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REVIEW ARTICLE

Recent Advancement of Solubility Enhancement

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ABSTRACT

In this review article, we conclude that the solubility of any compound is very important and plays an important role in the formulation and drug development. By increase, solubility also increases compliance with patients and also increases the less soluble drug's bioavailability. The selection of any method for improving the solubility is dependent upon nature, characteristics of the drug such as chemical nature, physical nature, and pharmacokinetic behavior.

Keywords: Solubility, Bioavailability, Pharmacokinetic

INTRODUCTION

Solubility is an important phenomenon and most of the time discussed but still or not completely resolved issue. Saturation and dissolution these are the fundamental ideas in the physical and chemical sciences, as well as their applications to biopharmaceutical and pharmacokinetic aspects of drug treatment. To increase a drug's solubilization in water and increase its bioavailability, a variety of approaches can be modified. A common problem in screening trials for novel medications is the solubilization of poorly soluble compounds.[1,2]

Since the drug's solubility and permeability play a key role in how well it is absorbed in the body, enhancing procedures may change or modify these properties. The maximum solute concentration that may be dissolved in a specific quantity of solvent is referred to as "solubility." As well as a qualitative definition, a quantitative one is possible. When the solute and solvent are in balance, a solution is said to be saturated. Soluble material is expressed using a variety of concentration expressions, including parts, percentages, molarity, molality, volume fractions, and mole fractions.[3,4]

Importance of solubility[5]

The fundamental issue with the design of oral dosage forms is, however, their limited bioavailability.

To attain the correct drug concentration in the systemic circulation and to produce the necessary pharmacological response, solubility is one of the key factors. To achieve therapeutic plasma concentrations following oral administration, poorly water-soluble medicines frequently need to be administered in high dosages. The main issue that arises while formulating novel chemical entities, as well as developing generics is low water solubility. The majority of medications has low water solubility and is either mildly basic or mildly acidic.

These poorly water-soluble medications' sluggish drug absorption causes insufficient and inconsistent bioavailability as well as harmful effects on the gastrointestinal mucosa. The most crucial rate-limiting factor for medications taken orally is solubility,

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which allows for the achievement of the required concentration of the drug in the systemic circulation for pharmacological response. A significant hurdle for formulation scientists is the solubility issue.

Poorly water-soluble medicines frequently result in limited bioavailability due to their poor solubility and slow rate of dissolution in aqueous gastrointestinal fluids according to the BCS, class II (low solubility and high permeability) drugs can have their bioavailability increased by increasing the drug's solubility and rate of dissolution in gastrointestinal fluids.

METHODS

Solubility enhancement techniques

Traditional solubility enhancement techniques

The solubility enhancement techniques are listed below:

1. Surfactant
2. PH adjustment
3. Co-solvency
4. Co-crystallization
5. Solubilizing agents
6. Formation of salt
7. Polymeric alteration
8. Size reduction of particle
9. Co-grinding and co-micronization
10. Microemulsion
11. Solvent evaporation
12. Sonocrystalization
13. Inclusion complexation.[6]

Advance techniques for solubility enhancement

The advanced techniques are given below:

1. Micronization
2. Homogenization
3. Nano suspension
4. Supercritical fluid process
5. Spray drying
6. Hydrotrophy[7]

Solubility[8]

Solubility is a phenomenon which is related to particle size and surface area thus it becomes important to reduce the particle size of the drug thereby increasing its surface area and enhancing its solubility [Figure 1]. There are conventional techniques to reduce the particle size, a few of which include comminution and spray drying. These techniques rely upon mechanical stress to disaggregate the active compound. However, due to the mechanical stress of communication and thermal stress of spray drying the drug substance may undergo degradation in both cases, and if thermo labile then spray drying. These techniques rely upon mechanical stress to disaggregate the active compound. However, due to the mechanical stress of communication and thermal stress of spray drying the drug substance may undergo degradation in both cases, and if thermo labile then spray drying would cause a problem. Thus, using some of these conventional and traditional approaches, solubility may not be enhanced up to the desired level.

Surfactants

Surfactant is the method which is used to reduce the void fraction from the liquid–solid, liquid–liquid, or liquid–gas. Surfactants are widely used for the purpose of improving the solubility of drugs. Surfactant is the best solubility-enhancing agents and for the dissolution purpose. It promotes to enhance in wetting and penetration in dissolution for solid drugs as a fluid. Examples are soap (fatty acid), propylene glycol, and sodium lauryl sulfate. The advantage is to improve the drug stability.[9,10]

PH-adjustment: PH is required for the solubility of a drug; more ionic drugs can easily solubilize. PH is the main parameter of a drug to maintain solubility and for the purpose of pharmacological response. PH is required for the purpose of administration of drug. The drug having low solubility can precipitate in the blood it cannot be soluble in the blood because blood has acidic in nature which affects the blood. A suitable PH should be required for the absorption of drugs. The PH of the stomach is 1–2 and the duodenum is 5–6. The degree of solubility is responsible for passing to the body.[11,12] This method is regularly used for examination as pre-clinically for pH adjustment. It is a new method to

measure efficiency of the low-soluble drugs. The advantage of this method is simple to formulate the formulation and uses of small quantity for the evaluation.[13,14]

Co-solvency[15,16]

Co-solvency is the mixture of one or more miscible liquids which is required in improving of the drug's solubility. The addition of co-solvent solution can increased the solubility and miscibility of the solution and shows a better dissolution [Table 1]. This is the easy method which can be done by the simple process by combining the solvent or having the mixture of solvents which increases the low solubility drug. The examples of co-solvent are ethanol, propylene glycol, polyethylene glycol (PEG) 300, etc. Co-solvent increased the low solubility drug more than a thousand times in comparisons between the simple drugs. This is extremely used in the scheme of different types of formulations. Its main purpose of use in the parenteral dosage is for the irritation or any special side effects of most surfactants. The lower effect of different co-solvents may have comparatively better skill of co-solvents to solubilize non-polar drugs. The use of co-solvent in low solubility drugs. The advantage is simple and rapid to formulate for formulation. The example for co-solvent is dimethylacetamide and dimethyl sulfoxide.

Co-crystallization[17,18]

Co-crystallization is a method which is most frequently used to enhance the solubility. Thus, the co-crystals typically raise the solubility in the drugs, which is not possible in the case of a different molecule. For example, telmisartan is the II class drug which has low solubility. The efficiency of drug therapy which is highly depends on equal to the drug in the blood, thus it is

Table 1: Poorly soluble drugs, co-solvent derivatives, and degree of solubility enhancement

Drug	Co-solvents	Solubility enhancement
Methylpropyl trisulfide	Ethanol and cremophur	2900 fold
Ethyl-Paraben	Nicotinamide	2 fold
6-mercaptopurine	Sodium benzoate and sodium hippurate	6 fold
Phosphoramidates	Tyrosine derivative	30 fold
Enrofloxacin	Ethanol, glycerol, PEG 400, propylene glycol	1.1–3.3 fold
Ferulic acid	Isopropanol	Approx. 53

PEG: Polyethylene glycol

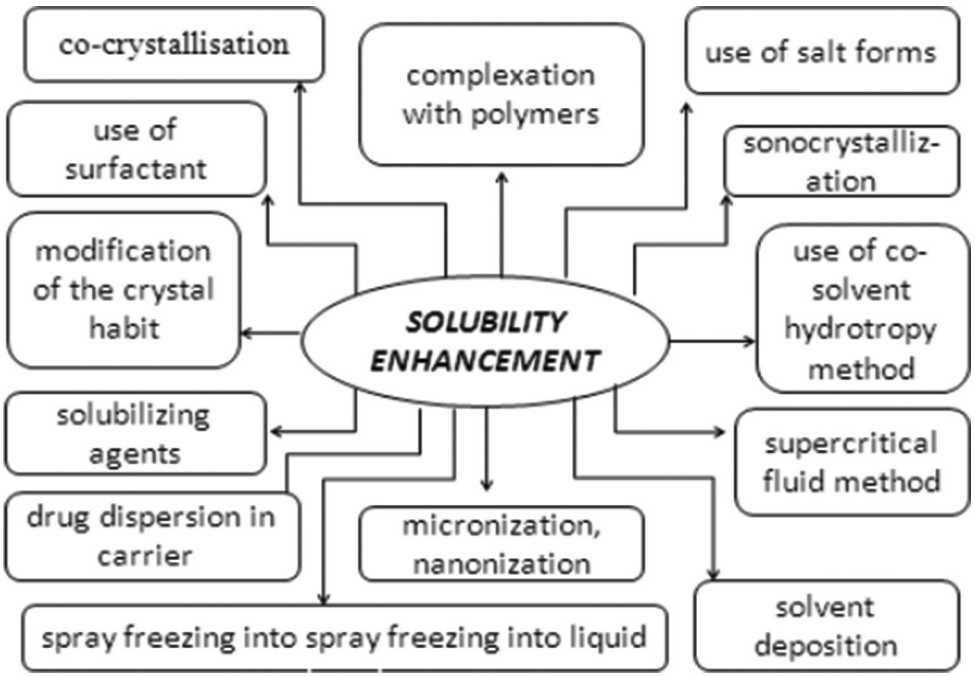

Figure 1: Various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolution

directly contingent on the nature of drug solubility. Solubility and dissolution are the most important factors in the pharmacological effect of the drug to show the pharmacological response. A drug with having good that shows better solubility properties will show good absorption, which in turn will lead to better bioavailability. However, nearly 40% of the drug shows low solubility in water. In line for low solubility, the drug is absorbed slowly through the body, and levels of the drug in the blood are lower than the essential levels. In the pharmaceutical industry, the deficiency of the properties of biopharmaceutical drugs such as unsuccessful medication constitutes 1% of the foremost cases in the market. These issues are through results of the solubility property of the drug. About 70% of applicant drugs have problems with solubility, therefore, it is a big dare in the field of pharmaceuticals to develop drug processes and drug dosage forms to show the good profile of solubility and dissolution rate of the drug, especially for oral preparations.

Solubilizing agent

This is the method in which solvents are used for better solubility and dissolving of drugs to the body and for the better therapeutic effects. The solubilizing agents like super-disintegrates such as cross-carmellose sodium and sodium starch glycolate which is used as solubilizing compounds in different kinds of preparation which develops the solubility and dissolve of drugs. Improved gum Arabic or gum karaya, an established material was estimated as carrier for dissolution and improved the low soluble of drugs like nimtop. The water solubility of drug antimalarial agent tablet of halofantrine hydrochloride was amplified by the adding of caffeine and niacinamide.[19]

Microemulsion

Microemulsion is the process which can dissolve the low soluble of drug. It can work to raise the solubility of many drugs which are closely insoluble in the aqueous form, along with a mixture of proteins administered to the body. Upon the interaction with water, the preparations easily dissolve to have the clear emulsion of very minor and uniform oil droplets which contain the solubilized soluble drug. This method is isotropic, thermodynamically steady pure systems of water, oil, and surfactant, often in the combination with a co-surfactant with a droplet size it shows the range of (20–200) nm. The major drawback of microemulsions is they have greater concentration of co-surfactant/surfactant, which makes them unsuitable for intravenous admin. The advantage of microemulsions it can be easily manufactured and have optimal bioavailability.

Advance technology

Micronization

Micronization is the process for the decrease of size. This is the process when it is used to progress dissolution rates of drugs into the biological method, to better bioavailability.

Micronization having the higher particle size reduced the granular particle converted into the <5 microns. It shows the narrow and uniform particle size essential for the development for the uniform dosage form. The different in which is utilized for the solubility enhanced in the micronization are micro precipitation, control crystallization, and micronizers. The advantage of micronization is having a tendency to give the uniform particle size with rise in the surface area and particle distribution.

Nanoionization

Nanosuspension is a method used for the low-soluble drugs for the purpose of parenteral drugs. The advantages of this process are the particle sizes are <1 micron and for the parenteral low-soluble drug. Nowadays the various nanonization methods have 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 the pharmaceutical industry for preparation of parenteral used drug this can easily bind and shows the pharmacological action of the drug. The various methods which are used for this nano

jet technology and nano edge process which give the better enhancement solubility of the product. Advantage of nanonization is to avoid any other organic solvent and give the uniform particle size which requires <1 micron.

Supercritical fluid method

This technology is used for the size reduction of the particles. Widely used for the nano-drug in which water is insoluble. Application is it can be used for the nonvolatile solution at the critical point of CO_2. The small working circumstances create the supercritical fluid approaches is an attractive for pharmaceutical research. Mostly it is varying in the temperature and the pressure which should be maintained around the critical point. This method is used in the pharmaceutical industry for the purpose to decrease in particle and in the food industry. The solvents used for supercritical fluid process are ethylene, ammonia, ethanol, propanol, CO_2, etc. Development of the supercritical solvents like recrystallization, gas antisolvents, bioactive material. Furthermore, it is widely used for the purpose of aerosols. Advantage of supercritical process is having the low operating condition and also they can be recrystallized and can reduce the particle size <2–5000 microns and can also have sub-micron change level of size of particles.[19]

FACTOR AFFECTING SOLUBILITY ENHANCEMENT

Particle size[20]

The solubility of a solid depends on its size since a smaller particle has a higher surface area to volume ratio. Greater contact with the solvent is possible because to the increased surface area.

Temperature[21]

Solubility will be affected by temperature. The temperature will rise as the solubility increases if the solution process consumes energy. The solubility will decrease with rising temperature if the solution process releases energy.

Pressure[22]

For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decreases the solubility.

Nature of the solute and solvent

In 100 g of water at room temperature, 200 g of zinc chloride may dissolve, whereas only 1 g of lead (II) chloride can. Because these two chemicals are quite different, their solubilities differ greatly. Hence, is the solubility of tiny particles, S is the solubility of infinitely big particles, V is molar volume, is the surface tension of the solid, and *r* is the radius of the fine particle T absolute temperature in Kelvin, and R universal gas constant.

Molecular size[23]

Less soluble substances are those that have bigger molecules or greater molecular weights. The quantity of carbon branching in organic compounds will enhance their solubility since more branching will result in a smaller (or volume-reduced) molecule and making it simpler to dissolve the molecules in a solvent.

Polymorphs

The capacity 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 enantiotropic [Table 2]. Polymorphs can vary in melting point. Since the melting point of the solid

Table 2: List of polymer used for solubility enhancement

Name of drug	Polymers used
Atenelol	PEG 6000
Celecoxib	PEG 400, Ethanol
Theophylline	HPMC
Cyclodextrins	PEG 4000
Escitalopram oxalate	Polyvinyl alcohol and urea
Fluconazole	Oleic acid, dimethylsulfoxide
Mefenamic acid	HPMC

PEG: Polyethylene glycol

is related to solubility, polymorphs will have different solubilities. Generally the range of solubility differences between different polymorphs.[24]

FORMULATION

Formulation-1: The solubility of ibuprofen in ethanol

Ibuprofen is sparingly soluble in ethanol. Its solubility in ethanol depends on several factors such as temperature, concentration, and pH. At room temperature (25°C), the solubility of ibuprofen in ethanol is approximately 21 mg/mL. However, as the temperature of the ethanol increases, the solubility of ibuprofen also increases. For example, at 40°C, the solubility of ibuprofen in ethanol is around 33 mg/mL. It is worth noting that the solubility of ibuprofen can also be affected by the pH of the solution. At a pH of around 7, the solubility of ibuprofen is at its maximum. However, at higher or lower pH values, the solubility of ibuprofen decreases. Overall, ibuprofen can dissolve to a limited extent in ethanol, but its solubility can be increased by raising the temperature and maintaining a neutral pH.

Formulation-2: The solubility of ibuprofen in methanol

The solubility of ibuprofen in methanol varies depending on the temperature and concentration of the solution. At room temperature (25°C), the solubility of ibuprofen in methanol is approximately 21 mg/mL. However, it is important to note that ibuprofen is more soluble in organic solvents such as methanol compared to water. The solubility of ibuprofen in water at room temperature is only about 0.21 mg/mL. It is also worth mentioning that the solubility of ibuprofen in methanol may be affected by other factors such as pH, the presence of other substances, and the purity of the ibuprofen sample.

Formulation-3: The solubility of ibuprofen in ethanol

Ibuprofen is a non-steroidal anti-inflammatory drug that is commonly used for pain relief, fever reduction, and inflammation reduction. Its solubility in propanol can vary depending on factors such as temperature and concentration. At room temperature (25°C), the solubility of ibuprofen in propanol is reported to be approximately 2.2 g/100 mL (g/100 mL). However, this solubility value may change at different temperatures or concentrations. For example, at higher temperatures, the solubility of ibuprofen in propanol may increase. It is also worth noting that ibuprofen is more soluble in some other solvents, such as ethanol and methanol than it is in propanol. Hence, the choice of solvent will depend on the specific needs of the application.

Table 3: List of some poorly soluble drugs, their salts forms, and degree of solubility enhancement

Drugs	Salt form	Solubility enhancement
Pyridoclax	Dihydrochloride	4 fold
Slidenafil	Glutarate	3.2 fold
Furosemide	Sodium salt	20 fold
Pheytoin	Sodium salt	60 fold
Bupivacaine	Chloride salt	200 fold
Indomethacin	Arginine and lysine	10000 and 2296 fold

Table 4: Poorly soluble drugs, hydrotropic agents, and degree of solubility enhancement

Drugs	Hydrotropic	Solubility enhancement
Nevirapine	Urea, lactose, citric acid, and mannitol	27, 11, 42, and 10 fold
Carbamazepine	Nicotinamide and urea	30 fold
Lurasidone	Nicotinamide, sodium citrate, urea, and sodium benzoate	12–61 fold
Furosemide	Urea, sodium acetate, sodium benzoate etc.	16–296 fold

RESULTS

The formulation 1 the solubility of ibuprofen in ethanol is the best solubility.

CONCLUSION

In this review article, we conclude that the solubility of any compound is very important and plays an important role in the formulation and drug development. All the above-mentioned techniques or methods which can be used alone or

in any combination with others help to improve or enhance the solubility of the compound or any poor soluble drugs [Table 3]. By increase, solubility also increases compliance with patients and also increases the less soluble drug's bioavailability. The selection of any method for improving the solubility is dependent upon the nature, and characteristics of the drug such as chemical nature, physical nature, pharmacokinetic behavior, etc [Table 4].[25]

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