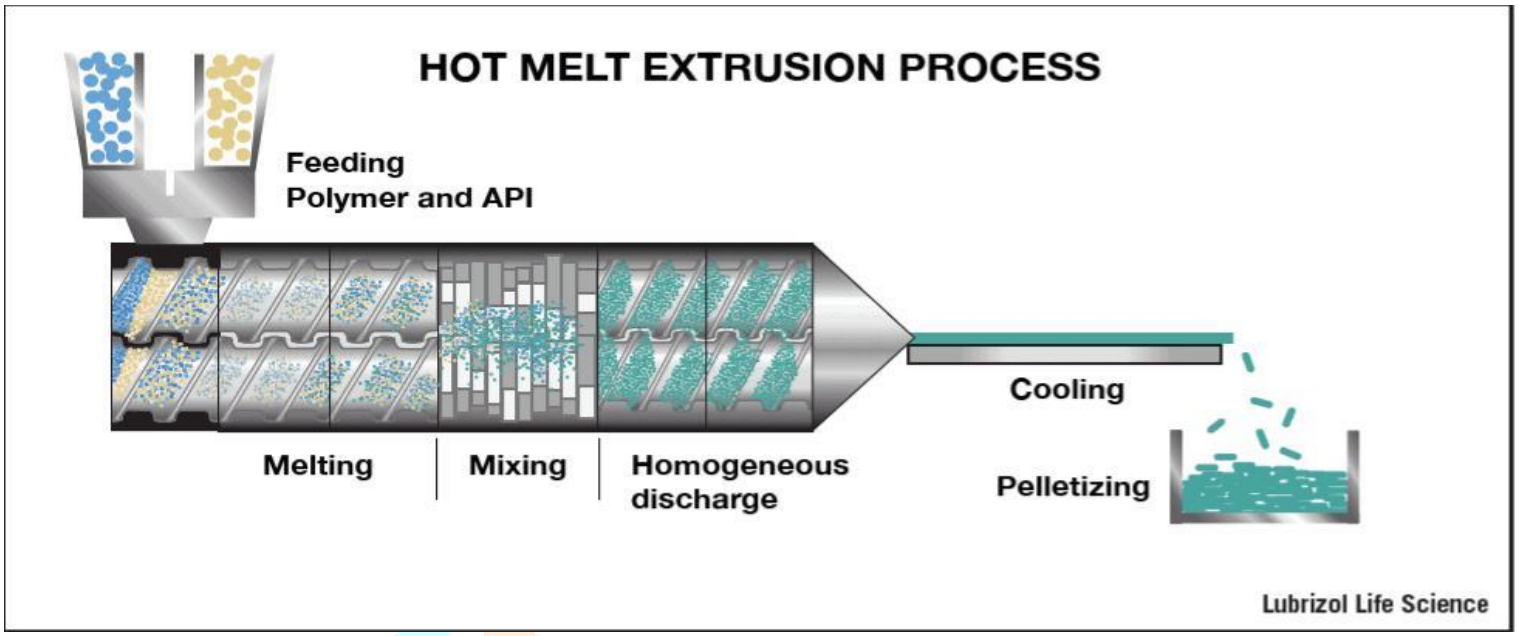


Figure3: Activities that take area all through the recent soften extrusion process.

4. SOLID DISPERSION:

Solid dispersion refers to a group of stable compounds consisting of a minimum component, typically a hydrophilic matrix. according to – Chiou and riegeman solid dispersions are "the dispersion of one or moreactive pharmaceutical elements in an inert service or matrix, in which the energetic elements may want to exist in finely crystalline, solubilized or amorphous"[21]. solid dispersion is one of the strategies used to boom the dissolution charge of the lipophilic drugs. solid dispersion is organized via way of means of the bodily triturating, solvent evaporation, fusion approach. the drug is included with inside the hydrophilic service which can be molecularly dispersed or can also additionally arise as nano crystals or amorphous nanoparticles.[22]

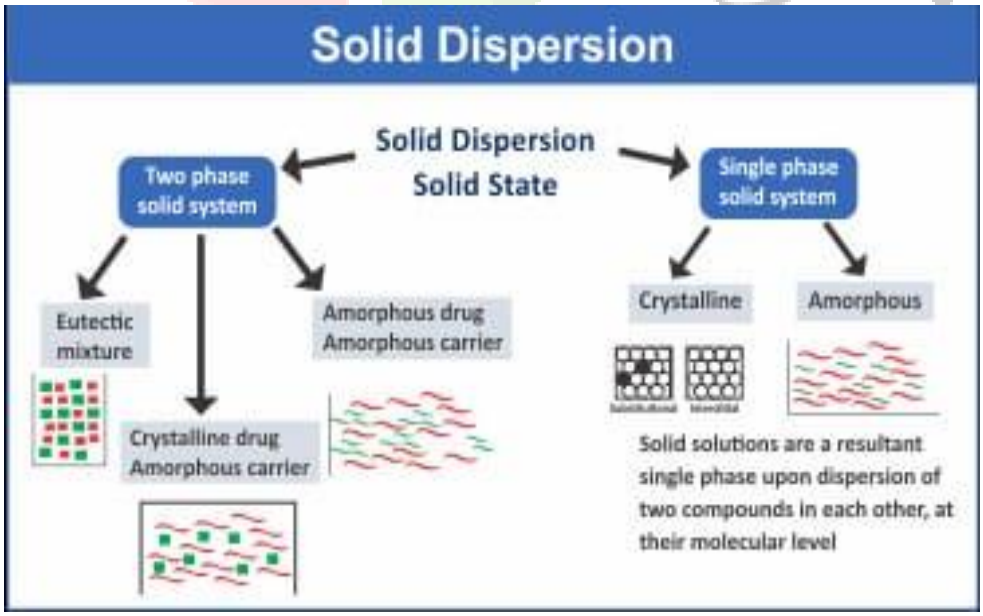


Figure 4: Solid Dispersion

Types of solid dispersion

There are five forms of stable dispersion are as follows:

A) Solid eutectic mixture

A simple eutectic mixture includes additives which might be completely miscible in liquefied however to a confined enlarge in stable state. these are organized via way of means of fast solidification of fused soften of two additives. when the mixture of poor water soluble drugs are dissolved in aqueous medium, the carrier is dissolved rapidly, liberating better crystal of the drug.[23]

B) Solid Solution

Solid solutions are different than liquid ones, consisting of simply one segment non responsive of the wide variety of Components. In the case of stable solutions, the drug's Particle length has been decreased to its absolute minimal viz. the molecular dimensions and the dissolution charge is decided via way of means of the dissolution charge of the service. Classified According to their miscibility

a) Continuous Solid Solutions:

In a non-stop stable solution, the additives are miscible in all proportions. theoretically, because of this the bonding electricity among the 2 additives is more potent than the bonding electricity among the molecules of every of the person additives. solid solutions of this kind have-now no longer been suggested the pharmaceutical international until date.

b) Discontinuous Solid Solutions:

In the case of discontinuous stable solution, the solubility of every of the additives the different factor is confined. due to sensible issues, it's been suggested via way of means of Goldberg et al that the term stable solution 'should best be implemented whilst the mutual solubility of the two additives exceeds 5%.[24]

C) Crystalline Solid Dispersion

A crystalline stable dispersion (or suspension) is shaped whilst the charge at which drug crystallizes from drug–Polymer miscible aggregate is more than the charge at which drug–polymer fluid aggregate solidifies.

D) Amorphous Solid Dispersion

If the drug–polymer fluid aggregate is cooled at a charge that doesn't permit for drug crystallization, then drug is Kinetically trapped in its amorphous or a "solidified-liquid" states. These forms of dispersions have the hazard of ability for conversion to an extra strong and much less soluble crystalline formation[25].

E) Glass solution

Solute dissolve in a glass type of carrier to forms the homogenous glassy system is called glass solution. glass suspension are aggregations wherein induced ppt are suspended in a glassy solvent its features are brittleness,transperancy under the glass transition temperature.[26]

5) SALT FORMATION:

Salt formation strategies are is used to development of the solubility and dissolution of drug. this approach is for the method of any response of various drug or chemical response. salt is formed with the drug is ionized shaped. It's having extraordinary approach like physiochemical belongings and impacts traits stability, bioavailability, Purification and manufacturability of the drug. Salt formation has been a method for several intervals to better solubility.Ex. Aspirin, Theophylline, Barbiturates etc.[27]

6) Lyophilization Technique:

Freeze-drying contains switch of heat and the mass to and from the product preparation. This approach changed into Proposed as an opportunity approach to solvent evaporation. lyophilization has been idea of a molecular blending technique in which the drug and service are co dissolved in a not unusual place solvent, frozen and sublimed to pick a lyophilized molecular dispersion. a critical benefit of freeze drying is that the drug is subjected to minimum thermal pressure at some point of the formation of the stable dispersion. and the maximum critical advantage of freeze drying is section separation is minimized as quickly as the solution is syrupy. the solvent is sprayed into liquid nitrogen or bloodless dry air and the frozen droplets are ultimately lyophilized. It is a phenomenon of switch of heat and mass from and to the product.[28]

7) MICRONIZATION

Micronization will increase the dissolution charge of drug through the Increasing in the surface area, it does now no longer growth equilibrium solubility. Decreasing the particle Size of those tablets, which motive growth in floor area, development their charge of dissolution. Micronization of medication is achieved through milling strategies the use of rotor stator colloidal mill, rotor Mills. These techniques had been implemented to Griseofulvin, spironolactonediosm, progesterone, in an fenofibrate. For every drug Micro ionization more advantageous their digestive absorption and as a result their bioavailability and Clinical efficacy. [29]

8) SUPERCRITICAL FLUIDS TECHNIQUES:

Supercritical fluid (SCF) techniques were significantly applied for pursuing Chemical reactions, extraction,crystallization,precipitation,purification,and improvement of micro- and Nanoparticles. To regulate solubility and Bioavailability of poorly soluble tablets thru SCF.SCF unearths a essential utility In the improvement of dry powder inhalers that as it should be supply particular Dose to the lungs. Furthermore, SCF era may be explored for the improvement of sustain and controlled release type ofstructure. This era is an eco-

friendly, inexperienced system that generates much less waste at some point of operation and produces satisfactory product at minimal cost.[30]

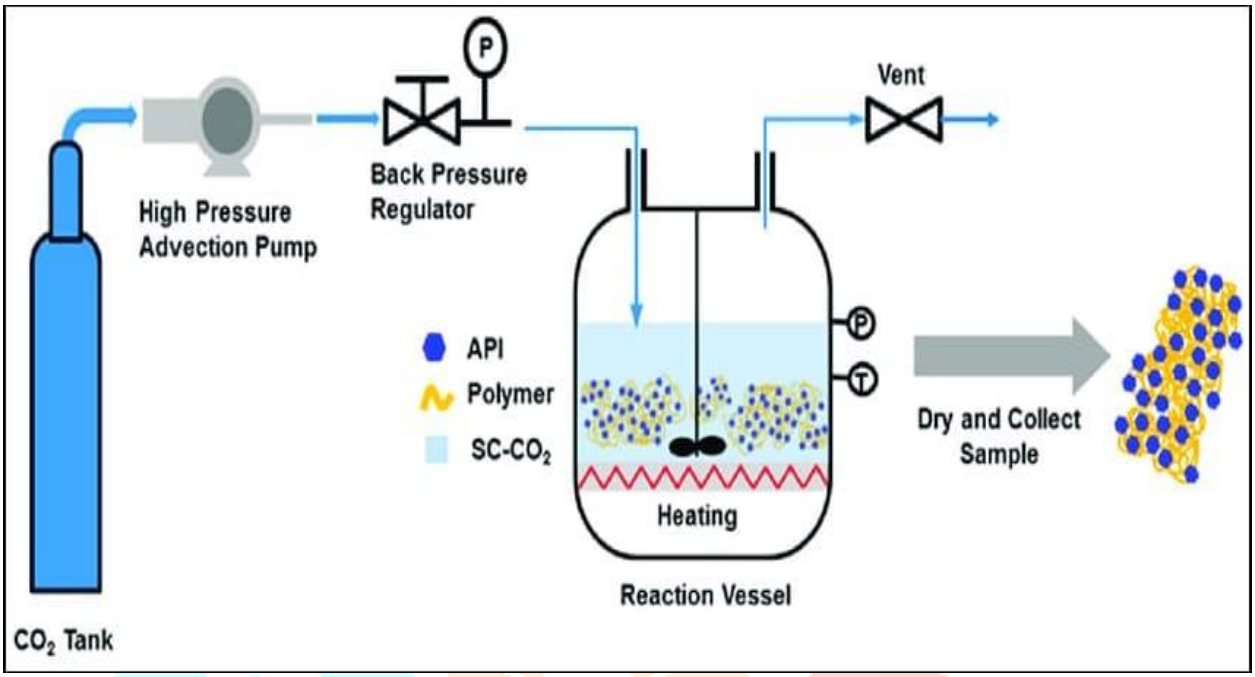


Figure5:flow chart of supercritical fluid process.

Procedure:

The physical compounds in specific ratios had been positioned in an CO2-permeable bag, and the bag changed into the positioned the excessive-strain vessel of the SCF tool and processed. when the vessel changed into closed and sealed, enough CO2 changed into pumped into the vessel to attain 25 MPa at 40°C. these response situations needed to be maintained for as a minimum 18 h to enable enough blending of the drug and polymer the CO2 medium. next, CO2 changed into step by step discharged from the vessel through a valve. the stable powders had been accrued and dried in an oven at 40°C for at least 24 h.[31]

Methods of preparation

A) COSOLVENCY

Co-solvent are aggregate of water and one or greater water miscible solvent used to create answer with more advantageous solubility or poorly soluble compound. co-solvent can improve with the solubility for the poorly soluble compound numerous thousand as compared to aqueous solubility of the drug alone. the amount of poorly water-soluble compounds are dissolve mostly as compared to solubilization approaches.[32]

B) KNEADING METHOD

Active drug with appropriate polymer in specific ratios is added to the mortar and triturated with small amount of ethanol to put together a slurry. slowly the drug is incorporated into the slurry with consistent

trituration. The prepared slurry is then air dried at 25°C for 24hrs. The resultant product is pulverized and exceeded thru sieve no. eighty and saved in desiccator over fused calcium chloride.

C) HYDROTROPY

Hydrotropic is a solubilization phenomenon wherein addition of huge quantity of a 2d solute effects in a growth the aqueous solubility of some other solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate were found to decorate the aqueous solubilities of many poorly water-soluble tablets. [33]

D) MILLING METHOD

The phrases milling, size reduction, comminution, grinding and pulverization are regularly used interchangeably. traditionally, milling is accomplished to facilitate the extractions of crude tablets, reduction generators, cutter generators, pestle and mortars and runner generators can be hired for this purpose. In those milling operation, the dried crude drugsarefinebythe sharp blades(cutter mill), impacted through hammers or compressed through the utility of strain (cutter mill, pestle and mortar. these residences can be measured through mild scattering strategies together with photon correlation spectroscopy and laser diffraction, respectively.[34]

E) SOLVENT EVAPORATION METHOD

Drug and service each are dissolved in natural solvent. after entire dissolution,the solvent is evaporated. The stable mass is ground, sieved and dried. solid dispersion of Ofloxacin with polyethylene glycol changed into organized through solvent evaporation method.

F) CO-PRECEPITATION METHOD

Accurately weighed service is dissolved in water and drug in natural solvent. After whole dissolution, the aqueous solutions of service is then poured into the natural solutions of the drug. The solvents are then heated and evaporated. The dispersion is pulverized with pestle and mortar, sieved and dried.[26]

G) HIGH PRESSURE HOMOGENIZATION

HPH has additionally been acknowledged to conquer the drawbacks of traditional size decreasing techniques such, polymorph transformation Amorphization, and metallic contamination because of excessive mechanical power related to conventional milling strategies HPH is like minded to be used in each aqueous as properly anon-aqueous fluid media and tries were made to apply different pressurized fluids like carbon dioxide HPH Has additionally been extensively utilized in formulating parenteral formulations of poorly water soluble tablets.

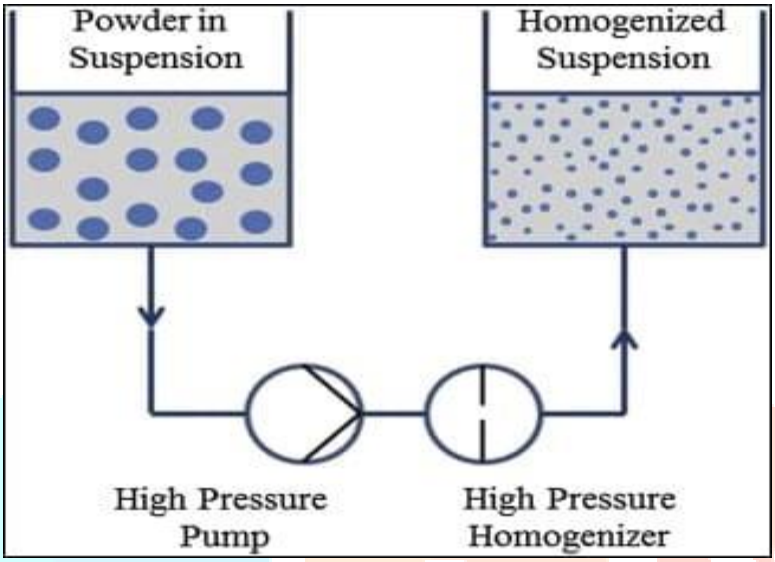


Figure 6:Scheme of excessive stress homogenization method[35]

NOVEL TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

1) LIQUISOLID TECHNIQUES:

When a drug dissolved in a liquid medium is delivered right into a service porous with a porous floor and fibers in its indoors, including cellulose, each absorption and adsorption occur; that is, the liquid is first of all absorbed the indoors of the debris and is captured via way of means of its inner structure, and after this method has reached saturation, the liquid is adsorption onto the inner and outside surfaces of the porous service debris. by mixing a liquid medicine with distinct powder excipient including the service and coating cloth, a liquid medicine may be become a dry, non-adherent, free-flowing, compressible powder. coating substances encompass microcrystalline and amorphous cellulose and silica powders.[36]

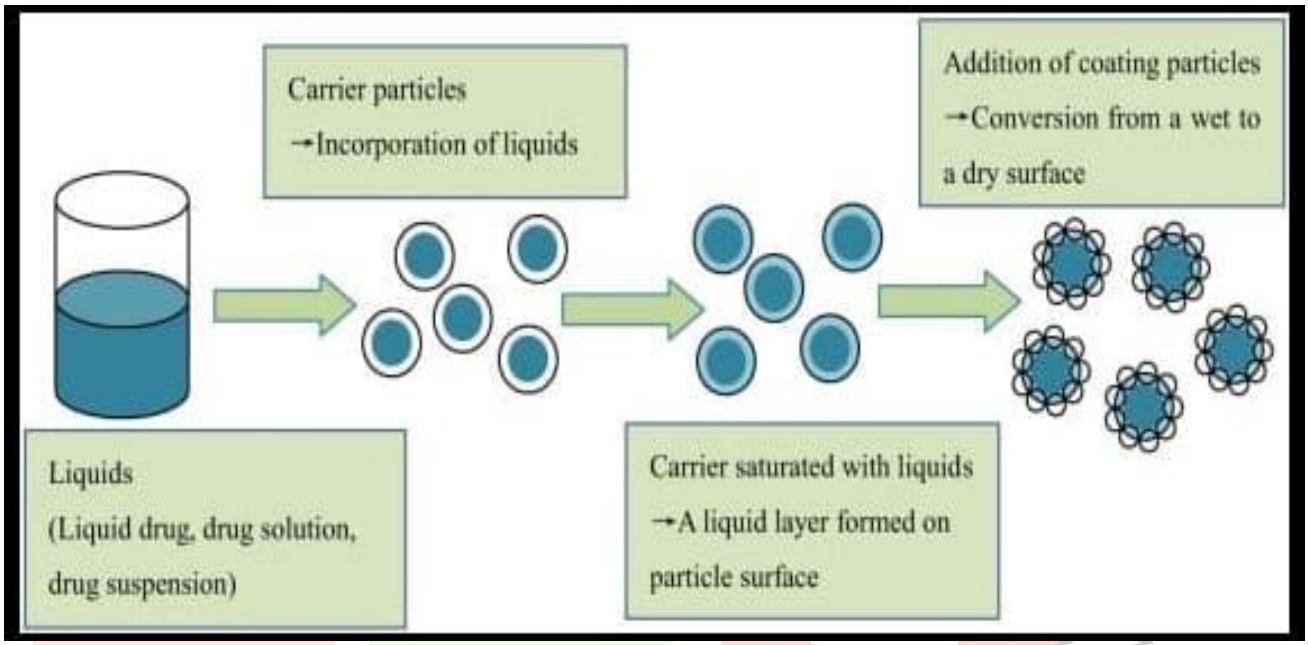


Figure 7: Mechanism of formation of liquisolid formulations.[37]

Advantages

1) A type of medicines which can be poorly soluble may be formulated into the medium.

2)In contrast to the introduction of smooth gelatin capsules, the value of manufacturing is minimal.

3)Allows liquid tablets to be pulverized in a flowable and compressible manner.

4)This technique is beneficial for manufacture of greasy and liquid tablets.

Disadvantages

1)they are not always appropriate to insoluble drugs with excessive doses (>one hundred mg)

2) It necessitates recipients with excessive precise floor location and adsorption characteristics.

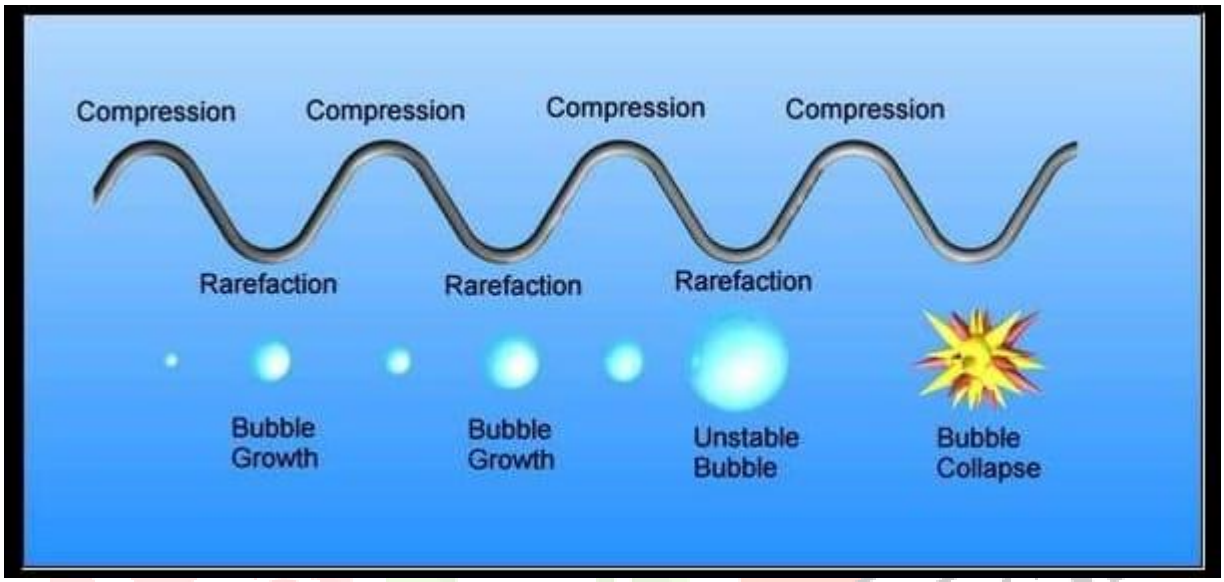
2) MELT SONO CRYSTALLIZATION:

Melt sono crystallization method is the advanced particle engineering method includes the utility of extremely Sound (US) power to the smooth or viscous molten mass dispersed in an immiscible liquid. Solidification/Crystallization from emulsified soften is completed the Influence of US power. Melt son

crystallization gives solvent and service much less technique for the formation of drug with enhanced solubility in water.

Mechanism of sono crystallization

Mechanism is primarily based totally at the actuality that the stress shockwave due to hollow space fall apart creates locally excessive pressures. There are materials for which the solubility reduces with stress, this will increase the nearby super saturation and will set off nucleation. Initiated because of separation of the solute and solvent close to the bubble wall. this is because of excessive pressures happening in the remaining segment of bubble fall apart. Solvent evaporating into the bubble or cooling of the liquid Interface layer will increase nearby brilliant saturation, that can lead to nucleation across the hollow space[38]



. **Figure 8:** method of ultrasound in soften son crystallization.[39]

In sono crystallization the power of ultrasound reason repeated compression and expansion. After numerous cycle the bubble forms, grows and collapses. due to bubble collapses the power produces. the power became accountable for breaking of debris. This consequences in excessive repeatable and predictable crystallization.

Process of melt sono crystallization

The generalized technique/method of soften Sono crystallization is as follows:

1.The required quantity of drug melted on a paraffin oil maintained temp. range of 190°C -193°C.

2.Molten drug then poured in vessel containing deionized water maintained at 50°C to 60°C.

3.The combination sonicated for 15-20min the use of Probe ultrasonication at exclusive amplitude.

4.The product received after solidification of dispersed droplet became separate via way of means of filtration and dried at room temperature.

3) NANOTECHNOLOGY:

Nanotechnology is described because the technology and engineering accomplish with inside the nanoscale this is 10-9 m. The drug micro debris drug powder is transferred to drug nanoparticles via way of means of strategies like Bottom-Up and Top-Down Technology. Nanosuspensions are submicron colloidal dispersions of Nano sized drug debris stabilized via way of means of surfactants. These may be used to beautify the solubility of medicine which are poorly soluble in water in addition to lipid media. as the end result of accelerated solubility, this technique is beneficial for molecules with negative solubility, negative permeability, or both, which poses a considerable undertaking for the formulators. The decreased particle length renders the opportunity of intravenous management of poorly soluble tablets with none blockade of the blood capillaries.[40] In drug shipping systems, nanotechnology provides vital method of improving drug accumulation at focused web sites and, in turn, improves its pharmacokinetics and bio distribution.

ADVANTAGES OF NANOSUSPENSION

• Higher drug loading may be achieved

• Dose discount is possible

• Enhance the bodily and chemical balance of medicine[41]

4) PRODRUG APPROACH:

The prodrugs can be Formed with any natural molecule having a chemically reactive practical group, Prodrugs are artificial derivatives (EX. Esters and amide) of the drug molecule that could have intrinsic pharmacological processes. however normally ought to go through a few transformations. In-vivo to free up the lively drug molecule. through the formation of prodrug, a lot of aspect chains or practical businesses can be introduced to enhance the organic or pharmaceutical residences of compound. In 1980, Amidon recommended that the practice of water soluble seasoned-tablets via way of means of the addition of unique amino acids are the substrates for enzymes placed in intestinal brush border using the lysine ester prodrug of estrone, the ability boom in absorption charge changed into discovered in vivo the use of perfused rat intestines [42]

5) SPHERICAL AGGLOMERATION:

Spherical agglomerates had been organized the use of diethyl ether as cross over liquid via way of means of neutralizing approach, spherical agglomeration approach, Quasi emulsion solvent diffusion approach. Spherical agglomerates had been evaluated for morphology, manufacturing yield, drug content, particle length and dissolution behavior in comparison with natural drug. [43]

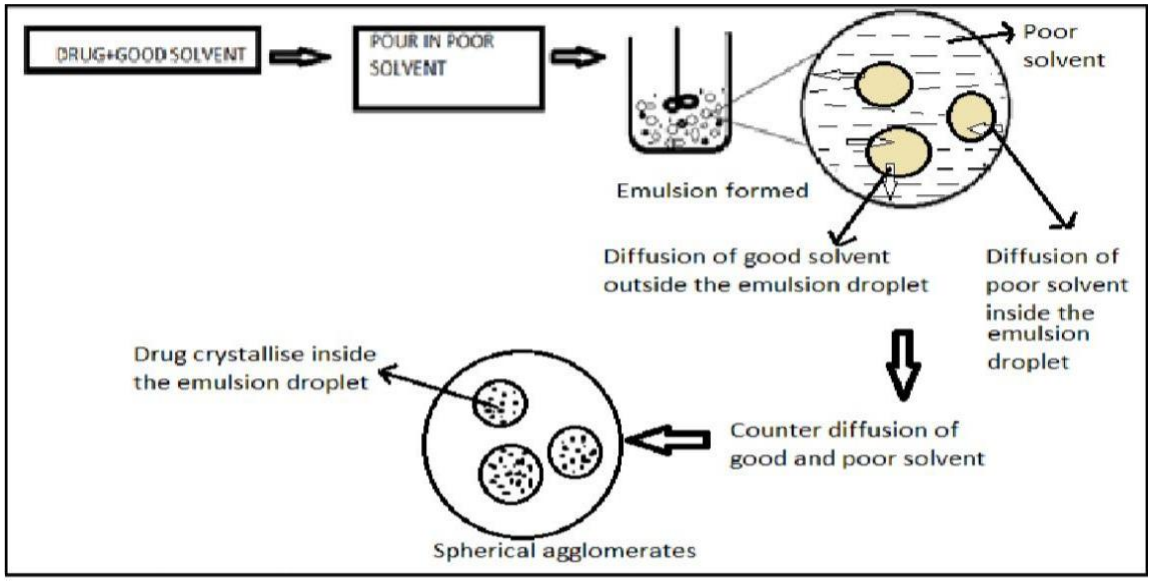


Figure 9: spherical Agglomeration process

Advantages of the round Agglomeration technique

1) Utilization of this technique improves wettability and dissolution rate of a few drug.

2) This approach may be used for protecting of the sour flavor of Drugs.[44]

Conclusion:

By this article we conclude that, the solubility of the drug is the most important factor that decides the formulation of the drug as well as therapeutic efficacy of the drug for quantitative analysis. dissolution of drugs is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is also the fundamental requirement for the formulation and development of different dosage forms of different drugs. The choice of any method for increasing solubility is determined by the drug's nature and properties, such as physical nature, chemical nature, pharmacokinetic behavior, and so on. with the use of various technical procedure, such as those mentioned above, it is now possible to enhance the solubility of poorly soluble drugs.

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