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Solubility Enhancement of Water Insoluble Drugs by Various Techniques: A Review

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ABSTRACT

Solubility is the property of a solid, liquid, or a gaseous chemical substance called solute to dissolve in a solvent to form a homogeneous solution. Poorly water-soluble drugs are a significant and ongoing issue for the pharmaceutical industry. The poor solubility of drugs is related to low bioavailability is a major concern for a large number of small molecule drugs, both on the market and in development. This study aimed to describe the solubility enhancement of poorly soluble drugs using different kinds of techniques. If the solubility of the drug is increased the absorption through oral delivery is also increased which means the increase in the bioavailability of the drug in systemic circulation which gives a therapeutic effect. There are many techniques developed to increase the solubility of poorly soluble drugs. This study describes the techniques used in the enhancement of solubility.

INTRODUCTION:

Solubility is defined as a solute that is solid, liquid and gases dissolve into the solvent to form a homogeneous solution at specific temperature and pressure. The solubility of a substance mainly depends on the solvent used as well as temperature and pressure conditions. The oral route of drug administration is the most preferred route of administration of drugs due to convenience and ease of administration.[1] During the last decades, the pharmaceutical industry has seen the development of new drug categories such as biologics and gene therapies. While these new drugs have significant therapeutic potential, small molecules still have an important place in the pharmaceutical landscape.[2] One of the most common concerns about small molecules is, in many cases, the relatively low solubility. This has been the main problem for years, leading to the development of different strategies: the low solubility is a limit both for the formulation development of drug delivery systems and for the in vivo bioavailability. Currently, it is estimated that nearly 70% of drugs in pipelines suffer from poor aqueous solubility. The synthetic pathways exhibit a higher number of steps, leading to new chemical entities with more complex structures, relative to high molecular weight and frequently, low solubility. [3]The orally administered drugs are completely absorbed only when they show good solubility in the gastric medium and such drugs show good bioavailability. To overcome all the difficulties in the formulation of poorly soluble drugs, many technologies have been evaluated and developed in the last decades. For example molecular modifications, entrapment into a polymer matrix to form amorphous solid dispersions, drug particle size reduction, production of nanocrystals.[4]

Bioavailability is affected by several other factors like drug solubility in an aqueous environment and drug permeability through lipophilic membranes. Mostly physical modification approach is used to enhance water solubility but chemical modification is also of great importance in solubility.[5]

It is estimated that more than 40% of the marketed drugs have poor water solubility and among the US Pharmacopeia the rate is larger than 30%.[6]

According to the biopharmaceutical classification system (BCS), drug candidates featuring poor solubility and high membrane permeability are categorized as BCS Class II drugs.[7]

It is well established that the poor solubility and dissolution property of water-insoluble drugs are one of the main reasons for poor or erratic bioavailability. As pharmaceutical approaches are key factors in improving the bioavailability of BCS class II drugs.[8]

POORLY WATER SOLUBLE DRUGS:

Poorly water-soluble drugs are now accounting for 40% of existing drugs and 70% of new chemical entities. The solubility performance of drugs remains one of the most challenging aspects in formulation development. The BCS classification system was introduced in 1995 as a systemic way of classifying drugs according to solubility and permeability properties. The biopharmaceutics classification system has been divided all the drugs into four classes. Class II drugs are highly permeable and poorly soluble, but class IV drugs have low permeability and low solubility.[9]

Table No. 1: BCS Classification of drugs

CLASS	SOLUBILITY	PERMEABILITY	ABSORPTION PATTERN	RATE LIMITING STEP IN ABSORPTION
I	High	High	Well absorb	Gastric emptying
II	Low	High	Variable	Dissolution
III	High	Low	Variable	Permeability
IV	Low	Low	Poorly absorb	Concentration

Table No. 2: Solubility Criteria's as per Indian Pharmacopeia[10]

DESCRIPTIVE TERM	PARTS OF SOLVENT REQUIRED FOR PART OF SOLUTE
Very Soluble	<1
Freely Soluble	From 1 to 10
Soluble	From 1 to 30
Sparingly Soluble	From 30 to 100
Slightly Soluble	From 100 to 1000
Very slightly Soluble	From 1000 to 10,000
Practically insoluble (or) Insoluble	10,000 or more

PROCEDURE OF SOLUBILISATION [11]

The solubilization process takes place as follows-

I. Breaking of intermolecular bonds in solute.

II. Separation of the molecules of the solvent to provide space in the solvent for the solute, interaction b/w the solvent molecule or ion.

This solubilization procedure occurs in 3 steps:

1. Holes open in a solvent.
2. Molecules of the solid breaks away from the bulk.
3. The free solid molecule is integrated into the hole in the solvent.

IMPORTANCE OF SOLUBILITY

The oral route of drug delivery is most convenient due to its ease of administration, high patient compliance, cost-effectiveness, least sterility constraints, and flexibility in the design of dosage form.[12]

The major challenge with the design of oral dosage forms lies in their poor bioavailability. The oral bioavailability depends on several factors including aqueous solubility, drug permeability, dissolution rate, first-pass metabolism. The most frequent causes of low oral bioavailability are attributed to poor solubility and low permeability.

Solubility also plays a major role in the other dosage forms, as it is one of the important parameters to achieve the desired concentration of drug in systemic circulation for achieving the required pharmacological response.[13]

NEED FOR SOLUBILITY ENHANCEMENT

For good drug absorption from the GIT, there is a need for solubility enhancement. There are various factors involved in the poor aqueous solubility and poor membrane permeability of the drug. Molecule when administered as an active drug by the oral route it must be freely soluble in gastric fluids before it can permeate the membranes of the GIT to reach the systemic circulation. Two areas of research that focus on improving the oral agents include: enhancing solubility and dissolution rate of poorly water-soluble drugs.[14]

FACTORS AFFECTING SOLUBILIZATION [15]

1) **Particle size:** Particle size is inversely proportional to solubility. As particle size decreases, the surface area increases thus increasing the solubility of the solute in the solvent.

2) **Temperature:** Increase in temperature increases solubility

3) **Pressure:** Solids and liquid solutes do not affect pressure. But gaseous solutes increase in pressure increases solubility and decrease in pressure, decreases the solubility.

4) **Molecular size:** Solubility of the substance decreases with an increase in molecular size and molecular weight. In the case of organic molecules, due to an increase in branching solubility increases.

5) **Polarity:** Polarity follows 'like begets like' phenomena. Similarly, polar solutes will dissolve in polar solvents only. Similarly, Non-polar solutes will dissolve in non-polar solvents.

6) **Polymorphs:** Polymorphs can vary in melting point. Generally, polymorphs are made as to the changes in the structure results in the change in its solubility.

SOLUBILITY ENHANCEMENT TECHNIQUES

There are many approaches employed to enhance the aqueous solubility and thus the bioavailability of poorly soluble drugs especially BCS Class II drugs involve solubilization by application of principles like pH adjustment, Co-solvency, etc. Each method is dealing with some merits and demerits. Hence the decision of the method is an important step in the formulation process.

Some of the Solubility techniques are as follows-

1) Surfactants

2) pH adjustments

3) Co-Solvency

4) Particle size reduction

5) Solid dispersion

a) Hot melt Method [Fusion Method]

b) Solvent evaporation Method

c) Hot Melt Extrusion Method

6) Nanosuspension

a) Precipitation technique

b) Media Milling

c) High-Pressure Homogenization

d) Combined precipitation and Homogenization

7) Cryogenic Techniques

a) Spray Freezing onto Cryogenic Fluids

b) Spray Freezing into Cryogenic Fluids

c) Ultra Rapid Freezing

8) Inclusion complex

a) Kneading Method

b) Lyophilization/Freeze Drying technique

c) Microwave Irradiation Method

9) Micellar Solubilisation

10) Hydrotropy method

SURFACTANTS

The conventional approach to solubilize a poorly soluble substance is to reduce the interfacial tension between the surface of the solute and solvent for better wetting and salvation interaction. A wide variety of surfactants like polyglycolic glyceride, Tweens, Spans, Polyoxyethylene stearates, etc., are very successful as excipient and carrier for dissolution enhancement. Improvement of drug solubility by using the amphiphilic surfactants is due to

lowering surface tension between drug and solvent, improvement of wetting characteristics, and Micellar solubilization.[16]

pH ADJUSTMENT

For Organic solutes that are ionizable, changing the pH of the system is the simplest and most effective means of increasing aqueous solubility. Adjustment of microenvironmental pH to modify the ionization behavior is the simplest and most commonly used method to increase the water solubility of ionization of a compound. As per the pH-hypothesis and Handerson-Hesselbatch equation, the ionization of a compound is dependent on the pH of media and PKa of a drug.[17]

CO-SOLVENCY

Co-solvency is prepared by mixing miscible or partially miscible solvents. Weak electrolytes and non-polar molecules have poor water solubility and it can be improved by altering the polarity of the solvent. It is well known that the addition of an organic co-solvent to water can dramatically change the solubility of drugs. The Co-solvent system works by reducing the interfacial tension between the aqueous solution and hydrophobic solute.

Examples: Triglycerides (Corn oil, peppermint oil, etc.,), Medium-chain triglycerides, Beeswax.

Advantages

- Compared to other solubilization approaches very high drug concentrations of poorly soluble compounds can be dissolved.
- Co-solvents can enhance the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone.
- Weak electrolytes and non-polar molecules have poor water solubility and it can be improved by altering the polarity of the solvents.
- It is a simple and rapid method to formulate and produce.[18]

PARTICLE SIZE REDUCTION

This is one of the most potent approaches to improve the bioavailability of lipophilic drugs by an increase in surface area and saturation solubility. Micronization is another conventional

technique for particle size reduction. Micronization increases the dissolution rate of drugs through increases surface area, it does not increase equilibrium solubility decreasing the particle size of these drugs, which causes an increase in surface area, improves their rate of dissolution. Micronization of drugs is done by milling techniques using a jet mill, rotor-stator colloid mills and so forth Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug.[19]

SOLID DISPERSION

Solid dispersion represents a useful pharmaceutical technique for increasing the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The most commonly used carriers are PVP, Polyethylene glycols. Surfactants like Tween-80, Sodium lauryl sulfate, etc.[20]

This solid dispersion technique involves 3 methods:

- Hot Melt Method (Fusion Method)
- Solvent evaporation Method
- Hot Melt Extrusion Method

Hot Melt Method

The main advantages of this direct melting method are its simplicity and economy. In this method, the physical mixture of a drug and a water-soluble carrier is heated directly until the two (drug + carrier). The melted mixture is then cooled and solidified rapidly in an ice bath with vigorous stirring. The final Solid mass is then crushed, Pulverized, and sieved, which can be compressed into tablets with the help of tableting agents. The melting point of a binary system is dependent upon its composition, that is, the selection of the carrier and the weight fraction of the drug in the system.

An important requisite for the fermentation of solid dispersion by the hot-melt method is the miscibility of the drug and the carrier in the molten form. Another important requisite is the thermostability of both the drug and carrier.[21]

Solvent Evaporation Method

Dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid dispersion of meloxicam, nimesulide using solvent evaporation technique.[22]

The main advantage of the solvent evaporation method is that thermal decomposition of drugs or carriers can be prevented because of the low temperature required for the evaporation of the organic solvent. The disadvantages include with this method are the higher cost preparation, difficulty in completely removing the organic solvent.[23]

Hot Melt Extrusion Method

Hot-melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, the miscibility of the drug and the matrix could be a problem. High shear forces resulting in high local temperature in the extruder are a problem for heat-sensitive materials. This technique offers the possibility of continuous production, which makes it suitable for large-scale production. The product is easier to handle because at the outlet of the extruder the shape can be adapted to the next processing step without grinding.[24]

NANOSUSPENSION

Nanosuspension technology has been developed as a candidate for the efficient delivery of hydrophobic drugs. A pharmaceuticals nanosuspension is a biphasic system consisting of nano-sized drug particles stabilized by surfactants for either oral or topical use.[25]

Various methods utilized for the preparation of nanosuspensions include precipitation technique, media milling, high-pressure homogenization in water, high-pressure homogenization in nano aqueous media, and a combination of precipitation and high-pressure homogenization.[26]

Precipitation technique

In the precipitation technique, the drug is dissolved in a solvent, which is then added to an anti-solvent to precipitate the crystals. The basic advantage of the precipitation technique is the use of simple and low-cost equipment, but the challenge is the addition of the growing

drug crystals to avoid the formation of microparticles. The limitation of this technique is that the drug needs to be miscible with anti-solvent.[27]

Media Milling

The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug, and stabilizer is rotated at a very high shear rate. Medium is composed of glass, Zirconium oxide, or highly cross-linked polystyrene resin. High energy shear forces are generated as a result of the impaction of the milling media with the drug resulting in the breaking of the microparticulate drug to nanosized particles.[28]

High-Pressure Homogenization

In this method, the suspension of a drug and surfactant is forced under pressure through a nanosized aperture valve of a high-pressure homogenizer. The principle of this method is based on cavitation in the aqueous phase. The cavitation's forces within the particles are sufficiently high to convert the drug microparticles into nanoparticles. The dissolution rate and bioavailability of poorly soluble drugs such as spironolactone etc. have been improved by reducing their particle size by high-pressure homogenization. [29]

Combined Precipitation and Homogenization

The precipitated drug nanoparticles tend to continue crystal growth to the size of microcrystals. They need to be processed with high-energy force. They are in completely amorphous, partially amorphous crystalline forms which create problems in long-term stability are subsequently homogenized which preserves the particle size obtained after the precipitation step. [30]

CRYOGENIC TECHNIQUES

This has been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with a high degree of porosity at very low-temperature conditions. [31]

Spray Freezing onto Cryogenic Fluids

In this technique, the drug and the carrier were dissolved in water and atomized above the surface of a boiling agitated fluorocarbon refrigerant. A Sonication probe can be placed in the stirred refrigerant to enhance the dispersion of the aqueous solution.

Spray Freezing into Cryogenic Liquids (SFL)

The SFL particle engineering technology has been used to produce amorphous nanostructured aggregates of drug powder with high surface area and good wettability. It incorporates direct liquid-liquid impingement between the automatization into microdroplets and consequently significantly faster freezing rates. The frozen particles are then lyophilized to obtain a dry and free-flowing micronized powder. [32]

Ultra-rapid Freezing

This technology has the flexibility to produce particles of varying particle morphologies, based on control of the solvent system and process conditions. This process involves freezing a dissolved drug in an aqueous or anhydrous polymer water solution onto the surface of a cryogenic substrate with thermal conductivity, collecting the frozen particles, and removing the solvent, resulting in highly porous, agglomerated particles. The polymer acts as a stabilizer acting as a crystal growth inhibitor. This technique is widely applicable to enhance *in-vivo* absorption for the BCS Class II compounds.[33]

INCLUSION COMPLEX

Formation Based Techniques

When compared to all the solubility enhancement techniques, the Inclusion complex formation technique has been employed more precisely to improve the aqueous solubility, dissolution rate, and bioavailability of poorly water-soluble drugs.

Inclusion complexes are formed by the insertion of the non-polar molecule or the non-polar regions of one molecule into the cavity of another molecule are cyclodextrins. The enzymatic degradation of starch by *cyclodextrin glycosyltransferase* (CGT) produces cyclic oligomers, cyclodextrins. These are non-reducing, crystalline, water-soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a donut-shaped ring having a hydrophobic cavity. Three naturally occurring cyclodextrins are α-cyclodextrins, β-cyclodextrins, γ-cyclodextrins. [34]

Kneading Method

This method is based on impregnating the cyclodextrins with a little amount of water or hydroalcoholic solutions to convert into a paste. The drug is then added to the above paste

and kneaded for a specified time. The kneaded mixture is then dried and passed through a sieve if required. On a laboratory scale, Kneading can be done by utilizing the extrudes and other machines. This is the most common and simple method used to prepare the inclusion complexes at a very low cost of production.[35]

Lyophilisation/Freeze-Drying Technique

To get a porous amorphous powder with a high degree of interaction between drug and cyclodextrins, the lyophilization/Freeze drying technique is considered suitable. In this technique, the solvent system from the solution is eliminated through a primary freezing and subsequent drying of the solution containing both drug and cyclodextrins at reduced pressure. Thermolabile substances can be successfully made into complex forms by this method.

The limitations of this technique are the use of specialized equipment, time-consuming processes, and yield poor flowing powdered product. This technique is the use of specialized equipment, time-consuming process and yield poor flowing powdered product. This technique is considered as an alternative to solvent evaporation and involves molecular mixing of drug and carrier in a common solvent. [36]

Microwave Irradiation Method

This technique involves the microwave irradiation reaction between the drug and complexing agent using a microwave oven. The drug and cyclodextrin in a definite molar ratio are dissolved in a mixture of water and organic solvent in a specified proportion into a round bottom flask. The mixture is reacted for a short time of about one to two minutes at 60°C in the microwave oven. After the reaction completes, an adequate amount of solvent mixture is added to the above reaction mixture to remove the residual uncomplexed free drug and cyclodextrins. The precipitate obtained is separated using Whatman filter paper, and dried in a vacuum oven at 40°C.

MICELLAR SOLUBILIZATION

The use of surfactants to improve the dissolution performance of poorly soluble drug products is probably the basic, primary, and oldest method. Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in an aqueous medium. When the concentration of surfactants exceeds their critical micelle concentration (0.05-0.1%), micelle formation occurs which entrap the drugs within the micelles. This known as micellization

surfactants also improves the wetting of solid and increases the rate of disintegration of solid into finer particles.[37]

Examples of poorly soluble compounds that use Micellar solubilization are anti-diabetic drugs, gliclazide, glimepiride, repaglinide.

HYDROTROPY METHOD

Hydrotropy is a solubilization process, whereby the addition of a large amount of the second solute, the hydrotropic agent increases the aqueous solubility of the first solute. Hydrotropic agents are ionic organic salts, consist of alkali metal salts of various organic acids. Additives or salts that increase solubility in a given solvent are said to "salt in" the solute and those salts that increase solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non-electrolytes called "hydrotropic salts "a phenomenon known as hydrotropism. [38]

The mechanism involved in Hydrotropy is related to complexation which involves interaction between lipophilic drugs and the hydrotropic agents such as urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubility of many poorly water-soluble drugs.[39]

Advantages of Hydrotrophy method

- In the Hydrotropy method solvent character is independent of pH has high selectivity and does not require emulsification.
- In this method simply mix the drug with the hydrotropes in water.
- It does not require chemical modification of hydrophobic drugs, use of organic solvents.

CONCLUSION:

Increasing the solubility of poorly soluble drugs plays a major role in showing the therapeutic effect of the drug. Many drugs have poor solubilities like the drugs which belong to the BCS Class II and BCS Class IV, but those drugs will show maximum therapeutic effect upon solubilization. To increase the solubility of such drugs some techniques were used. If those techniques were used then the solubility of the drug is increased the absorption through oral delivery also increases which means there will be an increase in the bioavailability of the drug in systemic circulation which gives the therapeutic effect.

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