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REVIEW ARTICLE

Novel techniques for solubility, dissolution rate and bioavailability enhancement of class II and IV drugs

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ABSTRACT

Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development, nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Among all newly discovered chemical entities most of the drugs are lipophilic and fail to reach market due to their poor water solubility. The ability to deliver poorly soluble drugs will grow in significance in the coming years as NCEs are relied upon for a larger share of the revenue within the pharmaceutical market by innovator companies. Similarly, generic drug manufacturers will need to employ economically efficient methods of delivery as more low solubility drugs go off patent, in order to maintain a competitive edge and sufficiently compete as profit margins shrink in this price-sensitive industry.

KEYWORDS: Bioavailability, Dissolution, Lipophilic, Poor solubility.

1. INTRODUCTION

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. [1]

More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties**.** Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties.[2]

Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bio-availability.[3]

Almost more than 90% drugs are orally administered. Drug absorption sufficient and reproducible bioavaiblity, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.[4] In this review attempt have been made on various novel techniques for solubility, dissolution and bioavailability enhancement of class II and IV drugs.

2. Methods for enhancement of bioavailability

Major approaches to overcome the bioavailability problems:

A) Pharmaceutics approach

Modification of formulation, manufacturing processes or physiochemical properties of the drug

B) Pharmacokinetic approach

Pharmacokinetics of drug is altered by modifying its chemical structure.

C) Biological approach

In this, route of drug administration may be changed such as parenteral form instead of oral form. Rate dissolution and its solubility are very important factors in third approach.[5,6]

Need of Solubility Enhancement

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Drug absorption from the gastrointestinal tract can be limited by a variety of factors, most significant contributors being poor aqueous solubility and poor membrane permeability of the drug molecule. When delivering an active agent orally it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs.[7] The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability.[8]

2. Techniques for Solubility Enhancement

1. Particle Size Reduction

The solubility of drug is often intrinsically related to drug particle size as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent which cause increase in solubility. Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound.[9]

2.1 Complexation

a. Physical Mixture

Active drug with suitable polymer in different ratios mixed in a mortar for about one hour with constant trituration. The mixture is passed through sieve no. 80 and stored in dessicator over fused calcium chloride.

b. Kneading method

Active drug with suitable polymer in different ratios is added to the mortar and triturated with small quantity of ethanol to prepare a slurry. Slowly the drug is incorporated into the slurry with constant trituration. The prepared slurry is then air dried at 25^{o}C for 24hrs. The resultant product is pulverised and passed through sieve no. 80 and stored in dessicator over fused calcium chloride.[10]

c. Co-precipitate method

Active drug is dissolved in ethanol at room temprature and suitable polymer is dissolved in distilled water. Different molar ratios of active drug and suitable polymers are mixed respectively. The mixture is stirred at room temprature for one hour and the solvent is evaporated. The resultant mass is pulverised and passed through sieve no. 80 and stored in a desiccators.[11]

2.2. Hydrotropy

Hydrotropy is a solubilization phenomenon whereby addition of large amount of a second solute results in an increase in the aqueous solubility of another solute. Concentrated aqueous hydrotropic solutions of sodium benzoate, sodium salicylate, urea, nicotinamide, sodium citrate and sodium acetate have been observed to enhance the aqueous solubilities of many poorly water-soluble drugs. [12-13]

2.3. Solid dispersion Techniques

The fusion (melt) method

Accurately weighed amounts of carrier(s) are placed in an aluminum pan on a hot plate and melted, with constant stirring, at a temperature of about 60°C. An accurately weighed amount of active drug is incorporated into the melted carrier(s) with stirring to ensure homogeneity. The mixture is heated until a clear homogeneous melt is obtained. The pan is then removed from the hot plate and allowed to cool at room temperature.

The solvent method

Accurately weighed amounts of active drug and carrier(s) are dissolved in minimum quantities of chloroform in a round-bottom flask. The solvent is removed using a rotary evaporator. The resultant solid dispersion is transferred to an aluminum pan and allowed to dry at room temperature. [14]

Dropping method

A solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape[12].

2.4. Spray drying techniques

Preparation of microparticles by spray drying

Spray dried particles consisted of active drug only and drug/suitable polymer in different ratios are prepared by dissolving the drug or drug/polymer mixture in ethanol/water solution. The solution is spray dried using Mini Spray Dryer. The formed microparticles are separated using cyclone separator, collected and stored in a desiccator at ambient temperature until ready to be used.

Preparation of microparticles by spray chilling

Spray chilled particles are prepared by melting the drug or drug/suitable polymer mixture in different ratios at 90°C. The melt is kept at 90°C and atomised with a specially constructed pneumatic nozzle into air kept at 20°C. The particles are collected using cyclone separator and stored in a desiccator.[13]

2.5. Supercritical Fluid Technologies

Supercritical Antisolvent precipitation

The SAS apparatus works in a continuous co-current mode and it consists of a precipitator in which the antisolvent and the liquid solution are separately fed to the top of the chamber and are continuously discharged from the bottom. The liquid solution is pumped into the chamber by a high pressure piston pump. The antisolvent is

delivered by means of a high pressure piston pump. The precipitator is a cylindrical vessel with an inner volume of 500cm^3. The liquid solution is delivered into the chamber through a stainless steel nozzle. The supercritical carbon dioxide is heated before entering the precipitator in a tube section by an electric cable, which is connected to a temperature controller. The precipitator is heated by means of two electric thin bands heater also connected to a temperature controller. A filter of sintered steel with sufficient porosity is placed at the bottom of the vessel to collect the particles produced. The solvents are separated and recovered from a second vessel.[14]

Gas Antisolvent Recrystallisation

It is possible to induce rapid crystallisation by introducing the antisolvent gas into a solution containing dissolved solute. One of the requirements for this approach is that the carrier solvent and the SF antisolvent must be at least partially miscible.

Solution-enhanced Dispersion by Supercritical Fluids

The drug solution and the SF are introduced simultaneously into the particle formation vessel using a co-axial nozzle arrangement causing rapid dispersion, mixing and extraction of the drug solution solvent by SF leading to very high supersaturation ratios. The temperature and pressure together with accurate metering of flow rates of drug solution and SF through a nozzle provide uniform conditions for particle formation. This helps to control the particle size of the product and by choosing an appropriate liquid solvent, it is possible to manipulate the particle morphology.[15]

2.6. Preparation Methods of Nanosuspensions

Media milling (Nanocrystal or Nanosystems)

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 under controlled temperatures for several days (at least 2-7 days). The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles.

Homogenization in water (Dissocubes)

Homogenization involves the forcing of the suspension under pressure through a valve having a narrow aperture. The instrument can be operated at pressure varying from 100 – 1500 bars (2800 –21300psi) and upto 2000 bars with volume capacity of 40ml.

Combined precipitation and homogenization (Nanoedege).

In this technique, the precipitated suspension is homogenized leading to reduction in particle size and avoiding crystal growth.

Nanojet technology

This technique called opposite stream or nanojet technology, uses a chamber where a stream of suspension is divided into two or more parts, which colloid with each other at high pressure. The high shear force produced during the process results in particle size reduction.

Emulsification-solvent evaporation technique

This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.[16]

2.7. Preparation of nanocrystals

The preparation process involves two steps

Preparation of drug solution in organic solvents: Different concentrations of drug solution is prepared by preparing solution of drug in organic solvent (based on solubility of drug in particular solvent).

Addition of drug solution in water: Nanocrystals are prepared by adding the microliter quantity of drug solution to milliliter quantity of water quickly with continuous stirring on magnetic stirrer at 1000 rpm Solvent is removed by overnight stirring at 500 rpm. Then it is centrifuged at 5000 rpm and the product is solidified.[17]

2.8. Nanopure XP technology

PharmaSol uses in its Nanopure XP technology a pre-treatment step with subsequent homogenization to produce particles well below 100 nm. Drug nanocrystals with a size of about 50 nm and below are distinctly smaller than the wavelength of the visible light, and so the nanosuspensions are translucent.[18]

2.9. Co-Solvent Evaporation Method

The solvent evaporation of drug and polymer solution in different ratio is carried out by using a suitable evaporator. The solutions are prepared by dissolving drug in methanol and polymer in distilled water and mixed both solutions, which produces clear solution. The clear solution evaporated in evaporator.

2.10. Spray Drying

The solvent evaporation of drug and polymer solution in different ratio is carried out by using spray dryer. The solutions are prepared by dissolving drug in methanol and polymer in distilled water and mix both solutions, which produces a clear solution. The solvent evaporated by using evaporator. The spray dried mixture of drug with polymer is obtained in 20–30 min.[20]

2.11. Formulation of Self microemulsifying drug delivery systems

A series of SMEDDS formulations are prepared using Surfactant/cosurfactant combination and oil. Accurately weighed active drug is placed in a glass vial and oil, surfactant and cosurfactant are added. Then the

components are mixed by gentle stirring and vortex mixing on a magnetic stirrer, until drug is perfectly dissolved. The mixture is stored at room temperature until further use.[21]

2. 12. A chitosan-based solvent change approach

The composition of different crystal formulations are prepared. Chitosan solution is prepared by soaking chitosan in 1% glacial acetic acid for 3 h. A weighed amount of the drug is dispersed in chitosan solution by using high dispersion homogenizer. This dispersion is then added to distilled water or sodium citrate solution to precipitate chitosan on drug crystals. The precipitate obtained is filtered through Whatmann No. 1 filter paper using vacuum filtration unit and dried. The dried product is then passed through sieve No. 60 to obtain a uniform size distribution.[22]

2.13. Preparation of dry elixir

Dry elixir is prepared by a spray drying technique. A laboratory scale spray drying is carried out using the spray dryer with a standard nozzle. Different compositions of spraying solution are prepared. Drug is dissolved in ethanol, while dextrin and SLS are dissolved in distilled water. Each solution is pre-warmed to 55–60 ◦C and then blended. SLS is employed to prevent spray- dried particles from attaching to the inner wall of spray-drying chamber, to produce free-flowing powder, to handle with easy and to increase the encapsulation of ethanol in the dry elixir. The final solution is delivered to spray dryer. The drug is collected in cyclone separator and stored in a conical tube.[23]

2.14. Preparation of drug composite particles

Active drug is dissolved in methanol and the solution is then filter through a nylon membrane to remove any particulate impurities. Next, polymers are dissolved in deionized water, which is used as an anti-solvent. The drug solution is poured rapidly into the anti-solvent with magnetic stirring at a rate of 2500 rpm. After stirring, a suspension containing drug nanoparticles are obtained. This suspension is then processed via spray drying to generate drug composite particles. Spray drying is carried out using a lab-oratory scale spray dryer. [24]

2.15. Preparation of dihydrochloride salt form

Active drug is suspended in 800 ml of acetone and into the suspension heated under reflux, the anhydrous gas of hydrogen chloride is bubbled slowly. After about 30 min, the suspension became a solution and in another 5–10min, the precipitate of the salt is formed. The pass of hydrogen chloride lasted for 2 h and the mixture is allowed to stand overnight at room temperature. The product is collected by filtration, washed with acetone and dried at 105 ◦C.[25]

2.16. Amorphous Systems

Amorphization is one of the techniques to enhance the dissolution rate and bioavailability of poorly water soluble drugs.[26] Delivering the pharmaceutical active ingredient in the amorphous form is very attractive due to the potentially large increases in drug solubility, dissolution rate, and bioavailability.[27-28] The amorphous form of drugs can have as much as a 10-1600 fold higher solubility than their crystalline forms.[29] The improvement in dissolution of amorphous systems can be attributed to improved wetting of the drug, deagglomeration and micellization of the drug with hydrophilic polymers and the high energy amorphous state of the drug.[30]

However, the amorphous forms of drugs are physically unstable due to their higher energy state and may recrystallize over pharmaceutically relevant time scales, negating any solubility advantage.[31] The most typically used approach to stabilize an amorphous system is to combine it with pharmaceutically acceptable polymers, such as polyvinylprrolidone, polyvinylpyrrolidone vinyl acetate, polyethylene glycol and various hydroxypropylmethyl cellulose and polyacrylic acid derivatives.[32,33] Thermodynamically the drug has a lower chemical potential when mixed with a polymer, resulting in a change of crystallization driving force.[34] The long polymeric chains can sterically hinder the association between drug molecules and, thereby, inhibit the recrystallization of drug. In addition, the interaction between the drug and polymer provides an increased energy barrier for nucleation and, consequently, enhances the physical stability.[35] Amorphous drug-polymer systems are commonly characterized in terms of physical properties such as the glass transition temperature (*Tg*), heat capacity and miscibility. Although it is still not completely clear as to how the polymer stabilizes the amorphous drug in the mixture, drug polymer miscibility is generally considered as one of the critical attributes that affect the stability of the amorphous systems, which in turn is dictated by the thermodynamics of mixing.[36] Amorphous systems are predominantly produced by solvent evaporation and melt extrusion methods.[37,38]

3. Conclusion

Use of solubility characteristics in bioavailability, pharmaceutical actions and solubility enhancement of various poorly soluble compounds is a challenging task for researchers and pharmaceutical scientists. Dissolution enhancement of poorly water soluble drugs constitute an innovative approach, which overcome the problems of solubility and dissolution rate limiting step and provide a quick onset of action.

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