“AN OVERVIEW ON SOLUBILITY ENHANCMENT OF POORLY SOLUBLE DRUGS "

Submitted in partial fulfillment for the requirements of

the degree of Bachelor of Pharmacy

BY

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CERTIFICATE

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This is to certify that the project entitled SOLUBILITY ENHANCMENT OF POORLY SOLUBLE DRUGS is a bonafide work of GHANKAR SHAISTA SIKANDARI (17PH10), QURESHI UZMA JAVED(17PH40), KHAN RIZWAN GULAM (15PH21), RAHUL RAMNARESH GUPTA (17PH11) submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutics.

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DECLARATION

We declare that this written submission represents our ideas in our own words and where other ideas or words have been included, we have adequately cited and referenced the original sources. We also declare that we have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in our submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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INDEX

ABSTRACT

Solubility is a spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. The extent of a solubility of substance in a specific solvent is measured as the saturation concentration , where adding more solute does not increase the concentration of solution. There are different factors which affects the solubility of drugs are temperature , particle size , solubility curves etc. Solubility of drug is the important parameter in achieving pharmacological activity. As efficacy of drug is depends on its solubility and bioavailability of drug. Poor solubility and dissolution create problems in manufacturing of various dosage forms. There are various techniques which enhances solubility of poorly soluble drug such as Solid Dispersion , Nanosuspensions . They improve solubility of drug and its efficacy. Solid dispersion is occurred by evaporating solvent. There are different surfactants which added to achieve stability of drugs and prevent recrystallization. Natural gums can be used as an excipient to improves the solubility .

INTRODUCTION

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. The extent of solubility of a substance in a specific solvent is measured as the saturation concentration where adding more solute does not increase its concentration in the solution. The solvent is generally a liquid, which can be a pure substance or a mixture of two liquids. One may also speak of solid solution, but rarely of solution in a gas. The extent of solubility ranges widely, from infinitely soluble (fully miscible) such as ethanol in water, to poorly soluble, such as silver chloride in water. The term insoluble is often applied to poorly or very poorly soluble compounds Solubility is not to be confused with the ability to dissolve or liquefy 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 hydrochloric acid, but does dissolve in it by chemically reacting into zinc chloride and hydrogen, where zinc chloride is soluble in hydrochloric acid. Solubility does not also depend on particle size or other kinetic factors; given enough time, even large particles will eventually dissolve IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent. Solubility may be stated in units of concentration, molality, mole fraction, mole ratio, and other units USP and BP classify the solubility regardless of the solvent used, just only in terms of quantification and have defined the criteria as given in Table.

USP and BP solubility criteria

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Solubility improvement techniques can be categorized into physical modification, chemical modifications of the drug substance, and other techniques

.Physical Modifications

Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and cocrystallization, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

Chemical Modifications

Change of ph, use of buffer, derivatization, complexation, and salt formation. Miscellaneous MethodsSupercritical fluid process, use of adjuvant like surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients.

PARTICLE SIZE REDUCTION

Particle size reduction is one of the oldest strategies for improving solubility of drugs since solubility of drugs is related to drug particle size. When the particle size is decreased, the larger surface area of the drug allows the increase in the surface area to volume ratio thus increasing the surface area available for solvation. size reduction is a safe method to increase solubility of drug substances without altering the chemical nature of the drug .

CONVENTIONAL METHOD

Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Particle size reduction is thus permitting an efficient, reproducible, and economic means of solubility enhancement.

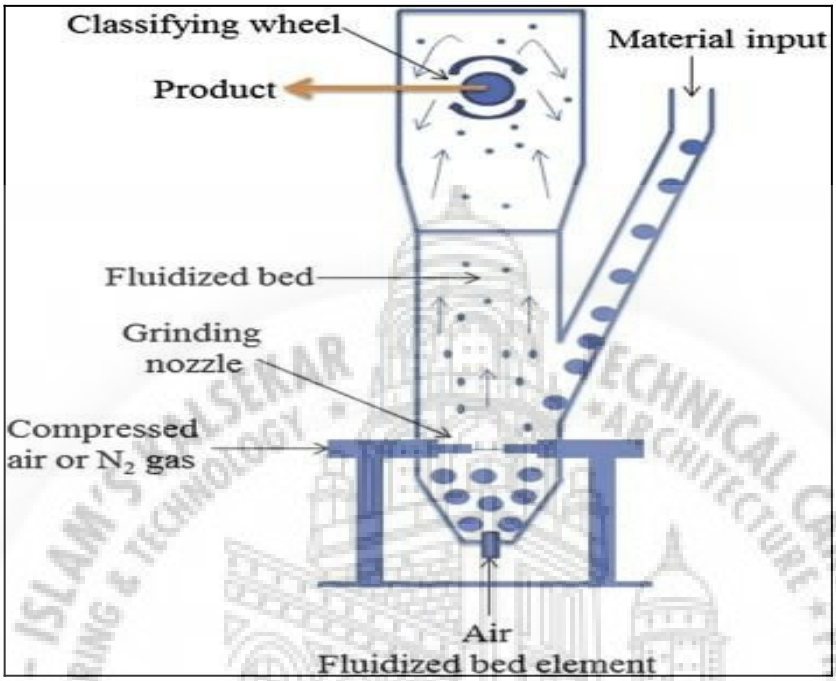
MICRONIZATION

Micronization is a commonly used method for increasing solubility of BCS class II drugs .It is a technique that refers to transfer of coarse drug powder to an ultrafine powder with the mean particle size in the range of 2–5 µm and only a very little fraction of the particles lie below 1 µm size range . Micronization does not increase the equilibrium solubility of the drug itself but it increases the dissolution rate by increasing the surface area to drug ratio by which the active ingredient can dissolve or diffuse from the drug particles.

JET MILLING

A fluid jet mill uses the energy of the fluid (high pressure air) to achieve ultra fine grinding of pharmaceutical powders .It has several advantages of being a dry process, size reduction of micron-sized particles with narrow size distributions, absence of contamination and is suitable for heat sensitive drugs.In a study conducted by Jinno et al., the in vitro dissolution rate of a poorly soluble drug cilostazol was improved by milling and a moderate enhancement of bioavailability was observed in absorption

from cilostazol suspension.

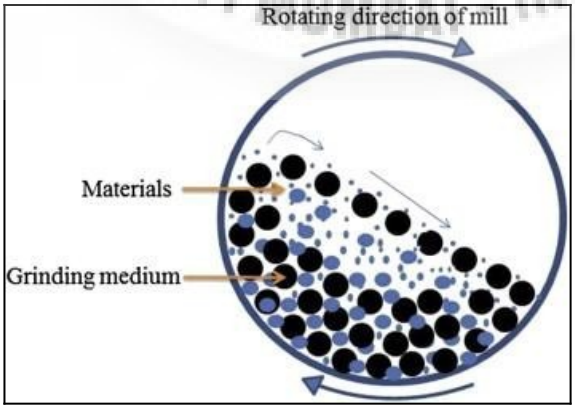


[FIG] 1

Schematic diagram of a pharmaceutical jet mill.

BALL MILLING

A pharmaceutical ball mill is usually a cylindrical crushing device that is used for grinding of pharmaceutical powders by rotation around a horizontal axis. The device is partially filled with the material to be ground plus the grinding medium usually ceramic balls, flint pebbles or stainless steel balls.



[FIG] 2

Schematic diagram of a ball mill.

Ball milling technique for size reduction is also essential in preparing amorphous powders of drugs if milled together with polymeric compounds[1]

SALT FORMATION:

Many a times an drug cannot be formulated in its pure form due to various issues of instability. Therefore they are converted to solid forms such as salts, co-crystals, solvates, hydrates, and polymorphs. Each of them imparts a different physiochemical property and affects it's characteristics stability, bioavailability, purification and manufacturability of the drug in their own better way. Salt formation of poorly soluble drug candidates (weak acids and bases) has been a strategy for several decades to increase solubility. Salts are formed when a compound is ionized in solution. It is an useful method in parenteral and other liquid formulations, as well as in solid dosage forms. Acidic or basic drug are converted into salt having more solubility than respective drug. Example. Aspirin, Theophylline, Barbiturates. Commercially available example of this approach is Progesterone; a water-insoluble steroid which is solubilized in peanut oil [2]

CO-SOLVENCY

The solubility of a poorly water soluble API can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as co- solvents. Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for insoluble compounds. This is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Parenteral formulations require the addition of water or a dilution step with an aqueous media to lower the solvent concentration prior to administration. .The most frequently used low toxicity cosolvents for parenteral use are propylene glycol, ethanol, glycerin, and polyethylene glycol. Dimethylsulfoxide (DMSO) and dimethylacetoamide (DMA).[3]

ADVANTAGES:

Simple and rapid to formulate and produce.

Co- Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone

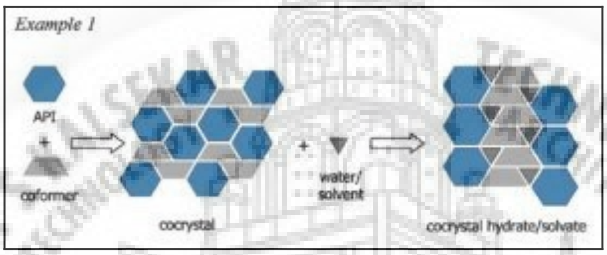
DISADVANTAGE:

As with all excipients, the toxicity and tolerability related with the level of solvent administered has to be considered. The precipitates may be amorphous or crystalline and can vary in size. Many of tcompounds are unsuited to co-solvents alone, particularly for intravenous administration.

CO-SOLVENT PRODUCT: Nimodipine Intravenous Injection (Nimotop®, Bayer) and Digoxin Elixir Pediatric (Lanoxin®, GSK)

CO-CRYSTALLIZATION:

Co-crystallization alters the molecular interactions and it is better alternative to optimize drug properties. A more refined definition of a co-crystal can be “multicomponent crystal that isormed between two compounds that are solids under ambient conditions, where at least one component is an acceptable ion or molecule". Co-crystallization overcomes various physical, chemical or physiological drawbacks of a drug. if both exists in solid form then they are termed as cocrystals. Pharmaceutical Co-crystals basically consists of two components that are the API and the cocrystal former(s).



[FIG] 3

Different Techniques of Co-crystallization: In pharmaceutical companies enhancement of solubility in case of API with limited aqueous solubility are becoming increasingly prevalent in the research and development portfolios..

a Solvent Evaporation: Solvent evaporation is the most convenient method in the case of crystallization. In this technique, the material is mixed with the common solvent and evaporated completely. In the evaporation stage, the solution of molecules is expected to undergo various hydrogen bonding reactions. The major disadvantage of this method is that it requires a large amount of solvent.

b Grinding: Solid state grinding is where the materials are mixed, pressed and crushed in a mortar and pestle or mill. In general aspects, this technique provides particle size reduction, but in case of co-crystallization, these have proved to be a viable method for solid-state grinding along with liquid state grinding.

c Slurrying: Slurry crystallization is a simple process which includes the addition of crystallization solvent in the API along with its acceptable former. example Trimethoprim and sulfamethoxazole through slurry technique, The major disadvantage of this method is that it requires a large amount of solvent.[4]

HYDROTROPHY

Hydrotrophy is a solubilisation process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to “salt in” the solute and those salts that decrease solubility “salt out” the solute. Several salts with large anions or cations that are themselves very soluble in water result in “salting in” of non electrolytes called “hydrotropic salts” a phenomenon known as “hydrotropism”. Hydrotropic solutions do not show

colloidal properties and involve a weak interaction between the hydrotropic agent and solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives.

Category	Example
Aromatic cationics	Para amino benzoic acid hydrochloride, Procaine hydrochloride
Aromatic anionics	Sodium benzoate,Sodium benzene sulphonate, Sodium benzene disulphonate
Aliphatics and linear anionics	Sodium alkanoate

ADVANTAGES:

Hydrotropy is suggested to be superior to other solubilization method, such as miscibility, micellar solubilization, co solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification. Solvent character is independent of pH, hydrotrophy has high selectivity and does not require emulsification.

It only requires mixing the drug with the hydrotrope in water and do not require chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system.[5]

USE OF NOVEL SOLUBILIZER: The solubility of poorly soluble drug can also be improved by various solubilizing materials. Ex. Conventional solubilizer Polysorbates, PEG 400 Sepitrap,Soluplus Povacoat, dendrimers, is improve the solubility of hydrophobic API.Sepitrap as novel Solubilizer In less than 5 minutes, 80 % of solubilizers are desorbed from SepitrapTM and therefore is available to solubilize the drug substance. The ratio of sepitrap and drug (2:1) is good for enhancing dissolution rate and at the same time does not affect tablets characteristics and can be used without any formulation constraints.

Dendrimers act as solubilizing agents to host both hydrophilic and hydrophobic drugs and are known for their three dimensional, monodispersed, highly branched, macromolecular nano-scopic architecture with number of reactive end groups obtained by reiterative sequence of reactions. Dendrimers enhance the solubility of hydrophobes probably due to hydrophobic interactions, hydrogen bonding and electrostatic interaction between terminal functional groups of the dendrimers and hydrophobes. Most common dendrimers are polyamidoamine (PAMAM) dendrimers polypropyleneimine (PPI) dendrimers. [6]

NANOSUSPENSION

Nanosuspension consists of the pure poorly water-soluble drug without any matrix material suspended in dispersion. Preparation of nanosuspension is simple and it is applicable to all water insoluble drugs. It not only solves the problems of poor solubility and bioavailability, but also alters the pharmacokinetics of drug and thus improves drug safety and efficacy.Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10–9 m. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom-Up Technology and Top-Down Technology.Nanosuspensions are submicron colloidal dispersions of Nano sized drug particles stabilized by dispersion.These can be used to enhance the solubility of drugs that are poorly soluble in water as well as lipid media. As a result of increased solubility, the rate of flooding of the active compound increases and the maximum plasma level is reached faster.

ADVANTAGES OF NANOSUSPENSION

Enhance the solubility and bioavailability of drugs Suitable for hydrophilic drugs Higher drug loading can be achieved Dose reduction is possible Enhance the physical and chemical stability of drugs Provides a passive drug targeting[7]

PH ADJUSTMENT

water insoluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change.
pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may precipitate because blood is a strong buffer with pH between 7.2 –7.4. To assess the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. Solubilized excipients that increase pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity.

ADVANTAGES	DISADVANTAGE
Simple to formulate and analyse. Simple to produce and fast track. Uses small quantities of	Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less

compound, amenable to high throughput evaluations.	soluble. Intravenously this may lead to emboli, orally it may cause variability.

Commercial products using pH adjustment : Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents.[8]

DRUG DISPERSION IN CARRIERS

SOLID SOLUTION

Solid solutions are comparable to liquid solutions, consisting of just one phase irrespective of the number of components. In the case of solid solutions, the drug's particle size has been reduced to its absolute minimum viz. the molecular dimensions and the dissolution rate is determined by the dissolution rate of the carrier[14]. Classified according to their miscibility (continuous versus discontinuous solid solutions) or second, according to the way in which the solvate molecules are distributed in the solvent (substitutional, interstitial, or amorphous) for example: Griseofulvin from such solid solution dissolves 6 to 7 times faster than pure griseofulvin.

SOLID DISPERSION

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulphonamide drug and a water-soluble carrier in the early 1960s. Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone (Povidone, PVP), polyethylene glycols (PEGS), Plasdone-S630. Surfactants like Tween-80, docusate sodium, Myrj 52, Pluronic-F68, and sodium lauryl sulphate (SLS) also find a place in the formulation of solid dispersion.
Solid dispersion can also be referred as the dispersion of one or more active. ingredients in an inert matrix at solid state prepared by the melting, solvent, and melting solvent method.

Advantages of solid dispersions

1) To improve wettability.
2)To improve porosity of drug.
3)To decrease the crystalline structure of drug into amorphous form.
4)To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.

5)To mask the taste of the drug substance.
6)To prepare rapid disintegration oral tablets.
7)To obtain a homogeneous distribution of the small number of drugs at solid state.
8)To stabilize unstable drugs.
9)To dispense liquid or gaseous compounds.
10)To formulate a faster release priming dose in a sustained release dosage form.
11)To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble.

Disadvantage of Solid Dispersion

The disadvantages of solid dispersion are listed below.
1) It leads to the poor scale-up for the purpose of manufacturing.
2) The polymers used in solid dispersion can absorb moisture and cause phase- separation crystal growth and convert amorphous form into crystalline form. The result in decrease solubility and dissolution rate.
3) It is laborious method of preparation.
4) It causes reproducibility of physicochemical characteristics.

APPLICATION OF SOLID DISPERSION:

1) To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption, and bioavailability.
2) To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo-oxidation, and other decomposition procedures.
3) To reduce a side effect of certain drugs.
4) Masking of unpleasant taste and smell of drugs.
5) Improvement of drug release from ointment creams and gels.
6) To avoid undesirable incompatibilities.
7) To obtain a homogeneous distribution of a small amount of drug in solid state.
8) To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.

FUSION METHOD

The melting or fusion method was first proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this method, the physical mixture of a drug and a water-soluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring the final solid mass was crushed, pulverized, and sieved, which can be

compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, Le., the selection of the carrier and the weight fraction of the drug in the system.

An important requisite for the formation of solid dispersion by the hot melt method is the miscibility of the drug and the carrier in the molten form. Another Important requisite is the thermostability of the drug and carrier.
The carrier is heated to a temperature just above its melting point and the drug is incorporated into the matrix. The mixture i cooled with constant stimming to homogeneously disperse the drug throughout the matrix other factors that may play a role include solubilizing effect conferred by the carrier itself, improved wetting or decreased surface hydrophobicity, complexation, and crystallization of the drug in a metastable polymorphic form of altered thermodynamic properties.
The main advantages of this direct melting method are its simplicity and economy.

SOLVENT METHOD

The carrier and the active ingredient are dissolved in a suitable organic solvent. This solvent is evaporated at an elevated temperature or under vacuum as the solvent is being removed, super saturation occurs followed by simultaneous precipitation of the constituents resulting in a solid residue. The co precipitate is then dried under vacuum to drain out any solvent freely adhering to the particle. Removal of even trace amounts of the solvent is implied. Extremely sensitive techniques such as differential thermal analysis (DTA). differential scanning calorimetry (DSC). thermogravimetric analysis (TGA). and less sensitive procedures like spectroscopy. gravimetry and can be used to demonstrate complete solvent removal.

The main advantage of the solvent method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of organic solvents.

Disadvantages are associated with this method such as

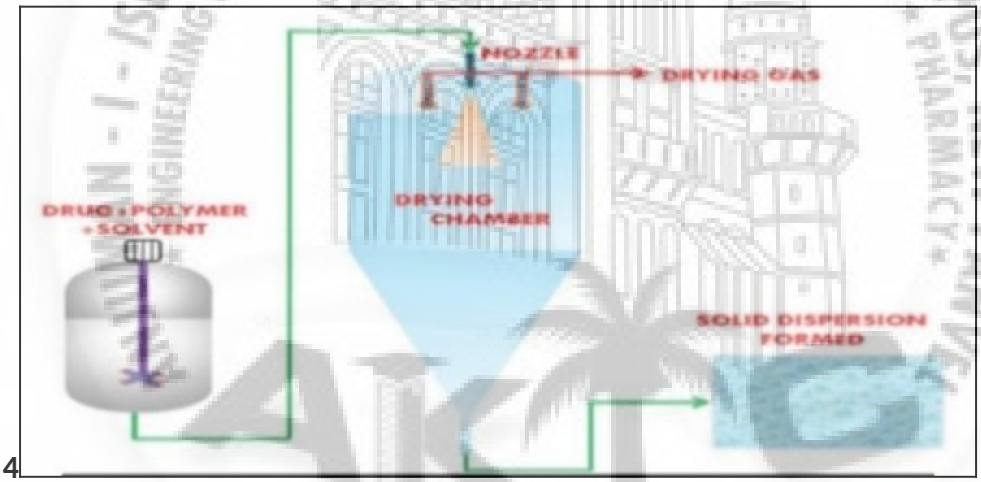
1) The higher cost of preparation.
2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability.
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form.

FUSION SOLVENT METHOD

Carriers are melted and the drugs are incorporated in the form of a solution[11]. If the carrier can hold a certain proportion of liquid yet maintaining its solid properties, and if the liquid is innocuous, the need for solvent removal is eliminated. Method is useful for drugs with high melting points or that are thermolabile.

SPRAY DRYING METHOD

This method was developed in 1920 in which the manufacture of milk powder was one of the first applications of spray drying Presently, this technique is having great utility in pharmaceutical industry owing[12].
to rapid drying and specific characteristics such as particle size and shape of the final product. In this method atomization of suspensions or solutions into fine droplets is done and drying of particles that m may lead to the formation solid particles. This process permits production of fine, dust free powder.
The carrier and the active ingredient are dissolved, suspend in a suitable solvent. This solvent is evaporated by drying it to apply a stream of heated air to remove the solvent. Due to the large surface area of the droplets, the solvent rapidly evaporates, and solid dispersion is formed quickly.



[FIG] 4

LYOPHILIZATION/FREEZE-DRYING TECHNIQUE

In this technique, solvent system from the solution is eliminated through a nary freezing and subsequent drying of the solution containing drug and CDs or suitable polymer at reduced pressure[13]. specialization in great measure dependent on unique properties of er and its role as solvent, gas, diluents, plasticizer, stabilizer. It in alternative to solvent evaporation and involves molecular of drug and carrier in a common solvent.

Advantage of lyophilization/freeze-drying technique Lyophilization freeze drying technique is considered worthy to get a porous, amorphous powder with high degree of interaction

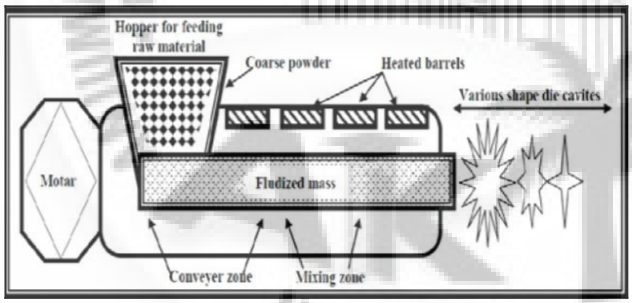
between drug and suitable polymer Thermolabile substances can be successfully made into complex form by this method.

Disadvantages of lyophilization freeze-drying technique Use of specialized equipment Time consuming process and yield poor flowing powdered product.

HOT MELT METHOD EXTRUSION

This is method of choice in the polymer industry. But Speiser and Huttentach were the first persons who use this technology for pharmaceutical purpose[13]. A melt extrusion consists of the following sections: An opening to feed raw materials, a heated barrel that consists of extruder screws to convey and mix the fed materials, and an exit port, which consists of an optional die to shape the extruding mass. The Active in gradients and the carrier are fed into the heated barrel of extruder at a constant rate. When the mixture of active ingredient and the carrier is conveyed through heated screws, it is transformed into its "Fluid like state". This state allows intimate and homogeneous mixing by the high shear of extruder screws. An exit port, which consists of an optional die, shapes the melt in the required form such as granules, pellets, films, or powder.

advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about one minute, which enables drug that are somewhat thermolabile to be processed.



[FIG] 5

DROPPING METHOD

A solid dispersion of a melted drug-carrier mixture is pipetted the dropped onto a plate, where it solidifies into round particles. The size, shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature dependent, it is important to adjust the temperature so that when the melt is dropped on the plate it solidifies to a spherical shape.

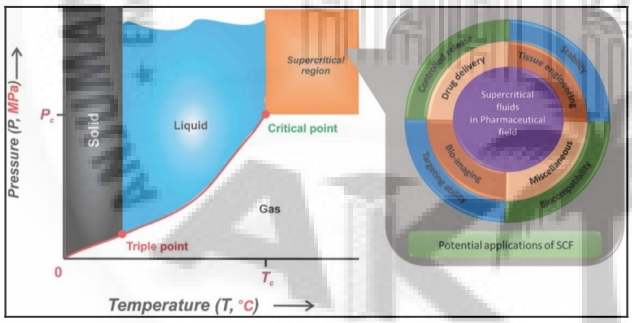
SUPERCRITICAL FLUID

super critical fluid process is increased in use for recent years for particle size reduction and solubilisation.It is the fluids whose temperature and pressure are greater than its critical temperature(Tc) and critical pressure(Tc), allowing it to assume the properties of of both liquid and gas(3). Supercritical Fluids are highly compressible. solubilization of drug particles can be recrystallized at a reduced particle sizes[5]. The flexibility by Supercritical fluids allows micronisation of drug particles. As of now the Supercritical Fluids processes can create nanoparticulate suspensions of paricles and the diameter is from 5-2000 nm. Some pharmaceutical companies like Nektar Therapeutics are using Supercritical Fluids process for particle engineering, for particle size reduction and enhancement for solubility[8]

There are several methods of Supercritical Fluids[8]-:

- Precipitation with compresses antisolvent(PCA)
- Solution enhanced dispersion(SEDS)
- Supercritical antisolvent process(SAS)
- Rapid expansion of supercritical solution(RESS)

Schematic representation of CO2 phase diagram elucidating CO2 existence as various phases along with the supercritical phase beyond the critical point (Tc=31.1 C, Pc=7.38Mpa)



[FIG] 6

ADVANTAGES	DISADVANTAGES
The higher diffusivity and the lower viscosity	The extraction must be operated at the high pressure (1,000 - 5,000 psi) required to maintain the solvent in supercritical state.
More controllable liquefaction atmosphere(density, solvent power) by pressure and temperature	Higher capital.
Easier separation of extract by the staged decompression, than in a conventional	Higher operating costs.

liquefaction process.	

INCLUSION COMPLEX FORMATION-BASED TECHNIQUE

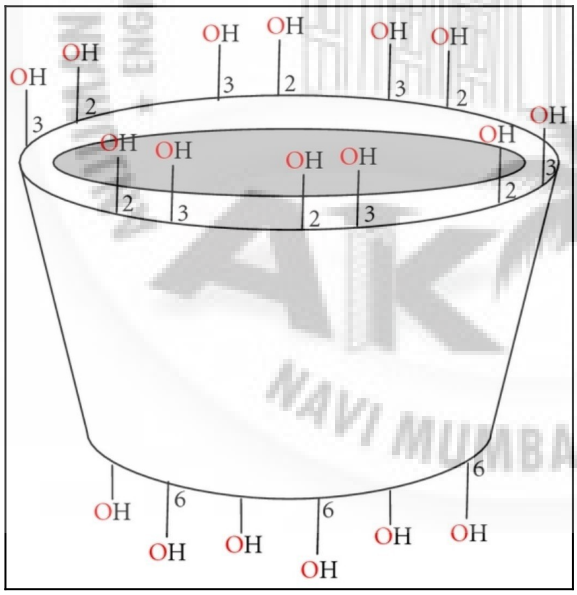
Inclusion complex formation technique is more precise technique to improve dissolution rate and bioavialability of poor water soluble drugs(4). Non polar molecule or non polar region of one molecule known as a guest forms complexes into the cavity of another molecule or group of molecules known as host.

Cyclodextrins are the most commonly used host molecules.The enzymatic degradation of starch by cyclodextrin-glycosyltransferase produces cyclic oligomers cyclodextrins[7]

There are three naturally occuring Cyclodextrins

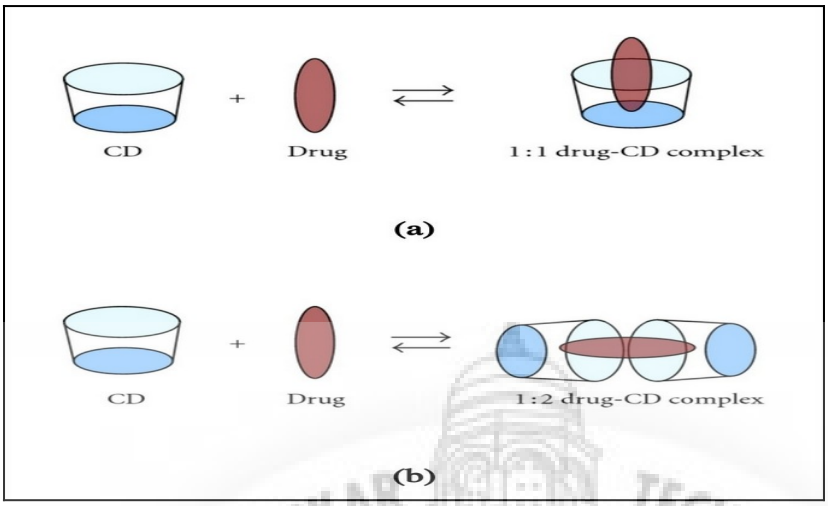
- Alpha Cyclodextrin
- Beta Cyclodextrin
- Gama Cyclodextrin

Schematic illustration of hydrophobic cavity and hydrophilic outer surface of cyclodextrin



[FIG] 7

The surface of the cyclodextrin molecules makes them water soluble, but the hydrophobic cavity provides a microenvironment for appropriately sized non-polar molecules. Based on the structure and properties of drug molecule it can form 1 : 1 or 1 : 2 drug cyclodextrin complex[7] as illustrated in Figure



[FIG] 8.

1 : 1 and 1 : 2 drug cyclodextrin complexes in figure (7.2)

Various technologies adapted to prepare inclusion complexes of poor water soluble drugs with cyclodextrins are-;

- Kneading Method
- lyophilization/Freeze-drying technique
- Microwave Irradiation Method

KNEADING METHOD

In this method Cyclodextrin is impregnated with short amount of water for the conversion into paste. same paste is added with drug and kneaded for a detailed time.The mixture which is been kneaded is dreid and passed through a sieve. Mortar and pestle are used for Kneading in laboratory scale. Extruder and other machines are used in large scale for kneading[9]. .Kneading method is most simple and common mehtod used to prepare inclusion complexes and it is also low cost process.

LYOPHILIZATION/FREEZE-DRYING TECHNIQUE

Lyophilization/Freeze-Drying Technique is very suitable and used technique to get a porous,amorphous powder with high degree of interaction between drug and cyclodextrin.

In this technique there is an elimination of solvent system from the solution via primary freezing and successive drying of the solution which contains drug and cyclodextrin at a reduced pressure. By this method thermolabile substances can be well made into comlex form[6]. There is an limitation of this tecnique which is the use of specialized equipment,time consuming and the poor outcome of flowing powdered product. Lyophilization/Freeze-Drying Technique is expressed as alternative to solvent evaporation and involve molecular mixing of drug and carrier in common solvent.[7]

MICROWAVE IRRADIATION METHOD

There is an involvement of the microwave irradiation reaction between complexing agent and drug using microwave oven. In the mixture of organic solvent and water the Cyclodextrin and drug are dissolved in precise molar molar ratio into a round bottom flask.For about one to two minutes the mixture is reacted at 60 C in the microwave oven. Fair amount of solvent mixture is added to the above mixture to remove the residual uncomplexed free drug and cyclodextrin after the reaction completes.The remaining precipitate which is obtained after the above reaction mixture is separated by the use of whatman foilter paper, and then it is dried at 40 C in microwave oven[10]. Microwave irradiation mehtod has shorter reaction time.and higher outcome of the product.

ADVANTAGES	DISADVANTAGES
Reduction of irritation: Drug substances that irritate the stomach, skin or eye can be encapsulated within a Cyclodextrin cavity to reduce their irritancy.	The cyclodextrin do not readily permeate the biological membranes due to its chemical structure, molecular weight and very low octanol/water partition coefficient.
Inclusion complexation with Cyclodextrins reduces the local concentration of the free drug	Only the free form of drug, which is in equilibrium with the D/CD complexes are capable of penetrating lipophilic membranes.

MARKETED PRODUCTS

Drug/cyclodextrin	Trade name	Formulation
Itraconazole	Sporanox	Oral and intravenous solution
Mitomycin	MitoExtra, Mitozytrex	Intravenous infusion
Aripiprazole	Abilify	Intramuscular solution

POLYMERIC ALTERATION

Substance which consist of a large number of repeating units of monomers and whose molecules have higher rate is known or considered as polymers.

There two types of occuring Polymers-;

- Naturally occurung Polymers
- Synthetic Polymers

Polymers like protien, starch cellulose etc are some examples of naturally occuring polymers

Polymers like plastic, resins etc comes under Synthetic Polymers

Only one monomer is used in synthetic but in some two or more different monomers can be combined.Solubilising polymers are amphiphilic in nature that is they have hydrophilic and hydrophobic both sites that helps them to ineract easily with low solubulity.It dissolves in aqueous enviroments such as gastrointestinal tract. Polymer interaction like self interaction with drug or wuth aqueous medium results in solubilizing structure like colloids and ionic complexes[8]

Polymers used in formulation and drug development Ethylcellulose, cellulose acetate phthalate (CAP), acrylate polymers, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate (PVAP) are some of the polymers used as solubilising excipients in formulation[9]. These polymers, commercially, are being manufactured by industries like DOW, FMC Biopolymer, BASF, Evonik etc., under trade names like Solutol HS, Soluplus, Aquacoat, Ethocel, Eudragit and many more. These products containing different polymers are used in a variety of ways to achieve the final purpose i.e. solubility enhancement

ADVANTAGES	DISADVANTAGES
Polymers are also suitable to succesfully increase the solubility of poorly soluble drugs in-vitro by forming stable solid dispersions with the drug.	limiting the future development of bitumen polymer modification
Because of to the increase in solubility, an increase in bioavailability in vivo will occur.	High cost, low ageing resistance and poor storage stability of polymer modified bitumen

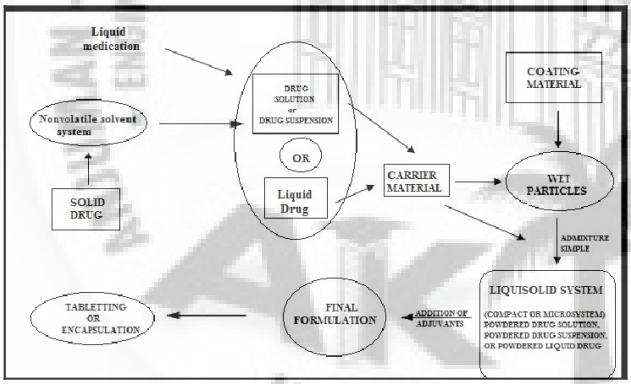
MARKETED PRODUCTS

Soluplus (BASF)	Kolliphore TPGS (BASF)	Eudragit (Evonik)
Soluplus is polyvinyl carpolactam-polyvinyl acetate-polyethylene glycol graft co-polymer. Soluplus have many applications but is generally used as a binder in wet	Kolliphore TPGS (d-a-tocopheryl polyethylene glycol 1000 succinate) is a D-alpha vitamin E ester derived from vitamin E. Kolliphore TPGS, is used for increasing solubility in tablets	It is basically used for BCS class II, III and IV drugs. Eudragit helps in enhancing solubility by using it as a carrier.

granulation or dry binder in direct compression for weak soluble drugs, thus increasing its solubilisation capacity in a simple process.	and capsules, by hot-melt granulation technique using TPGS as binder.	

LIQUISOLID TECHNIQUE:

- Liquisolid Technique is one of the noel approach for drug delivery system for oral route.
- Bioavailability of any drug is mainly dependent upon its dissolution rate and dissolution rate.
- Oral route is mainly preferred for administration of the drugs due to its patient compliance, convenience and low cost.[16].
- In market there are about 40% of the drugs having poor water solubility and about 55% drugs undergoing problems during formulation. (Specially class II drugs)
- Liquisolid technique is also one of the methods of solubility enhancement in which liquid drug or drug suspensions or drug solutions having poorly soluble drugs get converted in to freely flowing, dry, non adherent, readily compressible powder having less particle size.[16]



[FIG] 9

Ideal characteristics:

It should be inert.
It should have high boiling point.
It should be preferably water miscible.
It should not be highly viscous organic solvent system.

ADVANTAGES	DISADVANTAGES
Liquisolid technique is used	More efficient excipients are

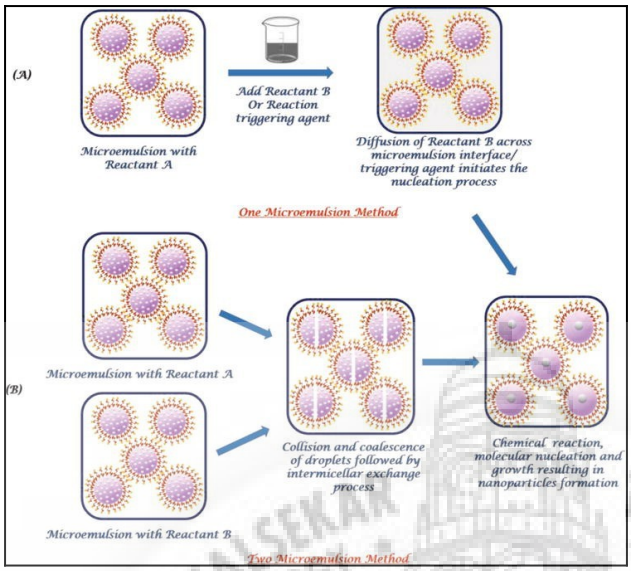
mainly for converting liquid drugs or drug suspensions or solutions of poorly soluble drugs in to solid dosage form.	required which have high adsorptive properties which can enhance release rates of the drug from the dosage form.
It is also used to formulate sustained release dosage forms.	The liquisolid systems have less drug loading capacity and it also require high solubility of the drug in a non-volatile solvent.
Production cost of liquisolid system is also less as compared to soft gelatin capsules.	

SOLUBILIZATION BY SURFACTANT:-

MICROEMULSION TECHNIQUE

A Micro emulsion is an optically clear, isotropic, thermo dynamically stable translucent system, Hydrophilic surfactant and hydrophilic solvent in which the poorly water soluble drug dissolves. When comes in contact with water the formulation is spontaneously disperse to form a very clear emulsion of exceedingly small as well as containing the solubilized poorly soluble drug.[17]

These systems employed to increase the solubility of many temperature which are practically insoluble in water along with incorporation of proteins for oral, parenteral as well as percutaneous or transdermal use.. The surfactants like polyoxy ethylene surfactants for ex. Brij 35 or sugar esters like sorbitan monooleate (Span 80) , cationic or anionic like alkyltrimethylammonium bromide and sodium dodecyl sulphate or zwitter ionic such as phospholipids like lecithin because of it exhibits excellent bio-compatability.[18]

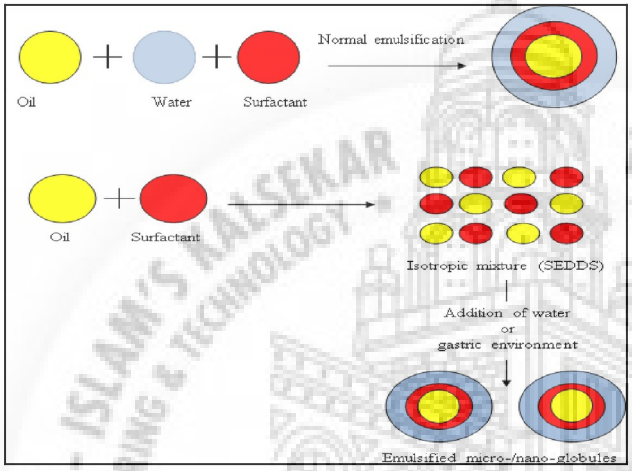


[FIG] 10.

ADVANTAGES	DISADVANTAGES
Pre-concentrates are relatively easy to manufacture.	The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
Well-developed microemulsion pre-concentrates are not normally dependent upon digestion for drug release	The tolerability of formulations with high levels of synthetic surfactants may be poor in cases where long term chronic administration is intended.
Therefore, optimal bioavailability and reproducibility can be also being expected without co-administration of food.	Formulations containing several components become more challenging to validate.

SELF EMULSIFYING DRUG DELIVERY SYSTEM

A self-emulsifying or self-micro emulsifying system is the concept of in situ formation of emulsion in the gastrointestinal tract. It is defined as the mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophillic drug dissolution and absorption. [18]



[FIG] 11.

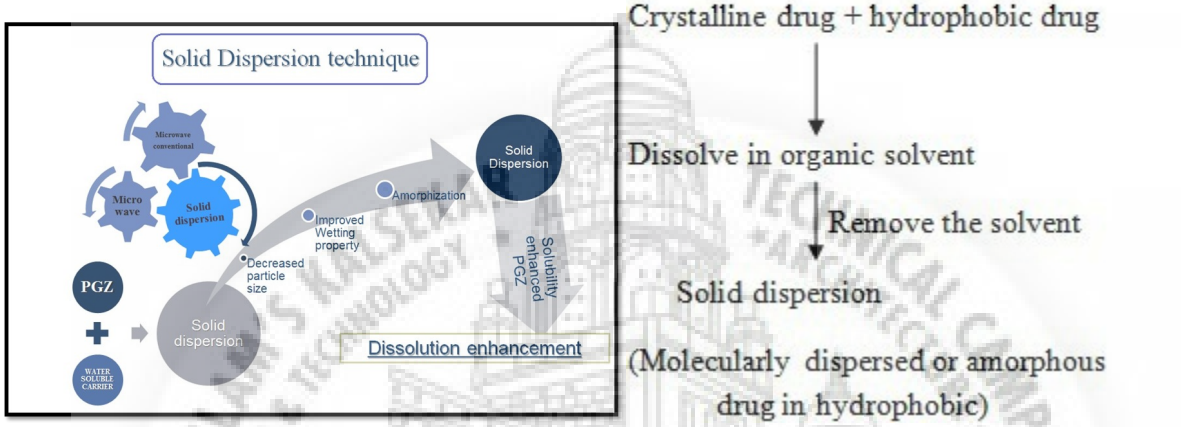
ADVANTAGES	DISADVANTAGES
They form spontaneously upon mixing their components under mild agitation. They are thermodynamically stable.	It includes chemical instabilities of drugs and high surfactant concentrations.

DRUG DISPERSION IN CARRIERS

SOLID DISPERSION:

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which increases the dissolution of the drug. Solid dispersion technique can yield eutectic (Non- Molecular Lebel mixing) or solid solution.(Molecular –lebel Mixing) products. Eutectic Dispersions are homogeneous dispersion of crystalline or amorphous drug in crystalline or amorphous carrier.

Solid dispersion is a useful pharmaceutical technique for increasing the dissolution of drug in dosage form. Some of the hydrophilic carriers which are used in yhe pharmaceutical industry are polyvinyl pyrrolidone, PEG, SLS , Tween 80 etc



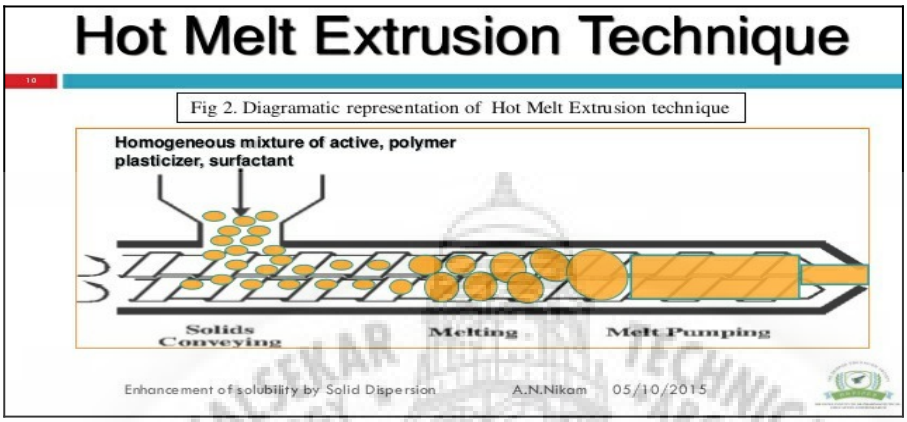
[FIG] 12.

ADVANTAGES	DISADVANTAGES
Improving drug bioavailability by changing their water solubility.	Most of polymers used in solid dispersions can absorb moisture , which may result in phase separation , crystal growth. This lead to decrease in solubility and dissolution rate.
Increase in dissolution rate and extent of absorption.	Drawback of solid dispersion is their poor scale-up for the purposes of manufacturing.

HOT MELT METHOD (FUSION METHOD)

In this method the physical mixture of a drug and water-soluble carrier was heated directly upto it

melted. Then thee melted mixture was cooled and solidified rapidly in an ice bath under the vigorous stirring. After that the final solid mass was crushed, pulverized and sieved, which can be compressed into tablets with the help of tablet excipient.



[FiG] 13.

ADVANTAGES	DISADVANTAGES
Continuous and reproducible process.	Thermal degradation is possible for highly sensitive material.
Efficient , highly automated.	Highly start-up costs.

CONCLUSION:

Dissolution of drug is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs. Proper selection of solubility enhancement method is the key to ensure the goals of a good formulation like good oral bioavailability, reduce frequency of dosing and better patient compliance combined with a low cost of production. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release and so forth, and regulatory requirements like maximum daily dose of any excipients and/or drug, approved excipients, analytical accuracy and so forth.

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