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REVIEW ARTICLE **OPEN ACCESS**

Solubility Enhancement of Poorly Soluble Drug of BCS Class II And IV By Using Different Techniques: A Review

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ABSTRACT
Oral route is the most commonly used route for administration of drugs to produce systemic therapeutic effects, but major disadvantage for this formulation is poorly solubility of drug. The bioavailability problem can arise due to drugs having insufficient solubility. Dissolution rate of molecule and pharmacokinetic parameters like absorption, distribution throughout body tissue and fluids, and excretion of a molecule depend upon its solubility properties. Depending on solubility, drugs can be classified into four different classes of the BCS classification. In BCS Class II and BCS Class IV drugs, there is major issue for the solubility and permeability of drugs. To overcome these problems there are many techniques to improve the solubility and bioavailability of poorly soluble drugs. Commonly used methods for solubility enhancement are Solid dispersion, Liquisolid, Complexation, Hydrotropy, Self emulsifying method. In the present review focused is made on enhancement of the solubility of drugs having poor aqueous solubility by using different techniques.
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INTRODUCTION

The solubility of any drug molecule principally depends on solvent system used, temperature and pressure. The saturation concentration is measure of the level of solubility of a molecule in a required solvent, where no increase in concentration of solution observed after further addition of more solute [1]. Oral administration is considered as the most safe and frequently used route of drug delivery because of easy to administer, high patient compliance, cost is less, least sterility limitation, and adaptability in the design of formulation. As a result, numerous generic drug companies are likely more to manufacture bioequivalent oral drug products [2]. While the common issue associated with the design of particular oral dosage forms due to their poor bioavailability. The oral bioavailability of drug molecule depends on factors like aqueous solubility of drug molecule, permeability through different biological membrane, rate of drug dissolution, first-pass as well as presystemic metabolism, and susceptibility of particular drug molecule to efflux mechanisms of body. Solubility plays an important role for dosage forms such as parenteral formulations.[3]

The enhancement of solubility and also the oral bio-availability of drug molecule is most challenging feature for drug development process particularly for oral-drug delivery system. There are many methods available to enhance the aqueous solubility drugs. The techniques are selected on the basis of properties of drug, nature of excipients to be required, and nature of required dosage form [4]. As bioavailability of drug molecule is directly responsible for its therapeutic efficacy, enhancement of bioavailability becomes crucial part in formulation development. Solubility as well as permeability enhancement ultimately leads to increased bioavailability of particular drug. Most of the recently invented drug molecules even fail to reach at their site of action because of non-optimal bioavailability.[5,6] Hydrophobic/poorly water soluble drug molecules possess great difficulty for their oral delivery, as aqueous solubility is key parameter for such type of delivery. Along with oral delivery, dissolution in gastric media and its overall pharmacokinetics relies on the solubility in aqueous medium. Permeability of drug molecule decides the absorption of drug molecules through different body cells.[7, 8, 9]

FACTORS AFFECTING SOLUBILITY10

For the solubility of any drug there is need of physical nature of the solid, the nature as well as composition of solvent medium used and also temperature and pressure applied for system.

Particle size:

Particle size of a solid affects its solubility. Smaller the particle size then increase in area to volume ratio. A drug molecule with larger surface area permits a greater bonding with the solvent.

Temperature:

Temperature influences the solubility. Absorption of energy by the solution leads to increase in solubility because of rise in temperature. If there is any transfer of energy by the solution process, decrease in solubility and increase in temperature occurs. Commonly a rise in solution temperature leads to enhancement of solubility of solute (solid state). Few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

Pressure:

For gaseous molecules, an increase in applied pressure increases solubility and vice versa. Change in pressure does not show any practically effect on solubility in case of solid and liquid solutes.

Molecular size:

If there is higher the molecular weights then there will be the lesser solubility of substance. Larger molecules possess difficulty in binding with solvent molecules so to solvate the substance. In case of organic compounds, solubility increases with the amount of carbon separating. If more branching of carbon atom it will reduces the size of molecule ultimately making it easier to dissolves the molecules with solvent.

Polarity:

Generally for dissolution of polar solute needs polar solvent and for dissolution of non polar solute require non polar solvent. The polar solute molecules possess a positive as well as a negative site to the molecule. Polar nature of solvent molecule gives rise to attraction of positive ends of solvent with negative ends of solute molecules. This type of interaction commonly recognized as a dipole-dipole interaction.

Polymorphs:

The shape of a crystal of a given drug substance may alter but the angles between the faces of crystal are always constant. A typical crystal is made from atoms, molecules or ions in a general geometric arrangement/lattice continuously repeated in three dimensional aspects. This repeating pattern of geometrical arrangement is known as unit cell. The capacity of a substance to crystallize out in more than single crystalline form is known as polymorphism.

MECHANISM OF INCREASED DISSOLUTION RATE [11, 12]

For solid dispersion, increase in dissolution rate of drug depends on number of factors. The main reasons supposed for the improvements in dissolution are as follows:

1. Particle size reduction:

The particle size can be reduced for glass, solid solution, amorphous diffusion. This can leads to improved dissolution rate due to increased surface area solubilization.

2. Solubilization effect:

The carrier material has a solubilization effect as it solubilized the drug molecule. This was indicated in case of Acetaminophen (APAP) and Chlorpropamide in urea as well as for many other drugs.

3. Wettability and dispersibility:

The carrier material has ability to increase effect on the wettability and dispersibility of a drug in the dissolution media. As it retard any agglomeration /aggregation of the drug particles, which leads to slow down the dissolution process.

4. Metastable Forms:

Faster dissolution rates is enhance due to formation of metastable type of dispersions as an effect of reduced lattice energy. It was shown that the activation energies required for dissolution of antidiabetic drug furosemide was 17 K Cal/mol, while that for furosemide: PVP (1:2) co precipitate was observed only 7.3 K Cal/ mol.

METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

Need of Solubility and Permeability Enhancement

Poor Solubility and poor permeability limits overall absorption of drug from the gastrointestinal tract. Poorly soluble drug possess problem of dissolution in GI fluid, while poorly permeable drug encounters with the difficulty of transport through GI membrane.10 For a successful oral delivery of drug, active agent must dissolve in gastrointestinal fluid before its permeation through the GI tract membranes to enter in systemic circulation. The areas of research that emphasize on an oral bioavailability improvement of drug include solubility enhancement and ultimate increase in rate of dissolution of poorly water-soluble drugs as well as enhancement of permeability of drugs. [11]

TECHNIQUES FOR SOLUBILITY AND PERMEABILITY ENHANCEMENT

Particle Size Reduction 5, 13, 16

The drug solubility is majorly related to particle size of drug. As particle size become smaller, surface area to the volume ratio increases. Larger surface area allocates grater interaction of drug molecule with the solvent leading to an increased solubility. The bioavailability of many poorly water soluble drugs is often associated to the particle size of drug. Particle size reduction involves conventional methods, micronization and nanosuspension.

Spray drying and comminution are the conventional methods used for particle size reduction.

Micronization is typically a high energy technique for reduction of the particle size which converts coarse particles to particles of size < 5 μ in diameter. Different Micronization Techniques are as follows

a) Jet milling /fluid energy mill or micronizer
b) Rotor stator colloids mills
c) Microprecipitation & microcrystallization
d) Controlled crystallization
e) Supercritical fluid technology
f) Spray freezing in to liquid

Nanosuspension is used for poorly soluble drugs, which insoluble in both water as well as oils. The distribution of particle size of solid particles is typically < 1 μ and ranging from 200nm to 600 nm in nanosuspension.

Hydrotropy [5, 17, 18]

Hydrotropy is a technique involving addition of high quantity of second solute leads to increased aqueous solubility of other solute. Hydrotropes are amphiphilic in nature and composed of hydrophilic type of functional group. Hydrotropes are usually organic salts which can enhance aqueous solubility of different organic substances while present in aqueous solutions. Concentrated aqueous solutions of hydrotropic substances like nicotinamide, urea, sodium citrate and sodium salicylate and sodium acetate are observed to improve an aqueous solubility of different drugs which have poor aqueous solubility.

Solid dispersion Techniques [5]

a) The solvent method [5, 19]

Specified amounts of an active drug substance and carrier(s) are first dissolved in least quantities of chloroform. The dissolving solvent is further removed by a rotary evaporator. Resultant solid dispersion is subsequently transferred in aluminum pan and further allowed to dry particularly at room temperature.

b) Fusion (melt) method [5, 19]

A specified amount of carrier(s) taken in in aluminum pan and is placed on a hot plate. It is then melted, with continuous stirring, at temperature about 60°C. Specified quantity of active drug is then incorporated with stirring into melted carrier(s) to ensure homogeneity. Then mixture is heated to a homogeneous melt and this clear melt is further allowed to cool down at RT.

c) Dropping method [5, 20]

Solid dispersion of mixture of melted drug-carrier is pipetted and is then dropped on a plate, on which it is converted into round particles upon solidification. The size as well as shape of the drug particles can be greatly influenced by different factors like viscosity of mixture of melt and the pipette size. Because viscosity is greatly dependent on temperature, so it's necessary to adjust the temperature in a way that as the melt is dropped on the plate, it should be solidified to a spherical shape.

Spray drying techniques

Spray dried particles involves preparation of ratios of active drug only with drug/suitable polymer by dissolving the drug in consideration or mixture of drug/polymer in solution of ethanol/water. The solution is then spray dried by means of Mini Spray Dryer. The formed microparticles can be separated by cyclone separator. Microparticles are collected and stored in desiccator at ambient temperature. Spray chilled particles can be prepared by melting the drug in consideration or mixture of drug/ polymer in diverse ratios at high temperature 90°C. The melt is then kept at same temperature i.e. 90°C and further atomized into air with especially constructed pneumatic nozzle which is kept at 20°C. Resultant particles are collected by means of cyclone separator and then stored in a desiccator. [21, 22]

Supercritical Fluid Technologies

The SAS (Supercritical Antisolvent) apparatus consists of a precipitator and works in a constant co-current mode. Antisolvent and liquid solutions are individually fed to top of precipitator chamber, also continuously discharged away from the bottom. The liquid solution and the antisolvent are pumped into the precipitator chamber using piston pump by applying high pressure, while stainless steel nozzle is used to deliver liquid solution in to a chamber. The supercritical CO2 is heated by an electric cable in a tube section prior to entering the precipitator. Sintered steel filters with sufficient porosity are located at the

bottom of the vessel to collect produced particles. The solvents are further separated and subsequently recovered from a another vessel. [5, 23]

Gas Antisolvent Recrystallisation

It is likely to get rapid crystallization by addition of antisolvent gas into a solution having dissolved solute. For this purpose the carrier solvent and the SF antisolvent should be at least partially miscible. The drug solution and the SF(Super critical fluid) are introduced at same time by means of a co-axial nozzle arrangement into the particle formation vessel leads to quick dispersion, mixing and further extraction of the drug solution and solvent with the help of Super critical fluid showing to elevated supersaturation ratios. The temperature and pressure combine with precise metering of flow rates of the drug solution. The SF with the help of nozzle provides same conditions for particle formation. This helps to control the particle size range of the product and by selecting a required liquid solvent, it is feasible to manipulate the particle morphology. [24]

Nanosuspension

a) Media milling (Nanosystems or Nanocrystals) [25]

High-shear media mills are used for preparation of nanosuspensions. The milling chamber is turned with higher shear rate under controlled temperature condition for few days (min. 2-7 days) when charged with milling media, drug, water and stabilizer. The produced high energy shear force leads to collision of the drug with milling media and leads to production of microparticulate drug with nanosized particles.

b) Homogenization in water (Dissocubes) [26]

It contains the forcing of the drug suspension by means of a valve with a narrow gap. The instrument is operated at pressure changing from 100 to 1500 bars (2800 to 21300psi) and may extended upto 2000 bars having volume capacity of 40ml.

c) Combined precipitation with homogenization (Nanoedege).1

In this method, the precipitated drug suspension is homogenized resulted into particle size reduction and inhibiting crystal growth.

d) Nanojet technology [27]

This technique is also called as opposite stream. A stream of suspension taken in chamber and is separated into two/ more parts, which is allowed to strike at high pressure with each other. So generated high shear force leads to decrease in particle size.

e) Emulsification-solvent evaporation method [28]

In this method solution of drug is emulsified in a non-solvent for that drug. Then the solvent is evaporated resulting into precipitation of drug. Crystal growth and particle collection can be governed by generating high shear forces by means of high-speed stirrer.

Preparation of nanocrystals

This process is consist of two steps

Preparation of drug solution in organic solvents: Various concentrations of drug solution are prepared in organic solvent (depend on solubility of drug in required solvent). Introducing drug solution in water: Nanocrystals are prepared by addition the micro liter (µL) quantity of drug solution to milliliter (ml) quantity of water rapidly with continuous stirring on magnetic stirrer at 1000 rpm. Then the resultant solvent is removed with the assist of overnight stirring at 500 rpm. Then solvent is centrifuged at about 5000 rpm and the product is solidified to get the desired product. [29, 30]

Nanopure XP technology

PharmaSol employs Nanopure XP technology a pretreatment process with later homogenization to form particles below 100 nm. Drug nano crystals having size about 50 nanometer and below are definitely lesser than the wavelength of visible light, therefore the nanosuspensions become translucent in nature.25

Co-Solvent Evaporation Method

The drug with polymer solution is evaporated in different proportion by using a suitable evaporator in co-solvent evaporation method. Drug in consideration is dissolved in methanol, while polymer is dissolved in distilled water and both solutions are mixed to produce clear solution. The clear solution evaporated in evaporator. 5

Spray Drying

The solvent evaporation of drug and different polymer solution in diverse proportion is carried out with the using spray dryer. Initial solutions of drug and polymer are prepared by separately dissolving drug in methanol while polymer is dissolved in distilled water. Both the solutions are mix well properly to get a clear solution. Solvent is then evaporated by means of evaporator. Spray dried mixture of drug and polymer solution is prepared in 20–30 min.[5]

Self micro emulsifying drug delivery (SMEDDS)

A series of SMEDDS formulations are prepared using Surfactant/cosurfactant combination and oil. Accurately weighed active drug and kept in glass vial and oil, surfactant and co-surfactant are added in that mixture. These components are mixed well by stirring followed by vortex mixing on a magnetic stirrer, till the drug is completely dissolved in that mixture. The mixture is kept at room temperature till next use. [5]

A chitosan-based solvent change approach

The composition of different crystal formulation is prepared. Chitosan solution is formulated by absorbing chitosan in 1% GAA (Glacial Acetic Acid) for 3 hrs. A weighed quantity of the drug is added in chitosan polymer solution by utilizing high dispersion homogenizer. This dispersed solution is then mixed up with distilled water or sodium citrate solution to form precipitation of chitosan polymer on drug crystals. Precipitate mixture is then filtered by using whatmann filter paper (1) applying vacuum filtration part and dried. The dried product is then transfer through sieve no. 60 to get a uniform particle size distribution. [5]

Preparation of dry elixir

Dry elixir is prepared by spray drying technique. Laboratory scale spray drying process is done by using spray dryer with a standard nozzle. Various formation of spraying solution is prepared. Drug is solubilizing in ethanol, and excipients like dextrin and SLS are dissolved in distilled water. Individual solution is pre-warmed to 55–60 ◦ C and then mixed. SLS is used to avoid spray dried particles attached to the inner layer of spray-drying chamber, and to form free-flowing powder. SLS is used to operate with easy process and to increase ethanol encapsulation in dry elixir. The final solution is delivered to spray dryer. The drug is accumulate in cyclone separator and placed in a conical tube.[5]

Preparation of drug composite particles

Active drug is dissolved in methanol; this solution is filter by using a nylon membrane to separate distinct impurities. Then the polymers are dissolved in deionized water, which is act as anti-solvent. The drug solution is poured quickly into the anti-solvent solution using magnetic stirring at speed of 2500 rpm. After stirring, a suspension containing drug nanoparticle is obtained. This suspension is then handled through spray drying to produce drug composite particles. Generally spray drying is done using laboratory scale spray dryer. [31]

Preparation of dihydrochloride salt form

Active drug is added in 800 ml acetone and the suspension is heated under reflux, slowly bubbles are formed due to formation of anhydrous gas of hydrogen chloride. After 30 min, suspension is converted into solution and in next 5– 10min, the precipitate of salt is generated. The hydrogen chloride gas remain for 2 hours and the mixture is allowed to keep overnight at RT. The product is collected by means of filtration, washed with acetone and dried at 105 0C to get desired product. [5]

Amorphous Systems

Amorphization is most popular method to increase the dissolution rate and also the bioavailability of drug with poor aqueous solubility. To increase the solubility, dissolution rate as well as bioavailability of drug the amorphous form of active drug moiety is necessary for releasing the drug. The amorphous nature of active ingredient must have a 10-1600 times more solubility than their crystalline forms. The enhancement of rate of dissolution of amorphous forms can be assigned to increase wetting property of the drug, deagglomeration of drug. And also to improve the properties like aggregation of the drug with hydrophilic polymers and the higher energy amorphous nature of the drug. [32]

The longer polymeric chains can sterically hamper the connection in between drug molecules which leads to inhibition of recrystallization of drug. In addition, the attachment in between the drug and polymer helps to increased energy obstacles for nucleation and accordingly to improve the physical stability of mixture.1 Amorphous drug-polymer mixtures are generally specified in terms of physical properties like glass transition temperature (Tg), heat capacity and miscibility. While it is not totally clear how the polymer stabilizes particularly the amorphous form of drug in that mixture. In drug polymer mixture the miscibility is commonly examine, which affects the stability of an amorphous system, which can be indicated by the thermodynamics of mixing. Amorphous forms of mixture are mainly formed by two methods like solvent evaporation method and melt extrusion method.[5]

Cyclodextrin inclusion complex

Cyclodextrins are cyclic oligosaccharides comprising of d (+) glucopyranose units which are attached by (1, 4) glucosidic bonds. They have inherent ability to produce inclusion complexes with different guest molecules due to their specific structures, possessing hydrophilic outer surface with hydrophobic space bound with protons. CDs have the capability to connect with poorly water soluble drugs and drug molecules which helps to increase in the drug's clear water solubility and dissolution rates. It is also described in the literature that CD complexation increases oral bioavailability of drug with poorly water solubility. The

increase in solubility also affects dissolution rate and oral bioavailability. It is feasible to move the class II drugs and sometimes class IV drugs into class I through cyclodextrin complexation. [33]

Bile salts

Bile, which contains taurine and glycine conjugates of cholic acid and chenideoxycholic acid, emulsifies dietary fat and enhances lipolysis and transport of lipid products with the assist of unstirred water surface of the intestinal mucosa by micellar solubilization process. The bile salts which separate from active re-absorption in the ileum; this bile salt is metabolized into secondary bile salts like deoxycholic acid and lithocholic acid by using the bacterial flora. Bile salts are able to attach calcium, their binding characteristic leads to increasing hydrophilicity. For improvement of mechanism of absorption by bile salts no any certain data is available. It may be bringing about by effects on the mucous membrane and on paracellular and transcellular absorption way. [33]

Saponin

Saponins are particularly glycosides of vegetable source with surface tension reducing properties and haemolytic action. They having ability to precipitate sterols and utilize intestinal and transdermal absorption upgrading properties. It is thinkable that the absorption helping properties of Saponins are moderated by their surfactants like properties. On the other side, a transcellular raising effect may also be generated by connection with the membrane stabilizer cholesterol. This shows that Saponins exhibit absorption promoting activity at relatively low concentrations. However; also for these compounds the issue of safety vs. efficacy requires further investigation. [33]

Straight chain fatty acids

The medium chain fatty acids like capric acid (C10), lauric acid (C12) and long chain fatty acids, like oleic acid (C18) have been exhibit to raise the permeability of a sequence of hydrophilic drugs by expanding the tight junction and/or changing the cytoskeleton of the intestinal epithelial cells without leading cytotoxicity. One of the foremost advantages of these excipients is the comfort of incorporating into the conventional oral dosage forms with no need for complex or expensive formulation technique. [33]

CONCLUSION

Use of solubility properties in bioavailability and solubility improvement of different poorly water-soluble compounds is a demanding job for researchers and scientists. Dissolution improvement of badly water-soluble drugs represent as a novel approach, which reduces the issue of poor solubility and dissolution rate as limiting step and give a rapid onset of action. Selection of method for solubility enhancement depends upon drug characteristics like solubility, chemical nature, melting point, absorption site, physical nature, pharmacokinetic behavior and so forth, dosage form requirement like tablet or capsule formulation, strength, immediate, or modified release.

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