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A REVIEW ON SOLUBILITY ENHANCEMENT TECHNIQUES

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ABSTRACT

Solubility plays a crucial role in the drug development of various formulations. The solubility of a drug varies or depends on various factors used in the formulations like binders, lubricants, colourants, and other excipients (potato starch, silicon dioxide, sodium starch glycolate, microcrystalline cellulose, croscarmellose, crospovidone) used. Apart from the formulation factors the medium where the drug has been exposed like dissolution medium, p^H , temperature, etc also influence the solubility. The poorly soluble drugs especially from BCS class II and class IV drugs solubility is the rate determining step. So for these drugs solubility is very low and the article represents some of the best techniques which suites enhancing the solubility of poorly water soluble drugs. The techniques used are the micronisation, nanonization, particle size reduction, using super disintegrants, potential drug carriers (beta cyclodextrin), solid dispersion, inclusion complexation and even more best suitable methods are been discussed. Among these Cyclodextrins (α, β, γ) are proved to be one of the best efficient methods of improving solubility of the drug. All these methods mostly aim to increase the surface area, and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states.

Key words: Surface area, Solubility, Excipients, Cyclodextrins, Particle size.

INTRODUCTION

The solubility is defined as the maximum amount of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Bioavailability of poorly watersoluble hydrophobic drugs is limited by their solubility and dissolution rate. The solubility can be improved by reducing the particle size which assists in increasing the surface area of the particle. As the solubility increases bioavailability of the drug may increases [1]. Solubility occurs under dynamic equilibrium, which means that solubility results from the simultaneous and opposing processes of dissolution and phase joining (e.g., precipitation of solids). Solubility equilibrium occurs when the two processes proceed at a constant rate. Under certain

conditions equilibrium solubility may be exceeded to give supersaturated solution, which is metastable [2].

Extensive use of solubility from different prospective has led to solubility being expressed in various manners. It is commonly expressed as a concentration, either by mass (g of solute per kg of solvent, g per dL (100mL) of solvent), molarity, molality, mole fraction, or other similar description of concentration [3]. The advantage of expressing solubility in this manner is its simplicity, while the disadvantage is that it can strongly depend on the presence of other species in the solvent (e.g., the common- ion effect). Apart from these temperature and partition-coefficient plays a crucial role in the solubility of a compound/drug. In the biopharmaceutical classification system (BCS)

drugs are classifying on the basis of aqueous solubility and membrane permeability. Many poor water soluble drugs were categorizes to the BCS classes of II and IV [4]. The process of drug absorption from oral route for such types of drugs is occurs via dissolution rate limiting step. So, that it is important to increase dissolution of these drugs to give maximum therapeutic effect of these drugs. Before studying many techniques to increase dissolution it is important to understand the dissolution process.

Table No: 1 USP and BP solubility criteria

S.No.	Description term	Part of solvent required per part of solute
1	Very Soluble	Less than 1
2	Freely Soluble	From 1 to 10
3	Soluble	From 10 to 30
4	Sparingly Soluble	From 30 to 100
5	Slightly Soluble	From 100 to 1000
6	Very Slightly Soluble	From 1000 to 10,000
7	Practically Insoluble	10,000 and over

In the dissolution process, solid substance (Active Pharmaceutical Ingredients) comes into the solution. The solubility of drug is directly proportional to its dissolution rate as per Noyes- Whitney equation and hence solubility is an important parameter for drug to determine its dissolution rate and absorption.

$$\frac{dw}{dt} = \frac{DA(C_s - C)}{L}$$

Where:

dw/dt is the rate of dissolution.

A is the surface area of the solid.

C is the concentration of the solid in the bulk dissolution medium.

C_s is the concentration of the solid in the diffusion layer surrounding the solid.

D is the diffusion coefficient.

L is the diffusion layer thickness.

Techniques for solubility enhancement

Solubility enhancement techniques can be categorized into physical modification, chemical modification of the drug substance, and other techniques.

Physical Modifications

Particle size reduction like micronization and nanosuspension, modification of the crystal habit like polymorphs, amorphous form and co-crystallization,

drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques.

Chemical Modifications: Change of p^H , use of buffer, derivatization, complexation and salt formation.

Solid Dispersion

The solid dispersion concept was proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a Sulphonamide drug and a water-soluble carrier in the early 1960s. The term solid dispersion can be defined as the distribution of one or more active ingredients (hydrophobic) into an inactive carrier or matrix (hydrophilic) at the solid state. Solid dispersion particularly mention to a group of solid products that consists of at least two different components, generally hydrophobic drug and hydrophilic matrix. The matrix can be either amorphous or crystalline. The drug can also be isolated molecularly, in amorphous particles (clusters) or in crystalline particles. Commonly used solvents for solid dispersions includes methanol, DMSO, water, ethanol, chloroform, acetic acid. Different types of carriers are used which are classified as follows.

First Generation Carriers

Example: Crystalline carriers: Organic acids, Urea, Sugars.

Second Generation carriers

Fully synthetic polymers include polyethylene glycols (PEG), povidone, and polymethacrylates. Natural product based polymers are mainly used by cellulose. Cellulose derivatives such as hydroxyl propylmethylcellulose (HPMC), ethyl cellulose or such derivative such as cyclodextrins.

Third Generation Carriers

Example: Surface active self-emulsifying carriers: Tween 80, poloxamer 408 and Gelucire.

Hot-Melt Method (Fusion/Direct Melting Method)

The best advantages of this direct melting method is its economy and very easy to operate. The fusion method was proposed by Sekiguchi and Obi to prepare fast release solid dispersion dosage forms. In this fusion method, the drug and a water-soluble carrier are heated directly until both of them were melted. The melted mixture is then cooled and further solidified instantaneously by ice bath with continuous stirring. The resulted final solid mass is then crushed, pulverized, and sieved, which can be compressed into tablets with the help of punching machine. An important prerequisite for the formation of solid dispersion by the hot-melt method is the miscibility and the thermo stability of the drug and the carrier [5].

Hot-Melt Extrusion

Hot-melt extrusion is similar to that of fusion method except that intense mixing of the components is induced by the extruder. Similar to fusion process, miscibility of the drug and the matrix could be a problem. High-shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials. However, compared to the traditional fusion method, this technique offers the possibility of continuous production, which makes it suitable for large-scale production. Furthermore, 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 [6].

Solvent Evaporation Method

In the solvent evaporation method first the drug is completely dissolved in the solvent and then the solvent is evaporated under vacuum to produce solid crystals or precipitate. The most commonly used solvents for this method include methanol, ethanol, and chloroform, sometimes a mixture of any mixable solvents also may be used (eg; ethanol and dichloromethane). Co-solvents may be used to completely solubilize the drug and the carrier. The major advantage for preferring solvent evaporation technique is that the thermal decomposition of the drug and carrier can be avoided as the temperature required to completely evaporate the solvent is very low, thus this method is very useful for heat sensitive drugs. The disadvantages include cost of solvent may be high, ecological and it is very difficult to find removable solvents, difficulty in reproducing crystal form [7].

Super Critical Fluid Method (SCF)

Super critical fluid is the existence of a fluid as single fluid above its critical temperature and pressure. Any fluid above critical temperature and pressure exhibit the properties of both the liquid and gas. The major advantage is that this method is eco-friendly, it's safe to perform and economically best. At near-critical temperatures, SCFs are highly compressible, allowing moderate changes in the pressure to greatly alter their density and mass transport characteristics of a fluid that are largely determined by its solvent power [8-9]. Once the drug particles are solubilized within SCF, they may be re-crystallized at greatly reduced particle sizes. Carbon dioxide is the most commonly used SCF because it is chemically inert, nontoxic and non-flammable. Other supercritical solvents include nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia and water.

Micronization

Micronization is one of the best conventional techniques for the particle size reduction. Micronization enhances

the dissolution rate of drug by increased surface area, it does not enhance equilibrium solubility. Decreasing the particle size of drugs, results in enhanced surface area and improves their rate of dissolution. Micronization of drugs is done by milling techniques by colloid mills, jet mill and so forth. Micronization is not appropriate for drugs having a high dose number because it does not change the saturation solubility of the drug [10-13].

Lipid-Based Formulations

Lipid based drug delivery systems like emulsions, micro emulsions, liposomes, microspheres, solid-lipid nanoparticles, etc have the ability to avoid resistant to chemical and physical barriers to oral absorption and which are most successful in enhancing the bioavailability of drug molecules that are poorly water-soluble but highly permeable drug molecules (BCS class II). Some proposed mechanisms of action, the lipid-based systems to enhance oral bioavailability of compounds include [14-15];

- ❖ Particle size reduction to molecular size yielding a solid-state solution within the carrier.
- ❖ Enhanced wetting of hydrophobic solids resulting in enhanced dissolution.
- ❖ Increased rate of dissolution into aqueous environment from oil droplets of high surface area.
- ❖ Promotion of absorption via intrinsic lipid pathways.
- ❖ Enhanced thermodynamic activity via super saturation of the aqueous environment of the gastrointestinal tract.

Hydrotropy

The term hydrotropy refers to enhance the solubility of insoluble drugs in water by the addition of additives. The mechanism through which it increases solubility is similarly associated with the complexation involving a weak interaction between the hydrotropic agents and the solute. Some hydrotropic agents used are sodium benzoate, urea, sodium alginate, sodium acetate etc. In hydrotropy techniques many different classes of drugs like antiviral, antipyretic, antitumor, anti-inflammatory and analgesic drugs used for solubility enhancement. Hydrotropy technique is applied for solubility enhancement of riboflavin, nimesulide, nifedipine and xanthine derivatives such as caffeine and theophylline [16-18].

Particle Size Reduction

The solubility of drug is often essentially related to drug particle size; as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area permits greater interaction with the solvent which causes an increase in solubility [19].

INCLUSION COMPLEXATION

This is the most widely used method to enhance solubility and stability of hydrophobic drugs by using cyclodextrins. Solid inclusion complexes can be prepared by using following methods;

Fig No: 1 a and b showed two different possible complexation

Kneading Technique

In this technique, cyclodextrin (CD) is impregnated with water and converted to paste. This method is based on the impregnating of the CDs with little amount of water or hydro alcoholic solutions converted 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 sieve [20-22]. This is the most common and simple method used to prepare the inclusion complexes and it is very low cost of production [23].

Co-precipitation

Required amount of drug is added to the solution of β -CD. The system is kept under magnetic agitation with controlled process parameters and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature in order to avoid the loss of the water structure from the inclusion complex [24, 25].

Neutralization

Drug is added to the alkaline solution like ammonium hydroxide, sodium hydroxide. A solution of β -Cyclodextrin is then added to dissolve the joined drug. The clear solution obtained within few seconds after agitation is neutralized by using HCl solution until reaching the equivalence point. At this moment, the appearance of a white precipitate could be appreciated, corresponding to the formation of the inclusion compound. The precipitate is then filtered and dried.

Co-grinding

Drug and cyclodextrin are mixed and the physical mixture is introduced in a suitable mill like oscillatory mill and grinded for suitable time. This technique is superior to other approaches from economic as well as environmental stand point; unlike similar methods it does not require any toxic organic solvents. This method differs from the physical mixture method where simple blending is sufficient and in co-grinding it requires to achieve extensive combined attrition and impaction on powder blend [26-30].

Spray-Drying Method

Drug is dissolved in suitable solvent and the required stoichiometric amount of carrier material like β -cyclodextrin is dissolved in water. Solutions are then mixed by sonication or other suitable methods to produce a clear solution, which is then spray-dried using spray dryer [31-33].

Sono-crystallization

Sono-crystallization is technique where particle size reduced by using pharmaceutical engineering, to increase solubility and dissolution of hydrophobic drugs and to study its effect on crystal properties of drug. Recrystallization of poorly soluble materials using anti-solvents and liquid solvents has also been employed successfully to decrease particle size by using ultra sound. Sono-crystallization employs ultra sound power characterized by a frequency range of 20-100 kHz for inducing crystallization. Most of the applications use ultrasound in the range of 20 kHz-5 MHz Melt sono-crystallization (MSC) is promising technique of sono-crystallization to find porous, amorphous material with high stability [33-38].

Microwave IR Radiation Method

Drug and cyclodextrin mixture is reacted in microwave oven to form inclusion. It is a novel method for industrial scale preparation due to its major advantage of shorter reaction time and higher yield of product [39- 40].

APPLICATIONS

- ✓ To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
- ✓ To reduce side effect of certain drugs.
- ✓ Masking of unpleasant taste and smell of drugs.
- ✓ To stabilize unstable drugs against hydrolysis, oxidation, re crimination, isomerization, photo oxidation and other decomposition procedures.
- ✓ Improvement of drug release from ointment creams and gels.
- ✓ To avoid undesirable incompatibilities.

- ✓ To obtain a homogeneous distribution of a small amount of drug in solid state.
- ✓ To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
- ✓ To formulate a fast release primary dose in a sustained released dosage form.
- ✓ To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.

CONCLUSION

Solubility and dissolution are the two major rate limiting steps for oral absorption of poorly soluble drugs(class II and IV). Solubility plays a key role for the bioavailability of the poorly soluble drugs in the GIT. Various techniques mentioned above can be effectively useful for enhancing solubility by the best compatible technique selection. Proper selection of the method for solubility is the important factor for achieving the good solubility. Selection of choice depends on the physico-chemical properties of the drug and the excipients to be used. Thereby increasing the solubility and stability of the drug.

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