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Solubility enhancement – A challenge for hydrophobic drugs

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Abstract: *Solubility is not only the ability to dissolve or liquefy a substance.It process occurs not only because of dissolution but also because of chemical reaction. There are many New Drug Applicants to be filed in the field of pharmacy but the limiting step is the solubility problems. The efficiency of a drug is based on its binding efficacy and response. The binding efficacy is based only on the dissolution of the drug and its bioavailability. On the basis of solubility alone drugs are classified into four expressed as concentration, molality, mole fraction, mole ratio, etc. More than 40% of new chemical entities are lipophilic. This solubility behavior of drug is the major challenge for the formulation scientist. To improve poor solubility of drug candidates, various strategies are followed. The main strategy is the reduction of the particle size of the drug. This article explains in detail about all the methods to enhance solubility. So that a formulation scientist can play with new chemical entities which surely have good bioavailability and improved efficacy.*

Keywords: *Solubility, Dissolution, Techniques, Super critical fluid technique, Inclusion complexation.*

I. Introduction

Drug discovery and development plays a major role in world and serves mankind .In development, major criteria to be considered and given importance is solubility of drug. Solubility plays a major role in drug delivery. Various technologies like high through put screening, combinatorial chemistry and computer aided designing is leading to vast number of drug candidates possessing a very good efficacy but statistically over 40% of drugs are identified as poorly soluble drugs through combinatorial screening. Poor solubility is not only a problem for development of formulation and clinical testing, also it is an obstacle at very beginning while screening new compounds for pharmacological activity. Nowadays oral route is considered as the most preferable route of administration than other routes due to its convenience and economy. The first requirement of drug which is supposed to be given in oral route should have good solubility, as the poor solubility leads to low absorption, inadequate and variable bioavailability and also gastrointestinal mucosal toxicity .To prevent these crisis several methods have to be developed and designed which are all based on the reduction of size of drug particles involved in formulation .There is quite a number of formulation approaches for poorly soluble drugs which can be specified as "specific approaches". In previous decades, the new chemical entity which have been synthesized are made into micro sized particles. For the production of micro particles several techniques have been developed. Few drugs are formulated as a nano sized particles. The stability was distinctly increased in comparison to the aqueous solution and the stability is achieved by the steric effect shown by the surfactants.

Fig.1. solubilization of solid dosage form

1.1. Solubility

Solubility is the property of a solid, liquid, or gaseous chemical substance termed solute, to dissolve in a solid, liquid, or gaseous solvent, to form a solution. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and the pH of the solution. The extent of the solubility of a substance in a specific solvent is measured as the saturation concentration, where adding more solute does not increase the concentration of the solution and begins to precipitate the excess amount of solute.

Solubility definition as per united states of pharmacopoeia is

DESCRIPTION FORMS (SOLUBILITY DEFINITION)	PARTS OF THE SOLVENT REQUIRED FOR ONE PART OF SOLUTE
Very soluble	<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

1.2.Solubilization

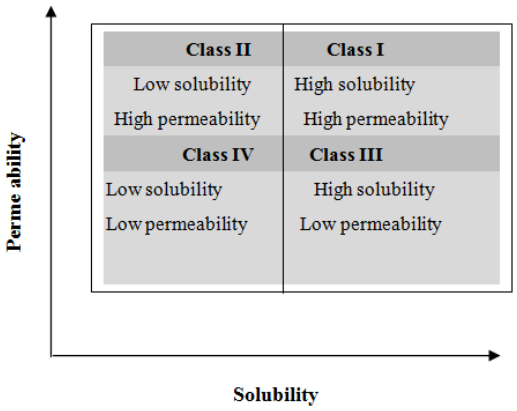
Solubilization is the process of incorporating the solubilizate (the component that undergoes solublization) into or onto small particles. Solublization may occur in a system consisting of a solvent, an association colloid, and at least one other solubilizate.

Process of solubilization utilizes the phenomenon such as

- The separation of molecules from the solvent to provide space for the solute.
- Breaking of intermolecular ionic bonds in solute.
- Interaction between solvent and solute.

1.3.Biopharmaceutics classification system (BCS) of drugs

The Biopharmaceutics Classification System is a system used to differentiate the drugs on the basis of their solubility and permeability. It is a guide for predicting the gastrointestinal drug absorption provided by the U.S. Food and Drug Administration (FDA).



II. Factors affecting solubility

- Particle size
- Temperature
- Pressure
- Molecular size
- Nature of solute and solvent
- Polarity
- Polymorphs

III. Techniques of solubility enhancement

There are numerous methods to enhance the solubility of a drug. The following are the standard techniques used by the researchers

1. Conventional method
2. Nanosuspension
3. Emulsification
4. Super critical fluid
5. Cryogenic techniques
6. Hydrotrophy
7. Cosolvency

8. pH adjustment
9. Sonocrystallisation
10. Inclusion complexation.

3.1 Conventional methods

The methods includes Comminution.

3.1.1 Comminution

Comminution is the reduction of solid materials from one average particle size to a smaller average particle size, by crushing, grinding, cutting, vibrating or other processes[1]. The formation of particles of drug which are heterogenous, cohesive but they tend to cause some potential effects in the down processing and production, are comminuted.

This includes micronization, milling and co-grinding.

3.2 Nanosuspension

The drugs which are not soluble in both oil and water prefers this method for solubility .Where the microsized particles are converted to nanosized particles. The biphasic systems consisting of nanosized particles are stabilized by surfactants .Particle size varies between 1µm to 200 or 600 nm. The preparation of nanosuspension includes two process bottom up technology and top down technology.

3.2.1 Bottom up technology

In this technique one starts from molecular level and goes through molecular association to the formation of solid particle .This technology includes precipitation technique .

This method is used to prepare submicron particles of hydrophobic drugs. In this method ,the drug along with the surfactant is dissolved in a solvent and then the solution is again added to a solvent in which the drug is insoluble. This leads to supersaturation of the drug which is an ultrafine amorphous or crystalline structure. This technique involves nuclei formation and crystal growth which are temperature dependent .High nucleation rate and low crystal growth with minimum particle size is essential requirement for the preparation of stable nanosuspension .

3.2.2 Top down technology

In this technique molecular association dissociates to form nanosized particles .This technology includes milling and high pressure homogenization.

3.2.2.1 Milling technique

1.Media milling
2.Dry co grinding

3.2.2.1.1 Media milling

The drug nanoparticles are obtained by subjecting the drugs to media mills. The milling chamber is charged with the milling media, water or suitable buffer ,drug and the stabilizer. High energy and high shear forces are generated due to the impaction of the milling media and disintegrates the microparticulate drug into the nanosized particle. The milling media or pearls are rotated at a very high shear rate so that the particles are obtained in the required particle size.

3.2.2.1.2 Dry co-grinding

Nanosuspensions are also prepared using dry milling techniques. It is done by using dry grinding of poorly soluble drugs with soluble polymers and co polymers. This technique increases the physiochemical properties and dissolution of poorly water soluble drugs because of the improvement in surface polarity and transformation from crystalline to amorphous drug.

This method can be carried out easily and economically without the use of organic solvents .This technique reduces particles to submicron levels.

3.2.2.2 High pressure homogenization

Homogenization is the conversion of two different phases into single phase ,the theme of this technique is to achieve a liquid form of suspension with a smaller nanosized particles in it.It is based on the principle of cavitation in hydrophilic or aqueous phase ,where the force of cavitation in particles are more sufficient to convert drug size from microparticle to nanoparticle.To achieve the required particle size the suspension of drug with small sample particle size and surfactant under high pressure is forced through a nanosized aperture valve in high pressure through a high pressure homogenizer.Many techniques involved in this method are as follows,

They are

1. Homogenization in aqueous media
2. Nanopure technology
3. Nano edge technology
4. Nano jet technology

3.2.2.2.1 Homogenization in aqueous media

The suspension is forced under pressure through a valve having narrow aperture. In this technique ,the pre suspension is passed through the small orifice that results in a reduction of static pressure below the boiling pressure of water which leads to boiling of water and forms bubbles .When the suspension leaves the gap and becomes normal the normal air pressure is attained ,so the gas bubbles implode and the surrounding part containing drug particles rushes to the centre and forms colloids causing a reduction in particle size. Most of the drug particles requires many cycles through the homogenizer that depends on the

i) Hardness of the drug
ii) Mean particle size of the drug
iii) Homogeneity of the product

To produce nanosuspension with high concentration of solids it is preferred to start homogenization with very fine drug particles .This can be accomplished by pre-milling high pressure homogenization along with media milling. This can be used for both diluted and concentrated suspensions and also allows aseptic production .The homogenizers employed in this technique are APV Gaulin micron lab 40 homogenizer, NS1001L-Panda 2K high pressure homogenizer.

3.2.2.2.2 Nanopure technology

The drug suspension in non-aqueous media is homogenized at 0°c or below the freezing point, this is called deep freeze homogenization. This method is preferred for suspensions that are homogenized in water free media or water mixture media because water,oils and fatty acids have very low pressure and a high boiling point.Hence the drop of static pressure will not initiate efficient cavitation. High pressure homogenization above 80°c improves disintegration but not suitable for thermolabile substances. So this technique perfectly suits for thermolabile drug substances.

3.2.2.2.3 Nanoedge technology

This method is a combination of both precipitation and homogenization,where the precipitated drug particles have tendency to aggregate and form microparticles so that particle size increases and decreases surface area and solubility is affected.In order to avoid that, the precipitated solution is subjected to homogenization to maintain the particle size.

3.2.2.2.4 Nanojet technology

It is an opposite stream technology .This technique includes the use of chamber where a stream of suspension is divided into two parts and allowed to collide with each other at high pressure . This results in a high shear force during the process ,and reduction in the size of the particle takes place. The equipments used in this process includes micro fluidizers M110L and M110S .Disadvantages is that high number of passes through the fluidizer makes the product to have larger fraction of micro particles.

3.3 Emulsification methods

This method includes

1. Microemulsion
2. Melt emulsification
3. Emulsification solvent technology
4. Solvent evaporation technique
5. Self emulsifying technique
6. Solubilization by surfactants

3.3.1 Microemulsion technique

Another way of producing nanosuspensions is by the use emulsions produced from conventional method ,by using a partially water miscible solvent as dispersed phase.By just diluting the emulsion ,these nanosuspensions are formed.Micro emulsions are thermodynamically stable and isotropically clear dispersions of two immiscible liquids such as oil and water stabilized by an interfacial film of surfactant and co-surfactant. The drug can be either loaded into the internal phase or the preformed micro emulsion can be saturated with the drug by intimate mixing. Suitable dilution of the micro emulsion yields the drug nanosuspension.This technique is used for drugs which are either soluble in volatile organic solvents or partially water miscible solvents. The organic solvent or mixture of solvent loaded with drug is dispersed in aqueous phase containing surfactants so that emulsion is formed[2]. An example of this technique is the griseofulvin nanosuspension which is prepared

by the microemulsion technique using water, butyl lactate, lecithin and the sodium salt of taurodeoxycholate .

3.3.2. Melt emulsification technique

In this method the drug is dispersed in aqueous solution of stabilizer and heated above the melting point of the drug and homogenized to give emulsion. During the time of process the sample holder was enwrapped with a heating tape fitted with temperature controller and the temperature of emulsion was maintained above the melting point of the drug .The emulsion was then cooled either slowly to room temperature or on an ice bath .Solvent diffusion method is avoided by this technique.

3.3.3 Emulsification solvent technique

This involves the preparation of solution of the drug and it is followed by emulsification in another liquid which is a non-solvent of the drug[3]. Evaporation of the solvent leads to the precipitation of the drug .Crystal growth at particle aggregation is controlled by the creation of high shear forces using high speed stirrer.

3.3.4 Solvent evaporation technique

The solutions of polymers are prepared in emulsions and volatile solvents. The emulsion is converted into nanosuspension by evaporating the solvent for the polymer which is allowed to diffuse through the continuous phase of emulsion. These methods require high speed homogenization followed by evaporation of solvent either under reduced pressure or by continuous magnetic stirring at room temperature .The nanoparticles are formed by ultracentrifugation ,the solidified nanoparticles are collected and washed with distilled water to remove the additives [4].The solvents dichloromethane and chloroform was now replaced by ethyl acetate which has a better profile of toxicology [5]. The particle size was influenced by concentration of polymer,speed of homogenizer and stabilizer. This method also includes

Hydrosol technique

This is similar to the emulsification- solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug antisolvent[6]. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

3.3.5 Self emulsifying technique

The mixture of oil ,water,surfactant and co-surfactant and one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution [7].They are isotropic solutions of oil and surfactants which forms oil in water microemulsions on mild agitation in water .The mixture of surfactant and oil makes the poorly water soluble drugs soluble such process is widely known as pro concentrate. Compared with microemulsions, self emulsifying technique have been shown to improve physical stability profile in long term storage[8]

3.3.6 Solubilization by surfactants

Surfactants are surface activity reducing agents with distinct polar and non-polar regions .In surfactants ,the hydrocarbon segment is connected to a polar group which may be either cationic or anionic or zwitter ionic or non ionic small polar molecules when added gets accumulated in the hydrophobic core of the micelles. The surfactants decreases the surface tension between the solute and the solvent and provides a way for easy interaction, in this way solubility is enhanced .This is possibly the fundamental, cheap and oldest method[9].They are also used to stabilize the drug suspensions .When the concentration of surfactants is more than their CMC(i.e critical micelle concentration), micelle formation takes place and causes entrapment of the drug within the micelles .This is known as Micellization.

3.4 Super critical fluid technique

This method is employed to produce nanoparticles from drug solutions.Super critical fluids are fluids whose temperature and pressure are greater than critical temperature and pressure which has properties of both liquid and gas[10] .

Those liquids have a solubilizing nature.When near critical temperature super critical fluids are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid that largely determine its solvent power and also has greatly reduced particle sizes at sub micron levels.Current super critical fluids process have demonstrated the ability to create nanoparticulate suspensions of particles 5 µm -2000µm in diameter,

Several methods of Super critical fluid tecnique includes

1. Compressed antisolvent process (PCA)
2. Solution enhanced dispersion by super critical fluids (SEDS)
3. Supercritical antisolvent process (SAS)
4. Rapid expansion of supercritical solutions (RESS)

They are explained as follows

3.4.1 Compressed antisolvent process

The solid is dissolved in the organic solvent then the solution is sprayed into the vessel containing super critical fluid like carbon di oxide. As liquid dissolves in supercritical carbon di oxide, nanosized particles are formed.

3.4.2 Solution enhanced dispersion by super critical fluids

The drug and the super critical fluid are introduced simultaneously into the particle formation vessel using co-axial nozzle arrangement[11] .This causes rapid dispersion ,mixing and extraction of the solvent by super critical fluid. This leads to higher super saturation which leads to precipitation .

3.4.3 Super critical anti solvent process

This method involves the use of super critical fluid like carbon di oxide for the formation of complexes. Super critical carbon di oxide has the properties of improved mass transfer and increased solvating power[12] .The drug and the cyclodextrin are dissolved in the solvent,then the solution is fed into a pressure vessel under supercritical conditions through a nozzle (i.e sprayed into antisolvent carbon di oxide).When the solution is sprayed the antisolvent diffuses into that liquid solvent ,this liqud solvent counter diffuses into the anti solvent[13].The supercritical fluid has low solvent power than the pure solvent ,so the mixture becomes super saturated that results in precipitation of the solute and solvent.

3.4.4 Rapid expansion of super critcal solutions

It is applicable for drug substances that are soluble in super critical fluids.In this process first the solute is dissolved in the super critical fluid then passed through the nozzle at supersonic speed. Pressure reduction in nozzle leads to rapid expansion this causes the super saturation of the solute and subsequent precipitation of the solute particles with nanosize distributions[14] .The product produced from this method is protected from agglomeration and precipitation by the addition of polymeric and oligomeric stabilization di oxide and high pressure required for these processing agents.

3.5 **Cryogenic techniques**

In this method the solubility is enhanced by creating nanostructured amorphous drug particles with high degree of porosity at very low temperature conditions.Cryogenic inventions can be defined by, Type of injection device (capillary,rotary,pneumatic,ultrasonic), Location of nozzle (above or below the liquid level), Composition of cryogenic liquid (hydrofluoralkanes,Ar,Oxygen,Nitrogen&organic solvents).After processing ,the dry powders can also be obtained by various drying process like atmospheric freeze drying, vaccum freeze drying ,spray freeze drying and lyophilization[9].

3.5.1 Techniques of cryogenic methods

3.5.1.1 Spray freezing onto cryogenic fluids

The drug and the carrier (mannitol,maltose,lactose,inositol or dextran) were dissolved in water and atomized above the surface of the boiling agitated fluorocarbon refrigerant.[15] To enhance the dispersion of the aqueous solution a sonication probe is placed in the stirred refrigerant.

3.5.1.2 Spray freezing into cryogenic liquids

This technique is employed to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability,[16] which is done by direct liquid-liquid impingement between the automatized feed solution and cryogenic liquid to provide intense automization into micro droplets and significantly faster freezing rates. The frozen particles are then lyophilized to obtain dry and free flowing micro ionized powders.

3.5.1.3 Spray freezing into vapour over liquid

This technique involves the freezing of drug solutions in cryogenic fluid vapours and subsequent removal of frozen solvent produces fine drug particles with high wettability .During this technique the atomized droplets typically starts to freeze in the vapour phase before they contact the cryogenic liquid .As the solvent freezes, the drug becomes supersaturated in the unfrozen regions of the atomized droplets have fine drug particles nucleate and grow.

3.5.1.4 Ultra rapid freezing

The nanostructured drug particles with greatly enhanced surface area and desired surface morphology

is produced by using solid cryogenic substances.Application of drugs solutions to the solid surface of the cryogenic substrate leads to the instantaneous freezing and subsequent lyophilization (for removal of solvent)forms microinized drug powder with improved solubility .Ultra rapid freezing hinders the phase separation and crystallization of pharmaceutical ingredients leading to the formation of amorphous drug carrier solid dispersions and solid solutions.

3.6 Hydrotrophy

Hydrotrophs are a diverse class of a chemical compound first described by Neuberg[17]. This technique includes the addition of secondary solute to enhance the solubility of the solute added before .Hydrotrophs are the compounds which contain both anionic group and hydrophobic aromatic ring or ring system[18] .The anionic group increases hydrophilicity and the rig system interacts with the solute to be dissolved. The salts that increase solubility in the given solvent are said to "salt in" the solute and those which decrease the solubility are said to "salt out" the solute.Several salts with large anions or cations that are themselves soluble in water results in salting of non electrolytes called "hydrotrophic salts" this phenomenon is known as hydrotrophism[19].The hydrotropic solutions do not show colloidal properties and involves weak interaction between the agent and the solute .The mechanism of improving the solubility is related to complexation involving a weak interaction between the hydrotrophic agents like sodium benzoate ,sodium acetate,sodium alginate,urea and poorly soluble drugs . The solvent used is independent of pH and do not require emulsification. It does not require the use of organic solvent.

3.7 Co-solvency

The solubility of poorly soluble drugs can be enhanced by mixing the drug with some water miscible solvent in which the drug is soluble [20] .Weak electrolytes and non polar molecules have poor water solubility. It can be improved by altering the polarity of the solvent. This can be achieved by another solvent [21] .This method is called co solvency and the solvent added to enhance the solubility is co solvent. This co-solvent reduces the interfacial tension between the aqueous solution and hydrophobic solute. This is also known as solvent blending.

The co-solvents have hydrogen bond donor or acceptor groups as well as hydrocarbon regions. Their hydrophilic hydrogen bonding groups ensure water miscibility, the hydrophobic hydrocarbon region interferes with water hydrogen bonding network reducing the overall intermolecular attraction of water. By disrupting water self association, co-solvents reduces waters ability to squeeze out non-polar hydrophobic compounds, so solubility is enhanced. Some of the non toxic co solvents used are PEG 300,propylene glycol or ethanol ,for parenterals the co-solvents employed are dimethyl sulfonide, glycerin, propylene glycol. dimethyl acetoamide[22] .

3.8 pH adjustment

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may be potentially dissolved in water by applying a pH change[23].To access the solubility of this approach, the buffer capacity and tolerability of the selected pH are important to consider[24].The excipients added in formulations increase environmental pH to a range higher than pKa of weakly acidic drugs increase the solubility of that drug, Those excipients that act as alkalizing agents may increase the solubility of weakly basic drugs .This pH adjustment is based on the solubility of the drug in the body where in different systems different pH level is maintained.

3.9 Sonocrystallisation

Application of ultra sound energy to modify the nucleation of crystallization process is known as sonocrystallisation .The energy produced from ultra sound results in compression and expansion [25].The recrystallisation process here involves the use of liquid solvents and antisolvents so that the particle size is reduced .The ultrasound power is characterized by frequency range of 20-100KHz for inducing crystallization and it also controls the size distribution of API. In most of the process the ultrasound is used in the range of 20KHz to 5MHz[26].

3.10 Liquid-solid technique

In this technique the liquid is transferred to free following, readily compressible and apparently dry powder by simple blending with selected carrier and coating material .The liquid portion used can be a liquid drug, drug suspension or drug solution in a suitable volatile liquid vehicle is converted to powders with great compressibility and free flow properties[27] .This condition is achieved by binding the liquid with suitable excipient.

3.11 Inclusion complex formation

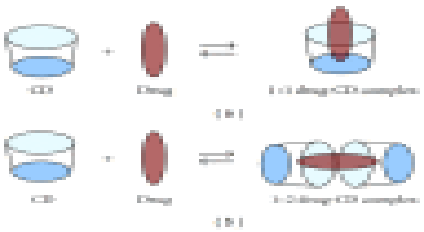


Fig.2 Schematic representation of inclusion complex formation

In this method solubility is enhanced by complex formation by increasing the stability of hydrophobic drugs by using cyclodextrins[28]. The cyclodextrin ring has a hydrophilic exterior and lipophilic core in which appropriate sized organic molecules can form non covalent inclusion complexes that results in solubility and chemical stability .This method includes many techniques as follows

1. Physical blending
2. Kneading technique
3. Co-grinding
4. Co-precipitate
5. Freeze drying technique
6. Spray drying
7. Neutralization precipitation
8. Microwave irradiation method

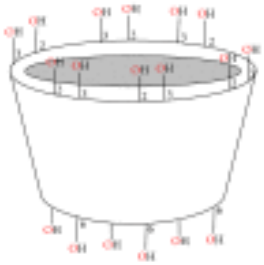


Fig. 3. Cyclodextrin

3.12.1 Physical blending

The drug and cyclodextrins are physically mixed by mechanical tituration .In laboratory scale this process is done in a mortar and the product is passed through appropriate sieve to get the desired particle size[29]. In industrial scale ,the physical mixture is prepared by blending of drugs with cyclodextrins in a rapid mass granulator for approximately 30 minutes . The physical mixtures are stored in room at controlled temperatures and humidity conditions .

3.12.2 Kneading method

The cyclodextrins are impregnated with water and made it into the form of a paste then the drug whose solubility to be enhanced is added to the above mixture and kneaded for a certain period of time.The kneaded mixture is then dried and passed through sieve if required.

3.12.3 Co-grinding

The physical mixture of the drug and cyclodextrins are mixed and introduced in a suitable mill like oscillatory mill and grinded for a suitable time.

3.12.4 Co-precipitate method

The drug is mixed with the required amount of cyclodextrins .The complex is protected from the light[30].The precipitate is separated by vaccum filtration and dried at room temperature in order to avoid the loss of structure water from the complex,thus the inclusion complex is formed.

3.12.5 Lyophilization

This technique is very much utilized for thermolabile substances ,where the solvent system from the solution is eliminated through primary freezing and subsequent drying of the solution containing both the drug and the cyclodextrins at reduced pressure This method is a time consuming process and the yield is a poor flowing powder.

3.12.6 Spray drying technique

Drying is dissolved in suitable solvent and stoichiometric amount of carrier material like cyclodextrin is dissolved in water .Both the solutions should be mixed together and they are mixed by sonication or by using many other suitable techniques to produce a clear solution ,so as to obtain the complex particles from the solution ,the obtained solution is spray dried using spray dryer.

3.12.7 Neutralization precipitation method

This method involves the formation of inclusion complex along with alkaline solution.Drug is added in alkaline solution like sodium hydroxide followed to that β-cyclodextrins are added and dissolved then forms complex.The clear solution obtained is agitated and then by adding hydrochloric acid the mixture is neutralized till it reaches the equivalence point.The appearance of white precipitate conforms the complexation of the process that corresponds to the formation of inclusion compound,the precipitate is then filtered and dried.

3.12.8 Microwave irradiation technique

The drug and cyclodextrin in definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion in round bottomed flask .The mixture is allowed to react for a short period of time i.e one to two minutes at 60°C .After the reaction is over ,adequate amount of solvent mixture is added to the reaction mixture to remove the uncomplexed drug and cyclodextrin.The precipitate is separated using whatman filter paper and dried in vaccum at 40°C for 48 hrs.It is the novel method preferred for high yield of product.

3.13 Solid dispersion methods

The term solid dispersion refers to the solid product or group of solid products that consists of a hydrophilic matrix in a hydrophobic drug[32,33] .The types of solid dispersion are as follows

Simple eutectic mixtures
Solid solutions
Glass solution
Compound or Complex formation
Amorphous precipitation.

3.13.1 Methods of preparation of soild dispersions

There are three methods involved in solid dispersion preparation. They are

1. Fusion method
2. Solvent evaporation
3. Hot melt extrusion method

3.13.1.1 Fusion method

In this method the drug and a suitable water soluble carrier is melted until it melts and then they are cooled gradually in an ice bath[33].Then the solid is crushed ,pulverized and sieved.They are then compressed into tablets using tableting agents .The melting point of a binary mixture depends upon the weight fraction of the drug and the selection of the carrier.

3.13.1.2 Solvent evaporation method

In this technique the drug and carrier are dissolved in a solvent in which both drug and carriers are soluble this combines and forms solution [34].The formed solution is then subjected to vaccum so that the solvent is evaporated and drug along with carrier is formed.

3.13.1.3Hot melt extrusion

A melt extruder consists of the following sections:

1.An opening to feed raw materials,
2.A heated barrel that consists of extruder screws to convey and mix the fed materials,
3. And an exit port, which consists of an optional die to shape the extruding mass.

The Active ingredients 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[34]. An important 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.

IV. 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 enlisted in this article are used in combination for enhancing the solubility of poorly water drug but the improvement mainly depends on the selection of proper method.Selection of method for solubility enhancement depends upon drug characteristics like solubility ,chemical nature ,melting point ,absorption site ,physical nature ,pharmacokinetic behavior ,dosage form requirement like tablet or capsule formulation, strength ,immediate or modified release.The solubility is an important concept to reach into systemic circulation to show its pharmacological response.In recent years a great deal of knowledge has been accumulated about nanosuspension technology,emulsification technique,supercritical fluid technique,Cryogenic technique,Hydrotrophy,Cosolvency,pH adjustment,Sonocrystallisation,Inclusion complex formation which are useful in pharmaceutical operations .The deep study is required to prevent the limitation of any method.

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