DIFFERENT APPROACHES FOR SOLUBILITY ENHANCEMENT TECHNIQUES OF TABLET

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Abstract

Solubility is a property of a material and can be defines as the amount of solute that can dissolve in the specific amount of solvent For achieving therapeutic effect in human , drug should be bioavailable and hence it depends on solubility of drug. Recent studies shows that Most drugs have limited water solubility, making them difficult to dissolve in the GIT area. and causes peptic ulcers , gastric irritation etc, whereas only 8% of drug candidates have high solubility and high permeability . The aim of review is to provide information about the various improvement techniques of solubility and bioavailability of poorly soluble drug and the drugs which causes adverse effects and toxicity due to less absorption and solubility. In BCS classification system class 2 drugs have solubility as rate limiting step hence the enhancement of solubility is an important parameter before formulation of dosage form of that drug.

Keyword**:** bioavailability, solubility enhancement techniques, poorly water soluble drugs.

INTRODUCTION:

Solubility or dissolution enhancement technique remains a most challengeable field for the researchers in the formulation design and developmental process [1]. Solubility is defined in terms of the number of parts by volume of solvent required to dissolve one part by weight of a solid or one part by volume of a liquid according to pharmacopoeias .Solubility occurs under dynamic equilibrium and results from the simultaneous and opposing processes of dissolution and phase joining.[2]. Solubility is the property of a solute that causes it to mix uniformly with a solvent [3]. The solubility of a drug may be expressed as parts, percentage, molarity, molality, volume fraction, and mole fraction [4]. IUPAC defines solubility as the analytical composition of a saturated solution expressed as a proportion of a designated solute in a designated solvent [5]. Solubility is a key characteristic in achieving the necessary amount of medication in blood stream in order for pharmacological effect to be demonstrated. The major problem encountered with formulation is low aqueous solubility of new drug molecule [6]. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown Currently only 8% of new drug candidates have both high solubility and permeability. Solubility is a major challenge for certain drugs to develop a suitable formulation for administration of drugs orally like Griseofulvin, Digoxin, Phenytoin, Sulphathiazole and Chloramphenicol. With the recent advent of high-throughput screening of potential therapeutics, the numerous drug candidates with poor solubility has increased severely and their formulation for oral delivery poses great challenge to formulation scientists in the pharmaceutical industry . The oral dosage forms have many advantages over other types of dosage forms like greater stability, accurate dosage, smaller bulk and easy production is possible [7] . by increasing the quantity of dose at a time can lead to increase in the efficacy by can also lead to produce more toxic effect . so best way is to enhance the solubility and release rate so that more amount of drug reach to systemic circulation of same dose that previous one.

Poor soluble drugs are often challenge in front of pharmaceutical industry . the improvement in solubility is one of the challenging aspect of drug development especially for oral drug delivery system.to solve problem in

solubility of drugs ,we go over many conventional and modern techniques for improving solubility[8]. The traditional methods of increasing solubility are solid dispersion , complexation and Ph enhancement whereas newer methods include liquidsolid , hydrotropy , sonocrysatallization , self emulsifying system [9]

Solubilisation process : it happens by breaking intermolecular and ionic bond in the solute , the separation of molecules of the solvent to provide space in the solvent for the solute , interaction between solvent and solute . this process occurs via break down of solute bond [10] .
Solubility is one of the most crucial aspects of achieving the targeted drug concentration or quantity in systemic circulation and required pharmacological response.[9]
After oral administration poorly water-soluble medication sometimes require considerable dosage to attain therapeutic plasma level . Poor drug solubility will result in a low dissolution rate resulting in a low bioavailability of orally administered drugs. The degree and rate at which a drug's active component enters the systemic circulation and allowing the drug to get to the action site, is known as bioavailability. When the bioavailability of a drug is low, it will result in a therapeutic potential that is minimal leading to unsatisfactory clinical results [11].
For purpose of absorption is most suitable and common employed for path of drug delivery .maximum of the drug like pharmacological reactions can be linked directly to plasma levels of drug which show the results in the drug to the body . bioavailability can be determines the better solubility of drug and how its showing the pharmacological response ,. Solubility is the key parameter to found out meditation of drug in complete movement to doing required pharmacological response to a particular drug [12]. Any drug which is administered drug or to be fascinated must be existing in the aqueous solution in the form of location the absorption which can easily show the response to the site of action, Liquids the maximum common using solvents for the liquids pharmaceutical formulation or in any solubility process , the drug having the weakly acidic or weakly basic have a poor aqueous solubility. The lower solubility drug and lower dissolution rate of the poorly water soluble drug in aqueous stomach liquids frequent that reason of inadequate bioavailability [14]

DESCRIPTIVE TERM	**PARTS OF SOLVENT /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 drug	From 100 to 1000
Very slightly soluble	From 1000 to 10000
Practical insoluble	10000 or above

Table- 1: Solubility classification, Solubility aspect of parameter [12]

According to Indian pharmacopeia they have been indicated by descriptive term in the accompanying table and have the following significance with reference to a temperature of 15 ° to 30 °

FACTOR AFFECTING OF SOLUBILITY

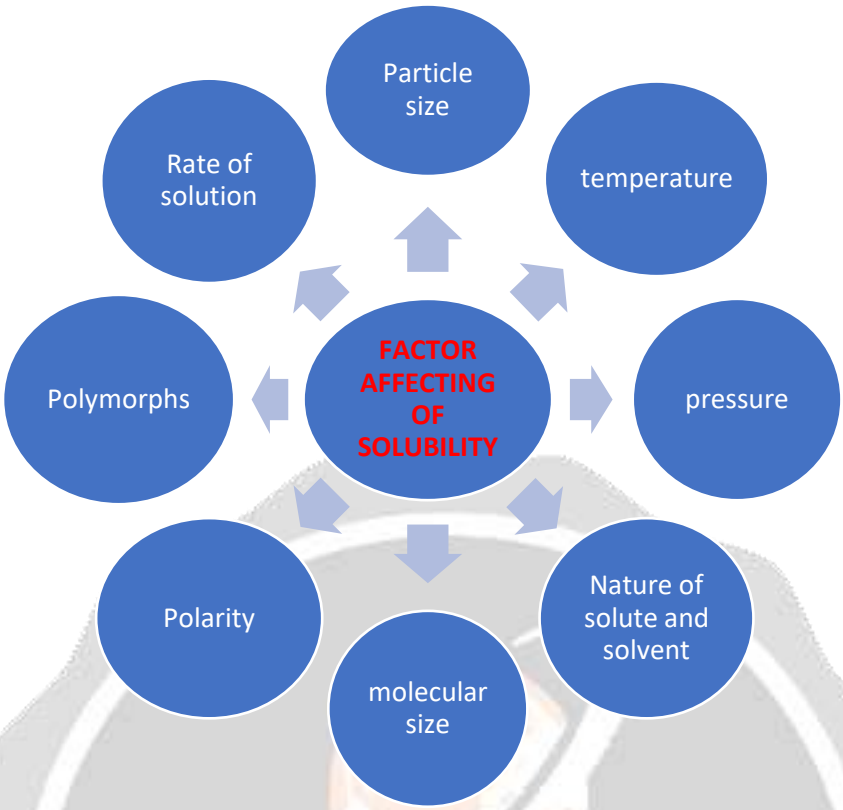
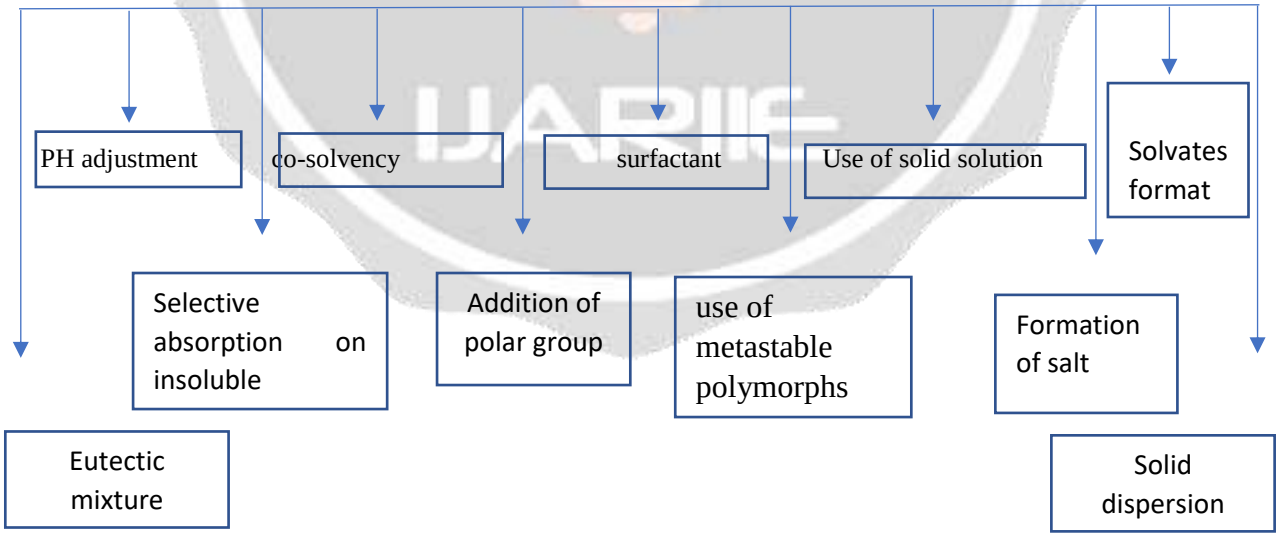


Fig - 1: Factor affecting of solubility

TRADITIONAL SOLUBILITY ENHANCEMENT TECHNIQUES:

The solubility enhancement technique is listed below:



Flow chart-1: Traditional solubility enhancement techniques.

A table of traditional solubility enhancement techniques with methodology and limitations

Methods	**Mechanism involved**	**Methodology**	**Limitation**	**Examples**
Use of suitable salts	Increase in dissolution	Salt formation with weak acid or base	It is highly reactive with CO_2 & water and results into ppt. in unionised drugs .	Chlordiazepoxide maleate, diclofenac maleate.15
Use of co-solvent	Increase in solubility of drug	Adding of co solvent , ethanol , propylene , glycol, glycerin	Precipitates may be amorphous or crystalline can vary in size.	Analgesic syrups of paracetamol
By addition of polar group	Increasing water solubility by increasing hydrogen bonding and interaction with water	Addition of polar group in the structure of drug (carboxylic acid and amine)	At high temperature many drug may get degraded.	CosolventsA
Solid dispersion	Decreasing the drug particle size changes the microenvironment of the drug particle which increase the dissolution rate and absorption	Prepared by fusion , solvent evaporation. 16	Low certainty of the solid dispersion conduct due to the lack of an elementary considerate of their material properties.	Paracetamol urea
Use of surfactant	By promoting wetting and penetration of dissolution fluid into the drug	Addition of suitable surfactant (polysorbate)	Micelle development happens which it entraps with the drug whithin micelles and mostly results in the raised solubility of below par soluble drugs.	Spironolactone is a drug whose bioavailaility is increased by this method
Alteration of ph solvent	Changing the pH of drug in solution	Salt formation , addition of buffer	Acceptability and poisonousness both native and complete relate to required of a non-physiological pH, dangerous pH should be considered	Buffered tablet of aspirin (22)

Use of metastable polymorphs	Metastable forms show better solubility than stable form	Converting the stable form to metastable form	Metastable polymorphs into a low energy crystal form having low solubility.	Using B form of chloramphenicol than A and C forms
Solvates formation	Powder of submicron size having increased surface area show the improved solubility	Freeze drying of solute with organic solvents.	Solvates formation can occur low solubility in most of organic compounds in SC-CO 2 .	Benzene solvate
Use of solid solution	Improving solubility by preparing sol-gel form of the drug	Fusion, melting	Solid solution ,solutes tend to have limited solubility in the solid solvents.	Succinic acid
Eutectic mixture	When exposed to water the soluble carrier dissolves leaving the drug in micro crystalline state which solubilize rapidly	Fusion	Eutectic mixture may not be compatible with all drugs and may result in drug degradation or inactivation. Eutectic mixture can be sensitive to moisture, oxidation, and other environmental factors, Which can affect stability	Paracetamol-camphor
Selective absorption on insoluble carrier	Weak physical interaction between adsorbate and adsorbant through hydration and swelling of clay in aqueous media improves solubility	Use of highly active adsorbant, clay like bentonite	Drug which are not attach by vander waal forces or can show dipole dipole interaction can not absorb on insoluble carrier .	Indomethacin, prednisone

Table-2:Traditional methods of solubility enhancement.

ENHANCEMENT: ADVANCE TECHNIQUES FOR SOLUBILITY

The advance techniques are given below
1 Micronization
2.Hot melt extrusion
3.Nano suspension
4 Hydro-tropy
5.Super critical fluid process
6. Spray drying [13, 17]

ADVANCE TECHNOLOGY

Traditional techniques of enhancement of technology were widely used but due to their limitations and new innovations in the field of pharmaceutics creates an opportunity to improve the techniques and minimize the limitation which results into design of modern technology in the pharmaceutical field of enhancement of solubility.

MICRONIZATION : It is the process for decrease of size of particle for better solubility of drug and it enhances dissolution rate of the drug. The size reduction of particle is to raise effective surface area in which its results the reduces of solubility and dissolution rate of drug .micronization having the highest particle size reduced the granular particle converted into the lesser than 5 micron . it helps in surface area is increase however it decreased in the particle size and solubility is rise . It shows the narrow and uniform particle size having essential for development for the uniform dosage form .The advantage of micronization tendency to give the uniform particle size with rise in the surface are and particle distribution.[2,24]

In micronization techniques many different types of mill are used i.e

Ball mill, Roller mill, Hammer mill, Colloid mill ,Rotary cutter mill.

Ball mill

Principle: The ball mill works on the impact between the rapidly moving ball and the powder material, both enclosed in a hollow cylinder. Thus, in the ball mill, impact or attrition or both are responsible for the size reduction.

Advantages:

1) It can produce very fine powder
2) Used for batch operation.
3) Suitable for both wet and dry grinding processes.

Disadvantages:

1) Noisy machine
2) Not suitable for soft, tacky &fibrous material..

Roller mill

Principle: The material is crusted by the application of pressure. The mill works on the principle of compression of material by applying a pressure on it.

Advantages:

1) Energy efficient uniform particle –size distribution .
2) Less dust generation no sig. Heat prod.
3) Decreased fire risk excellent physical appearance .

Disadvantages:

1) Little or no effect on fiber
2) When required, maintenance can be expensive.
3) May have high initial cost (depends on system design)

Hot melt extrusion

HME can be simply define as the process of forming a new material (the extrudate) by forcing it through an orifice or die under controlled condition, such as temperature , mixing, feed-rate, and pressure HME differs from simple extrusion in that, polymer, drug and excipients blends are mixed thoroughly in the molten state in this process, needing no solvents for granulation. The molten polymer serves as the thermal binder .It is very common method used in the polymer industry. But Speiser and Huttenrach were the first persons who use this technology for pharmaceutical purposes .A melt extrusion consist 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 mas. 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 consist of an optional die, shapes the melt in the required from such as granules, pellets, films, or powder. An important advantages 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.

Principle:

Extrusion is the process which is used to create new materials with desirable properties by manipulating additive ingredients through a number of staged unit operation.
Dosing – metering- melting – mixing- pumping- forming
Advantages:

1) Improve the bioavailability and solubility of poorly soluble compunds.
2) Processing in the absence of solvents and water.
3) Good stability at varying PH and moisture levels.

Disadvantages:

1) Not applicable to heat sensitive material.
2) This method requires high energy input.
3) Limited number of available polymer.

NANOSUSPENSION:

Nanosuspension is the method used for the low soluble drug for the purpose of parenteral drug. The advantage of this process are the particles sizes is less than one micron and for the parenteral low soluble drug. Nowdays the various nanonization methods have been emerged to raise the bioavailability and dissolution rate of frequent drugs that have low soluble in water. This method is used for both water and oil insoluble compounds widely used for the purpose of pharmaceuticals industry for prepration of parentral used drug this can easily bind and shows the pharmacological action drug. By this technique can obtained the particles size less than 1micron or in the average of 200 to 600mm. 31 In nanosuspension the particle size of drug reduce which increase the surface area and therefore the dissolution rate and solubility Increases which enhance bioavailability . basically Nanosuspension is submicron colloidal dispersion of pure particles of drug which is stabilized by surfactants. Compound that are insoluble in water (but are soluble in oil) with high log P value, high melting point and high doses for that nanosuspensipon is favourable method. nanosuspension technology can also be applicable for drugs which are insoluble in both water and organic solvents.
Advantages:

1) Rapid dissolution and tissue targeting can be achieved by IV route of administration.
2) Oral administration of nanosuspension provide rapid and improved bioavailability.
3) Can be applied for the poorly water soluble drugs.
4) Long-term stability up to 2 years at room temperature or 5°C.
5) Can be used for controlled and targeted delivery of drug.

Disadvantages:

1) Physical stability, sedimentation and compaction can causes problems.
2) It is bulky sufficient care must be taken during handling and transport.
3) Uniform and accurate dose cannot be achieved unless suspension .

HYDROTROPY:

The Hydrotropy is solubilisation process in which other solvent is used to raise the soluble of mixture .Due to incidence of large amount of additive it can make the better solubility in the water. Its mechanism is solubility because it related to the complexation which involved in the weak interaction between the hydrotropic agents through the process being used in the works to be in non-micelle –forming materials, whichever solids or solids, inorganic or organic, capable of solubilizing insoluble compounds. The example of different Hydrotropy agents is sodium acetate, sodium alginant etc.[21,32]

Mechanism of action of hydrotropes:
Hydrotropes are the compounds having both an anionic group and a hydrophobic aromatic ring or ring system. The hydrophillicity increases by anionic group and the ring system interacts with the solute to be dissolved .the mechanism involved in hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium aligant, sodium benzoate etc.[14]
Advantages:

1) The use of hydrotropic solubilizers as permeation enchancers.
2) Application of mixed – hydrotropy to develop injection dosage forms of poorly water-soluble drugs.
3) Application of hydrotropic solubilisation in nanotechnology (by controlled precipitation).

Disadvantage:

1) Slight increases in solubility with high concentration of hydrotropic agents, which sometimes leads toxicity.

SUPERCRITICAL FLUID METHOD:

In the supercritical fluid technique, carbon dioxide is used as anti-solvent for solute but as a solvent with respect to the organic solvent. The use of supercritical carbon dioxide is advantageous as its low critical temperature and pressure makes it attractive for processing heat-labile pharmaceuticals. The technology is used for the size reduction of the particle , it is widely used in the formation of nanowater insoluble drug . it can use for the non volatile solve at the critical point of co2 . Super critical fluid happen as a single stage above its critical pressure and temperature . this method is very useful and utilized in the intermediate into the pure liquid and gas . and widely used in the pharmaceutical fields for the purpose to decrease in particle and food industry.[3,17] This method is important for improving bioavailability of pharmaceutically active compounds. Supercritical carbon dioxide due to its properties of improved mass transfer and increased solvating power it proved as a new complexation medium. In this technique, first, drug and CD are dissolved in a good solvent then the solution is fed into a pressure vessel under supercritical fluid anti-solvent .when the solution is sprayed into supercritical fluid anti-solvent , the anti-solvent rapidly diffuses into that liquid solvent as the carrier liquid solvent conter diffuses into the anti-solvent. Because of the supercritical fluid expanded solvent has lower solvent power than the pure solvent, the mixture becomes supersaturated resulting in the precipitation of the solute and the solvent is carried away with the supercritical fluid flow.[14]

Advantages:

1) Lower operating temperatures
2) Improved yield
3) Improved product properties
4) Lower production cost.

Disadvantages:

1) Elevated pressures required
2) Relative high costs of investment
3) Complicated phase behaviour
4) Unusual operating condition.

SPRAY DRYING :

It atomizes the liquid into small droplets , providing a large surface for mass and heat transfer . Using hot air , the drops are srapyed so that they dry into solid particle. In spray drying ,a liquid feed (solution or suspension)is sprayed into a hot gas stream with the intent to isolate products in a solid form state as well-defined powder. By application of spraying ,the liquid evolves as small droplets with precisely defined volumes. These droplets are then transported with the gas flow along a drying chamber (referred to as flight time).During the flight time, the solvent evaporates from the droplets until only residual solids remain. The hot gas becomes saturated with solvent vapour during this process.[18]

Construction: drying chamber with conical bases comprise it . All the parts are stainless steel . An inlet for hot air is also provide at the bottom, and a second one is provide at the top for the spray disk atomizer. A cyclone separator is connected to the drying chamber for atomization using single-fluid or dual-fluid nozzles. In the bottom of the separator, the dry product is collected.

Working: it this process when something moved under hot gaseous drying medium, it produces a dry droplet . spray drying involves many steps in which atomization is the first and most important step followed by mixing spray air, evaporation of moisture , separation of the dry product from the exit air .first of all liquid converted into small droplet through atomizer then solute is separated from solvent .Then droplet dried into powder form .hot air is used to dry the powder .

Advantages:

1) This technique is very quick and take between 3 to 30 seconds.
2) Product sizes can be controlled and uniform.
3) It is very easy to dry solutions or suspensions.

Disadvantages:

1) Equipment is bulky and expensive.
2) Keep it clean after use is a challenge.
3) Spray dryers cannot be used to dry solid materials because it requires liquid materials.

CONCLUSION : Solubility enhancement techniques which improves the solubility of the drug through different parameters. Solubility is the concept of any physical and chemical including the pharmacokinetics therapy in consideration of medicine and biopharmaceuticals. There are various traditional techniques such as pH , particle size distribution , co – solvency , micro-emulsion , complexation , micellar solubilisation , supercritical fluids process , solid dispersion , hydrotrophy, to enhance the solubility of drug with certain limitations and now-a- days the advance techniques are used to overcome the limitations of traditional methods

such as micronization , nano suspension , and homogenization , salt formation, spray drying , solvent evaporation , hot melt extrusion and conventional method for solids dispersion etc. These days, solubility enhancement methods are quite helpful, for increasing a drugs solubility and dissolution .

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