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Review Article

Techniques for Dissolution and Bioavailability Enhancement of Poorly Water-Soluble Drugs

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A B S T R A C T

Solubility, the phenomenon of dissolution of solute in solvent to give a homogenous system, is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired pharmacological response. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as for the generic development. A success of formulation development depends on how efficiently it makes the drug available at the site of action. Poorly soluble and dissolution profile creates problem in pharmaceutical industry for development of dosage form. The ability to increase aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects (Adverse drug reaction) for drugs. This is true for parenterally, topically and orally administered solutions. Biopharmaceutical classification system (BCS) highlights the dissolution as rate limiting step for oral absorption of BCS class II and class IVdrugs. BCS class II and class IV drugs have low solubility.Increasing dissolution directly correlated to bioavailability of drug at site of action or systemic circulation. In this article we discuss, concept of dissolution, factors affecting dissolution,different techniques used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation with hydrophilic excipients.

Keywords: Solubility, Bioavailability, dissolution enhancement, crystal engineering

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INTRODUCTION

Solubility is defined in quantitative terms as the concentration of the solute in a saturated solution at a certain temperature and in qualitative terms, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion. A saturated solution is one in which the solute is in equilibrium with the solvent. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction. Solubility of a substance fundamentally depends on the solvent used as well as on temperature and pressure. Due to this major reason Solubility enhancement is one of the important parameters which should be considered in formulation development of orally administered drug with poor aqueous solubility. Solubility is the characteristic physical property referring to the ability of a given substance, the solute, to dissolve in a solvent. Drug absorption, sufficient and reproducible bioavailability and/or pharmacokinetic profile in humans are recognized today as one of the major challenges in oral delivery of new drug substances.[1,2]

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. [2]

Table 1: IP, USP solubility criteria

Descriptive term	Part of solvent required per 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 and over

The Bio-pharmaceutics Classification System (BCS) is a scientific basis that classifies drugs into four classes according to their dose, their aqueous solubility across the gastrointestinal pH range and their permeability across the gastrointestinal mucosa. A drug is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 8. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water.

A drug substance is considered highly permeable when the extent of absorption in humans is to be >90% of an administered dose based on mass balance determination. [3]

Table 2: BCS Classification

Bio-Pharmaceutical Classification	
BCS Class I • High Solubility • High Permeability	**BCS Class II** • Low Solubility • High Permeability
BCS Class III • High Solubility • Low Permeability	**BCS Class IV** • Low Solubility • Low Permeability

Class I drugs: Class I drugs will dissolve rapidly when presented in immediate-release dosage forms, and are also rapidly transported across the gut wall. Therefore (unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance) it is expected that such drugs will be rapidly absorbed and thus show good bioavailability. Examples of class I drugs are the β-blockers propranolol and Metoprolol. [3,4]

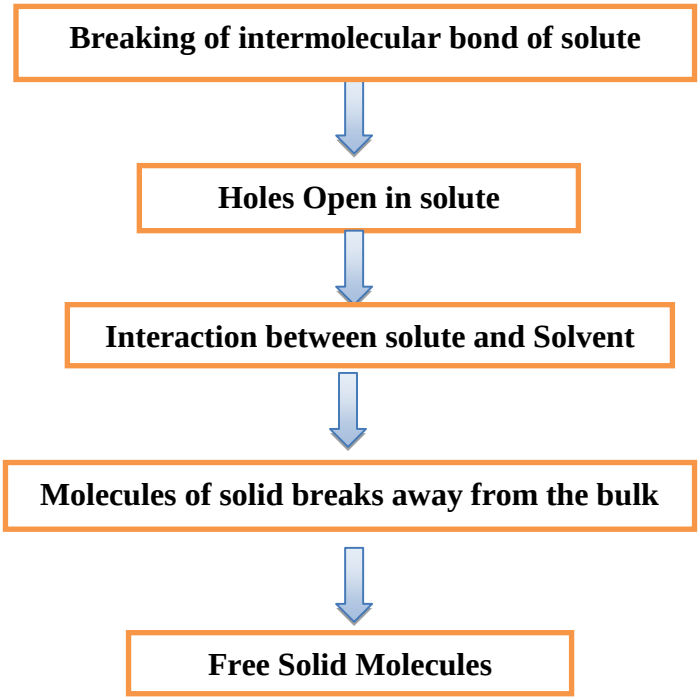
Class II drugs: For drugs in class II, the dissolution rate is the rate-limiting step in oral absorption. For class II drugs it is therefore necessary to generate a strong correlation between in vitro dissolution and in vivo absorption. Examples of class II drugs are the non-steroidal anti-inflammatory drug like ketoprofen, aceclofenac and the antiepileptic drug like carbamazepine. This class of drug are subjected to various formulation approaches which improve the dissolution rate and hence oral bioavailability. [4]

Class III drugs: Class III drugs are those that dissolve rapidly but which are poorly permeable. Examples are the H2-antagonist ranitidine and the β-blocker atenolol. It is important that dosage forms containing class III drugs release them rapidly in order to maximize the amount with time these drugs, which are slow to permeate the gastrointestinal epithelium, are in contact with it. [4]

Class IV drugs: Class IV drugs are those that are classed as poorly soluble and poorly permeable. These drugs are liable to have poor oral bioavailability, or the oral absorption may be so low that they cannot be given by the oral route. The diuretics hydrochlorothiazide and furosemide are examples of class IV drugs. [4]

Process of solubilization

The process of Solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion. [5].



Factors Affecting Solubility

Molecular size & weight: Increasing the molecule size or its molecular weight of substance will decrease its solubility. Larger molecules are not easy to encircle with solvent molecules in order to solvate the substance. In the case of organic compounds the quantity of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.[6]

Temperature: If the solution process absorbs energy then the temperature is increased as the solubility will be increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. For all gases, solubility decreases as the temperature of the solution increases.[6]

Particle size & Surface area: The dimension of the solid element influences the solubility because of particle size. Particle size inversely proportional to the surface area. The larger surface area allows a greater interaction with the solvent.[6]

Polymorphs: Depending upon the internal structure, a solid can exist either in crystalline and amorphous form. The ability for a substance to crystallize in more than one crystalline form is polymorphism. It is possible that all crystals can crystallize in different forms or polymorphs. If the change from one polymorph to another is reversible, the process is called enantiotropy. If the system is monotropic, there is a transition point above the melting points of both polymorphs. The two polymorphs cannot be transformed from one another without undergoing a phase transition. Polymorphs can differ in solubility, density melting point.[6]

Theory of Dissolution [7]

Diffusion layer model/Film Theory:-

It involves following steps: -Solution of the solid to form stagnant film or diffusive layer which is saturated with the drug. Diffusion of the soluble solute from the stagnant layer to the bulk of the solution; this is rate determining step in drug dissolution.

Noyes and Whitney Equation:-

$dc/dt = k (C_s - C_b)$

Where, dc/dt= dissolution rate of the drug, K= dissolution rate constant, Cs= concentration of drug in stagnant layer, C_b= concentration of drug in the bulk of the solution at time t

Modified Noyes-Whitney's Equation:-

$dC/dt = DAKw/o (Cs – Cb)/Vh$

Where, D= diffusion coefficient of drug, A= surface area of dissolving solid, Kw/o= water/oil partition coefficient of drug,V= volume of dissolution medium, h= thickness of stagnant layer. $(Cs – C_b)$= conc. gradient for diffusion of drug.

Danckwert's model/Penetration or surface renewal Theory

Danckwert's takes into account the eddies or packets that are present in the agitated fluid which reach the solid-liquid interface, absorb the solute by diffusion and carry it into the bulk of solution.These packets get continuously replaced by new ones and expose to new solid surface each time, thus the theory is called as surface renewal theory.

The Danckwert's model is expressed by Equation:-

$$V\frac{dC}{dt} = \frac{dm}{dt} = A(Cs - Cb).\sqrt{\gamma D}$$

where,
m = mass of solid dissolved, and
γ = rate of surface renewal (or the interfacial tension).

Interfacial barrier model/Double barrier

In this model it is assumed that the reaction at solid surface is not instantaneous i.e. the reaction at solid surface and its diffusion across the interface is slower than diffusion across liquid film. Therefore the rate of solubility of solid in liquid film becomes the rate limiting than the diffusion of dissolved molecules.

Equation:-

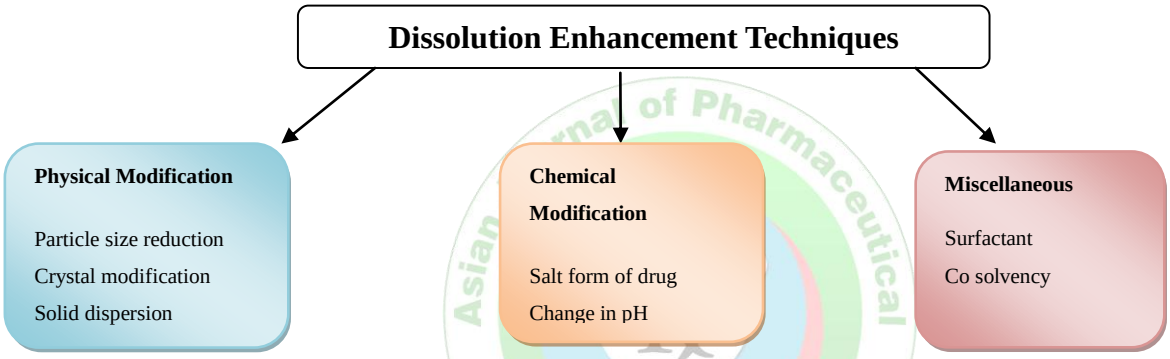
G = Ki (Cs – C)

Where,

G=dissolution rate per area unit

K = effective interfacial transport rate constant

Techniques for Dissolution Enhancement [8,9]



Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows greater interaction with the solvent which causes an increase in solubility.

Surface area divided into two types

(A) Absolute surface area: - which is total area of solid particle surface of any particle.

(B) Effective Surface area: -the area of solid surface exposed to the dissolution media.

Conventional methods of particle size reduction, such as combination 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. However, the mechanical forces inherent to combination, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation. The thermal stress which may occur during combination and spray drying is also a concern when processing thermo sensitive or unstable active compounds. Using traditional approaches for nearly insoluble drugs may not be able to enhance the solubility up to desired level. Micronization is another conventional technique for the particle size reduction. Micronization increases the dissolution rate of drugs through increased surface area, it does not increase equilibrium solubility. Decreasing the particle size of these drugs, which cause increase in surface area, improve their rate of dissolution. Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills and so forth micronization is not suitable for drugs having high dose number because it does not change the saturation solubility of the drug. The effect of particle size on bioavailability of drugs or their absorption in gastrointestinal tract is very important for pharmaceutical companies and their decision on which form and technology to use while producing medicinal products. In the pharmaceutical industry, particle characterization of powder materials has become one of the crucial aspects in drug product development and quality control of solid oral dosage forms. The particle size distribution (PSD) of the drug substance may have significant effects on final drug product performance (e.g., dissolution, bioavailability, content uniformity, stability, etc.). In addition, many publications have shown that the PSD of pharmaceutical powders has an impact on almost every step of manufacturing processes of solid oral dosage forms, including premixing/mixing, granulation, drying, milling, blending, coating, encapsulation, and compression. The pharmaceutical powders and granulates, in a physical sense, have the particles with different shapes: spherical, cubes, plates, fiber and other. Only the size of the spherical particles can be expressed numerically.[10,11]

Solid Dispersion (SD)

Solid dispersions are a dispersion mixture of one or more active ingredients in an inert carrier (Excipients) atthe solid state prepared by melting, solvent, solvent-melting or other methods. The approaches used for preparing SDs are referred as solid dispersion techniques. According to Noyes–Whitney equation, the dissolution rate of a drug in a given medium depends on the concentration difference between the dissolving interface and the bulk solution. For poorly water-soluble drugs, the dissolving rate on the interface is positively associated with the particle size of drug, especially above 100 nm. SDs can maximize the reduction of a drug‘s size by dispersing it in a large quantity of carrier excipient, thus increasing the absorption area, hence the bioavailability. In SDs, the drug can be in presence as molecular, amorphous, microcrystal or colloidal state, which is dependent on the formulation and preparative process thereof. The high-energy or metastable state of drug in SDs makes it tend to dissolve in a medium, as opposed to the bulk drug. Apart from drug solubilization, SDs canalso improve the gastrointestinal absorption of poorly soluble drugs by affecting the absorptive epithelia, in particular those surfactant-based and absorption enhancer-containing SDs. Solid dispersion technique is more suitable for those drugs with low viscosity, less hygroscopicity and high glass transition temperature.[12,13]

Carrier Excipients of (SD)

Carrier excipients play an essential role in formation of SDs, drug dissolution and absorption, and stability of SDs. Pharmaceutical excipients that have been used for production of SDs are exhaustively collected in Table 3. The carrier excipients of SDs are generally classified into low-molecular-weight carriers, polymeric carriers and surfactant carriers. They are highly water-soluble or hydrophilic in nature in the case of poorly water-soluble drugs. In physical property, low-molecular-weight carriers are generally crystalline (e.g., saccharides), amphiphilic copolymer carriers are semi-crystalline (e.g., Poloxamer), and homopolymer carriers are amorphous, such as polyethylene glycol (PEG) and polyvidone (PVP). In the early development of SDs, low-molecular-weight carriers were tentatively used, such as urea, saccharides and organic acids. These carrier excipients have high requirements for drug and solvent used. Moreover, the resulting SDs tends to become aging and unstable. In some cases, the low-molecular-weight compounds such as glucose and lactose negatively affect the gastrointestinal absorption of API, since the body preferably takes up the nutrients rather than the non-nutritive excipients. Compared to low-molecular-weight carriers, polymeric carriers possess larger molecular weight that can afford higher dispersibility and stronger recrystallization inhibition for drugs. For this end, polymeric carriers are currently widely used for the preparation of SDs, such as PEG, PVP and hydroxypropylmethylcellulose (HPMC). Nevertheless, the high viscosity, plasticity and hygroscopicity associated with macromolecules that make problems for production compromise their application in SDs. Polymeric carriers, not including surfactants, have inadequate absorption-promoting effect for poorly permeable drugs, which just provide necessary dispersibility. Carriers that possess a surfactant property, beyond dispersion powder, have the advantage of increasing drug absorption through interaction with the absorptive epithelia and inhibiting drug efflux transporters. To improve the performance of polymeric carriers, copolymers and functionalized polymers (e.g., PEG polymers) are developed for SDs. These novel carrier excipients are provided with excellent amphiphilicity, formability, solubilization or absorption-promoting characteristics. Examples include fatty acidmacrogolglycerides (e.g., Gelucire 44/14 and Gelucire 50/13), poly (vinylpyrrolidone-co-vinyl acetate) (PVP/VA), and poly(vinyl acetate-co-vinyl caprolactame-co-ethylene glycol) (Soluplus®). [15,16]

Tablet 3:-Summary of commonly use excipients used in Solid dispersion

Carrier excipients	Example	Comments
Saccharides	Sucrose Glucose Lactose Dextrose Mannitol Sorbitol	Ordinary dispersibility; having potential effect on drug absorption.
Organic acids	Citric acid Tartaric acid Fumaric Acid	Effervescent dispersion, Simple dispersing Material, not applicable for acid-labile API.
Polyethylene glycol	PEG 4000 PEG 6000	High dispersibility, able to solubilize drugand delay aging of SDs.
Polyvidone	PVP k15 PVP k30	High dispersibility, able to inhibitrecrystallization.
Cellulose derivative	HPMC HPC MC	High dispersibility, less plasticity andhygroscopicity, easy to process
Poly (oxyethylene–co oxypropylene)	Poloxamer 188 Poloxamer 407	High dispersibility, able to solubilize drugand having absorption-promoting effect
Poly(vinylpyrrolidone-co-vinyl acetate)	PVP/VA	Fine dispersibility but low hygroscopicity;superior to PVP in function.
Carboxypoly methylene	Carbopol 947 Carbopol 907	Ionic polymers, good dispersibility, rapiddrug release in the intestine.

Polyo xyethylene stearate	Polyoxyethylene (40) stearate	Fine dispersibility, contribute less to dissolution, used rarely

Methods of solid dispersion:-

(a) Solvent evaporation method

This method was developed mainly for heat unstable components because drug and carrier are mixed by a organic solvent instead of heat as in melting method. Therefore, this method allows use of carriers with an excessively high melting point. The basic principle of this method is that drug and carrier are dissolved in a volatile solvent (IPA, MDC, and Hydro alcoholic solvent) for homogeneous mixing. SD is obtained by evaporating the solvent under constant spray in FBP Top spray granulation method. Then, the granulated mass is crushed and sieved suitable sieve. The main advantage of this method is avoidance of decomposition of drug and carrier because the required temperature for evaporation is low temperature.

(b) Hot melt extrusion

Hot-melt extrusion is a common method for improving solubility and oral Bioavailability of poorly water-soluble drugs, in which the amorphous SD is formed without solvent, thereby avoiding residual solvents in the formulation. This method is conducted by a combination of the melting method and an extruder, in which a homogeneous mixture of drug, polymer, and plasticizer is melted and then extruded through the equipment. The shapes of products at the outlet of extruder can be controlled and may require grinding in the final step.

3.3Crystal Modification

Pharmaceutical active ingredients (APIs) can exist in a variety of distinct solid forms, including polymorphs, solvates, hydrates, salts, co-crystals and amorphous solids. Each form displays unique physicochemical properties that can profoundly influence the bioavailability, manufacturability purification, stability and other performance characteristics of the drugs.[17]

Crystal engineering techniques are developed for the controlled crystallization ofdrugs to produce high purity powders with well-defined particlesize distribution, crystal habit, crystal form (crystallineor amorphous), surface nature, and surface energy. By manipulating the crystallization conditions (use of different solvents or change in the stirring or adding other components to crystallizing drug solution), it is possible to prepare crystals with different packing arrangement; such crystals are called polymorphs. [18]

As a result, polymorphs for the same drug may differ in their physicochemical properties such as solubility, dissolution rate, melting point, and stability. Most drugs exhibit structural polymorphism and it is preferable to develop the most thermodynamically stable polymorph of the drug to assure reproducible bioavailability of the product over its shelf-life under a variety of real-world storage conditions. [20]

Depending upon the internal structure, a solid can exist into two forms. When a substance exist more than one crystalline form named as polymorphs, phenomenon called polymorphism.

(a) Crystalline:- Well shaped crystal structure

(b) Amorphous:-Having no internal structure

Method for crystal modification

1. Co crystal
2. Eutectics mixture
3. Solid solution
4. Coamorphous solids

4. Chemical Modifications:-

4.1 Salt form of drug

Salts have improved solubility and dissolution characteristics in comparison to the original drug. It is generally accepted that a minimum difference of 3 units between the pKa value if the group and that of its counter ion is required to form stable salts. Alkali metal salts of acidic drugs like penicillin's and strong acid salts of basic drugs like atropine are water soluble than the parent drug. Salt formation is frequently performed on weak acidic or basic drugs because it is a relatively simple chemical manipulation, which may alter the physicochemical, formulation, biopharmaceutical, and therapeutic properties of a drug without modifying thebasic chemical structure. The ideal characteristics of a salt are that it is chemically stable, not hygroscopic, presents no processing problems, and dissolves quickly from solid dosage forms. Theoretically, every compound possessing acidic and/or basic properties can participate in salt formation.Most drugs are either weak acid or weak base. Generally with weak acidic drug, a strong base salt is prepared such as sodium and potassium salt of barbiturates and sulphonamide. In case of weak base, a strong acid salt is prepared like hydrochloride or sulphate salt of alkaloid drugs. [21]

4.2 Change in pH:-

It is well documented that the influence of the changes in pH inside the gastrointestinal tract upon the bioavailability of pharmaceuticals. The absorption of drug is largely dependent upon diffusion, which vary with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water. While the significance of critical parameters like salt selection and pH adjustment has been stressed on pre-formulation, the use of pH altering excipients within drug delivery systems is also of significant utility. pH adjustment can in principle be used for both oral and parenteral administration. Because blood is a strong buffer, upon intravenous administration the poorly soluble drug may be precipitate with pH between 7.2 – 7.4. To assess the suitability of 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. Solubilized excipients that boost environmental pH within a dosage form (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. [21]

4.3Complexes:-

Cyclodextrins are a group of cyclic oligosaccharides obtained from enzymatic degradation of starch. The three major cyclodextrins α, ß, and γ-CD are composed of six, seven, and eight D-(+) -glucopyranose units. These agents have a torus structure with primary and secondary hydroxyl groups orientated outwards. Consequently, cyclodextrins have a hydrophilic exterior and a hydrophobic internal cavity. CD and their derivatives have been employed as complexing agents to increase water solubility, dissolution rate and bioavailability of lipophilic drugs for oral or parenteral delivery. These are non-reducing, crystalline, water soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a donut shaped ring having hydrophobic cavity and hydrophilic outer surface. 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 cyclodextrins complex. [22]

Tablet 4:-Some characteristics of (α, β, γ, δ)

Type of CD	Cavity diameter A	Molecular weight	Solubility(g/100ml)
α – CD	4.7 – 5.3	972	14.5
β - CD	6.0 – 6.52	1135	1.85
γ - CD	7.5 – 8.3	1297	23.2
δ - CD	10.3 -11.2	1459	8.19

Mechanism of formation of Inclusion complexes:

Cyclodextrins are able to form solid inclusion complexes (host–guest complexes) with a wide range of solid, liquid and gaseous compounds by a molecular complexation. in these complexes, a guest molecule is held within the cavity of the cyclodextrin host molecule. Complex formation is a dimensional between host cavity and guest molecule The lipophilic cavity of cyclodextrin molecules provides a microenvironment into which appropriately sized non-polar moieties can enter to form inclusion complexes. No covalent bonds are broken or formed during formation of the inclusion complex. Complexes can be formed either in solution or in the crystalline state and water is typically the solvent of choice. Inclusion complexation can be accomplished in a cosolvent system and in the presence of any non-aqueous solvent.

5.0 Miscellaneous Technique:-

5.1 Surfactant:-Surfactants are also commonly known as surface active agents, wetting agents, emulsifying agents or suspending agents based on their use and application. Surfactants exhibit some superficial or interfacial activity and have characteristic structures possessing both hydrophobic (non-polar) and hydrophilic (polar) groups. The polar groups generally contain heteroatoms such as, O, S, P or N, as part of the functional groups such as alcohol, thiol, ester, acid, sulfate, sulfonate, phosphate, amides, amines etc. The polar groups of surfactants have a strong affinity for polar solvents, particularly water and are termed hydrophilic whereas the non-polar part of surfactant is called hydrophobic and the surfactant which has dual affinity are termed as amphiphilic. [23]

Surfactants can be classified into four categories based on theirdissociation in water:

- Anionic Surfactants
- Cationic Surfactants
- Amphoteric/Zwitterionic surfactants
- Nonionic surfactants

Anionic surfactants

Anionic Surfactants on addition to water dissociate to form an amphiphilic anion and a cation. These are most commonly used surfactants. Examples include sodium lauryl sulfate (SLS), alkyl benzene sulfonates, etc.

Cationic surfactants

Cationic surfactants dissociate in water to form an amphiphilic cation and an anion. These are commonly used for their disinfectant and preservative properties since they have good bactericidal properties and belong to quaternary ammonium compounds. Examples include cetrimide, benzalkonium chloride, etc.

Nonionic surfactants

Nonionic surfactants do not dissociate in aqueous solution. These are less irritant than anionic and cationic surfactants. The hydrophilic region contains polyoxypropylene, polyoxyethylene or polyols derivatives and hydrophobic region contains saturated or unsaturated fatty acids or fatty alcohols. The most commonly used nonionic surfactants are poloxamers, polysorbates, etc.

Amphoteric/Zwitterionic surfactants

Amphoteric/Zwitterionic surfactants exhibit both cationic and anionic dissociations. These surfactants are mild in nature and they can be anionic or cationic or nonionic depending on the pH of the water. Alkyl betaine is an example of amphiphilic surfactant.

5.2 Co-Solvency

The addition of a water-miscible or partially miscible organic solvent (i.e. co-solvent to water) is a common and effective way by which to increase solubility of a non-polar drug. The technique is known as cosolvency. Examples of solvents used in cosolvent mixtures are PEG 300,

propylene glycol or ethanol Solubility enhancement as high as 500-fold is achieved using 20% 2pyrrolidone.

6.0 Characterizationof solid dispersion

6.1 Vibrational spectroscopy

For polymorph identification, the prominent methods among the vibrational spectroscopy are infrared and raman spectroscopy. Both techniques offer information on structure and molecular conformation in the solid state by probing vibrations of atoms. Other information gained from vibrational spectroscopies, which can be helpful in distinction of polymorphs, includes low energy lattice vibrations caused by differences in crystal packing. Several limitations of the technique are worth considering especially for studies involving smallquantities of sample or single crystals.

6.1.1Fourier Infrared spectroscopy (IR)

FTIR spectroscopic imaging is regarded as more beneficial than other methods because it takes into account the specific absorbance of molecular vibrations in the sample for quality assessment of biomedical materials. IR can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in purematerial. It can be applied to follow changes inbonding between functional groups.

6.1.2 Raman spectroscopy

Raman spectroscopy is a powerful light scattering technique used to diagnose the internal structure of molecules and crystals. In a light scattering experiment, light of a known frequency and polarization is scattered from a sample. A Raman spectrometer interfaced to a microscope has an additional advantage of being able to pinpoint small crystalline samples, which do not have to be removed from crystallization vials for analysis, thus eliminating sample preparation. In addition, the spatial resolution of Ramanmicroscopy is limited by the wavelength of the visible light probe rather than infrared radiation, making this technique suitable for examining minute sample quantities in complexmatrices.

6.1.3 Nuclear magnetic resonance spectroscopy

Solid-state nuclear magnetic resonance spectroscopy can be used to investigate polymorphism by probing the environments of atoms in the solid state; nonequivalent nuclei will resonate at different frequencies and these changes in chemical shift can often be connected with changes in conformation or chemical environment of the compound. It is also useful because it is able to determine the number of crystallography in equivalent sites in a unit cell. Unlike powder x ray diffraction, solid state nuclear magnetic resonance spectroscopy is well-suited to studying amorphous forms of pharmaceuticals and solvates that are usually small to detect. Collecting spectra at various temperatures is a powerful tool in understanding polymorphic transformations and molecular motion in the solid.

6.1.4 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is the most reliable thermoanalytical technique. It is a thermalprocess to find out the heat flow and temperature related with substance transitions as a function of time and temperature. With the help of DSC we can find melting temperatures as well as monitor and study the thermal behavior of various substances. Processes in which energy is either required or produced can be quantitatively observed with the help of DSC. Interactions between drugs and polymer are generally said to cause the changes in the exothermic and endothermic peaks17. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting-and(re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

6.1.5 Scanning Electron Microscopy (SEM)

As this method is automatic and gives precise measurements, it is time saving as well as reliable,

Therefore, it gives valid conclusions with smaller number of observations. The characteristic properties of drug crystals like particle size and morphological surface can be known by the preparation method andchemical composition. Additionally, the shape and granulometric properties of the powder particles can be explained through the range of parameters automatically obtained by connecting SEM with an image processor.

CONCLUSION:-

Solubility of the drug is the most significant factor and prime requirement for to achieve good bioavaibility after the absorption of drug so it is most critical factor in the formulation development.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.There are various method to increase the solubility; some of techniques are described above. Selection of solubility enhancement method depend on solubility, pH, melting point, polymorphism, absorption site, chemical nature, physical nature, dosage form like tablet and capsule, and regulatory requirement, like maximum daily dose of any excipients.

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