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APPROACHES AND EVALUATION PARAMETERS OF SOLUBILITY ENHANCEMENT OF DRUG

DAMINI.S.PATIL*,TRUSHA.P.SHANGRAPAWAR

PDEA'S Shankarrao Ursal College Of Pharamaceutical And Research Center,Pune,Maharashtra,India 411014.

Corresponding Author,

DAMINI.S.PATIL

Student,

PDEA'S Shankarrao Ursal College Of Pharamaceutical And Research Center,Pune,Maharashtra,India 411014.

Abstract

Orally administered drugs solubility is one of the rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response. Problem of solubility is a major challenge for formulation scientist, which can be solved by different technological approaches during the pharmaceutical product development. Solid dispersion, Salt formation, are some of the vital approaches routinely employed to enhance the solubility of poorly soluble drugs but each approach has some limitation and advantages. Novel techniques like Nano-suspension, Supercritical processing, Cryogenic technology may allow greater opportunities in the delivery of poorly soluble drugs. The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. The major problem is low aqueous solubility similar with formulation development of new chemical entities. Any drug to be absorbed should be present within the form of associate solution at the site of absorption. Water is the solvent of choice for liquid pharmaceutical formulations.

KEYWORDS: Solubility, Solid dispersion, bioavailability,low solubility.

Introduction

Solubility is one of the most important physiochemical properties of drug because low solubility can affect the bioavailability of orally administered dosage forms. For the enhancement of the process solubilization of poorly water soluble drugs and further enhance the bioavailability of the drugs variety of methodology can be determined. Does it is very important to enhance the solubility of a poorly soluble drug. For absorption a drug must be present in the form of an aqueous solution at the site of absorption increasing the bioavailability of poorly soluble drugs is considered as one of the biggest challenges for scientist working in the field of medicine and the healthcare. The main cause of insufficient bio-viability is poor solubility and low dissolution rate in aqueous gastro-intestinal fluid. According to the biopharmaceutics classification system (BCS) especially for Class II and

class IV substance the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastric intestinal fluids.

Solubility

Solubility is the property of a solid liquid or gaseous chemical substances called solute to dissolve in a solid, liquid or gaseous solvent to form a homogeneous solution of the maximum quantity of solute in a certain quantity of solvent at specified temperature and the pressure. A saturated solution is the one in which the solute is in equilibrium with the solvent. The solubility of the drug may be expressed as parts percentage, molarity, molality volume fraction and mole fraction. Drug solubility is the maximum concentration of a drug solute dissolved in the solvent under specific condition of temperature, pH and pressure. The drug solubility is saturated solution is a static property where as the drug dissolution rate is dynamic property that relates more closely to the bioavailability rate.

The Indian Pharmacopeia classified the solubility of drugs in seven classes as in Table 1.

Terms	Parts of Solvent Required for One Part of Solute
Very Soluble	Less than 1 part
Freely Soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly Soluble	30 to 100 parts
Slightly Soluble	100 to 1,000 parts
Very Slightly Soluble	1,000 to 10,000 parts
Practically Insoluble or Insoluble	More than 10,000 parts

PH ADJUSTMENT

Poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water by applying a pH change. pH adjustment can in principle be used for both oral and parenteral administration. Upon intravenous administration the poorly soluble drug may be precipitate because blood is a strong buffer with pH between 7.2 – 7.4. To assess the suitability of the approach, the buffer capacity and tolerability of the selected pH are important to consider. In the stomach the pH is around 1 to 2 and in the duodenum the pH is between 5-7.5, so upon oral administration the degree of solubility is also likely be influenced as the drug passes through the intestines. Ionizable compounds that are stable and soluble after pH adjustment are best suited. The compound types may be acids or bases or zwitterionic. It can also be applied to crystalline as well as lipophilic poorly soluble compounds.Solubilized excipients that increase environmental pH within a dosage form, such as a tablet or capsule, to a range higher than pKa of weakly-acidic drugs increases the solubility of that drug, those excipients which act as alkalizing agents may increase the solubility of weakly basic drugs.15, 16 The solubility of the poorly soluble drug is increased compared to water alone, so if compounds can permeate through the epithelium orally, the fraction of orally absorbed drug may be increased. pH adjustment is also frequently combined with co-solvents to further increase the solubility of the poorly soluble drug. precipitation upon dilution is fine or amorphous, bioavailability can be increased due to an increased concentration gradient and enhanced surface area for dissolution. In situations where the drug precipitates into poorly soluble particles that require dissolution and do not rapidly redissolve, bioavailability may not be sufficiently increased. This approach is used frequently in Survey as pre-clinically pH adjustment is a good technique to assess the efficacy of poorly soluble drugs due to its universality and relative simplicity. However, if precipitation of the poorly soluble drug occurs uncontrollably after contact with a pH at which the drug is much less soluble (oral as well as parenteral), the interpretation of the results may be misleading.

Advantages

- Simple to formulate and analyse.
- Simple to produce and fast track.
- Uses small quantities of compound, amenable to high throughput evaluations.

Disadvantages

- Risk for precipitation upon dilution with aqueous media having a pH at which the compound is less soluble. Intravenously this may lead to emboli, orally it may cause variability.
- Tolerability and toxicity (local and systemic) related with the use of a non physiological pH and extreme pHs.
- As with all solubilized and dissolved systems, a dissolved drug in an aqueous environment is frequently less stable chemically compared to formulations crystalline solid. The selected pH may accelerate hydrolysis or catalyze other degradation mechanisms.

Commercial products using pH adjustment

Phenytoin Injection (Epanutin® ready mixed, Pfizer) 50mg/ml with propylene glycol 40% and ethanol 10% (1.1 mmol Na+ per 5 ml ampoule) is an example of a pH adjusted formulation containing co-solvents. CO-SOLVENCY The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents.17 Co-solvents are mixtures of water and one or more water miscible solvents used to create a solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Co-solvent formulations of poorly soluble drugs can be administered orally and parenterally. Parenteral formulations may require the addition of water or a dilution step with an aqueous

TECHNIQUES FOR SOLUBILITY ENHANCEMENT:

There are various techniques available to improve the solubility of hydrophobic drugs. Some traditional and novel approaches to improve the solubility are:

1. Particle Size Reduction
2. Solid Dispersion
3. Nanosuspension
4. Supercritical Fluid Technology

5. Cryogenic Technology

6. Inclusion Complex Formation Techniques

7. Floating Granules Particle Size Reduction

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. The critical parameters of comminution are well-known to the industry, thus permitting an efficient, reproducible and economic means of particle size reduction. However, the mechanical forces inherent to comminution, such as milling and grinding, often impart significant amounts of physical stress upon the drug product which may induce degradation.

2.Solid Dispersion

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, who investigated the generation and dissolution performance of eutectic melts of a sulfonamide drug and a water-soluble carrier in the early 1960s. 8 Solid dispersions represent 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 hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, PlasdoneS630.

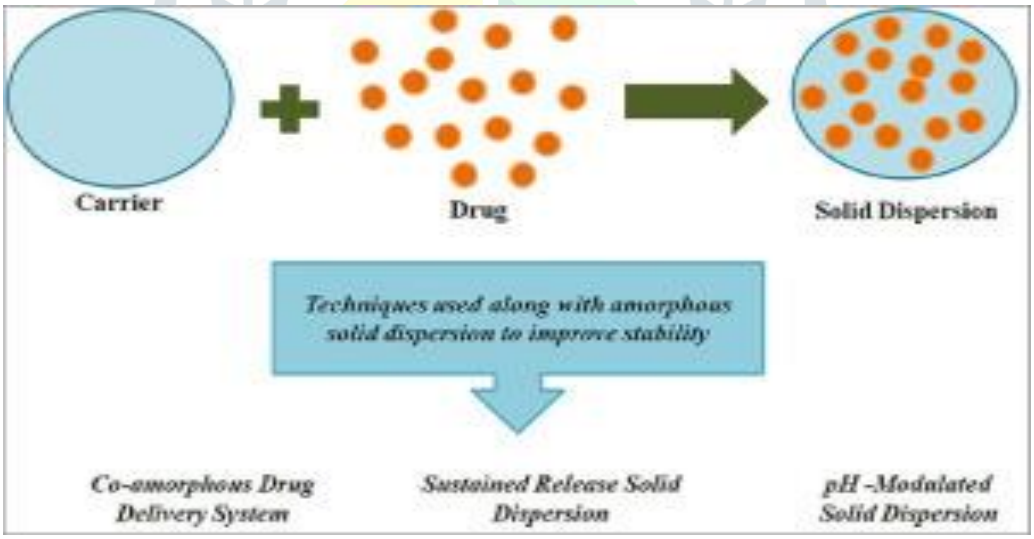


Fig. solid dispersion

Nanosuspension

Nanosuspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. A pharmaceutical nanosuspension is a biphasic system consisting of nano sized drug particles stabilized by surfactants for either oral and topical use or parenteral and pulmonary administration. The particle size distribution

of the solid particles in nanosuspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm [25, 26]. Various methods utilized for preparation of nanosuspensions include precipitation technique, media milling, highpressure homogenization in water, high pressure homogenization in nonaqueous media, and combination of Precipitation and high-Pressure homogenization.

Supercritical Fluid (SCF):

Process Another novel nanosizing and solubilisation technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. Supercritical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. At near-critical temperatures, SCFs, are highly compressible allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of the fluid that largely determine its solvent power. Once the drug particles are solubilised within the SCF (usually carbon dioxide), they may be recrystallised at greatly reduced particle sizes. The flexibility and precision offered by SCF processes allows micronisation of drug particles within narrow ranges of particle size, often to submicron levels. Current SCF processes have demonstrated the ability to create nanoparticulate suspensions of particles 5–2,000 nm in diameter. Several pharmaceutical companies, such as Nektar Therapeutics and Lavipharm, are specializing in particle engineering via SCF technologies for particle size ISRN Pharmaceutics 5 reduction and solubility enhancement.

Cryogenic Techniques:

Cryogenic techniques have been developed to enhance the dissolution rate of drugs by creating nanostructured amorphous drug particles with high degree of porosity at very lowtemperature conditions. Cryogenic inventions can be defined by the type of injection device (capillary rotary, pneumatic, and ultrasonic nozzle), location of nozzle (above or under the liquid level), and the composition of cryogenic liquid (hydrofluoroalkanes, N2, Ar, O2, and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes like spray freeze drying, atmospheric freeze drying, vacuum freeze drying, and lyophilisation.

Inclusion Complex Formation-Based Techniques:

Among all the solubility enhancement techniques, 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 nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. The enzymatic degradation of starch by cyclodextrin-glycosyltransferase (CGT) produces cyclic oligomers, Cyclodextrins (CDs). These are nonreducing, crystalline, water soluble, and cyclic oligosaccharides consisting of glucose monomers arranged in a donut shaped ring having hydrophobic cavity and hydrophilic outer surface as illustrated in Figure 1.

Three naturally occurring CDs are α-Cyclodextrin, β-Cyclodextrin, and γ-Cyclodextrin.

BCS Classification:

Class I-High Solubility, High Permeability

Class I drugs show a high absorption number and a high dissolution number. For those Class I compounds formulated as immediate release products, dissolution rate generally exceeds gastric emptying so, nearly 100% absorption can be predictable if at least 85% of a product dissolves inside 30 min of in vitro dissolution testing across a range of pH values accordingly, in vivo bioequivalence data are not necessary to assure product comparability. E.g. metoprolol, diltiazem, verapamil, propranolol.

Class II -Low Solubility, High Permeability

Class II drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption apart from at a very high dose number. The bioavailability of these products is likely

to be dissolution-rate limited, for this reason, a correlation between in vivo bioavailability and in vitro dissolution rate may be observed. e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

Class III – High Solubility, Low Permeability

In this class for drug absorption permeability is rate limiting step. These drugs show a high variation in the rate and amount of drug absorption. Dissolution will most likely occur very rapidly but absorption is permeability-rate limited so there has been some proposal that as extended as the test and reference formulations do not contain agents that can modify drug permeability or GI transit time, waiver criteria similar to those associated with Class I compounds may be appropriate. e.g. Cimetidine, Acyclovir, Neomycin B, Captopril.

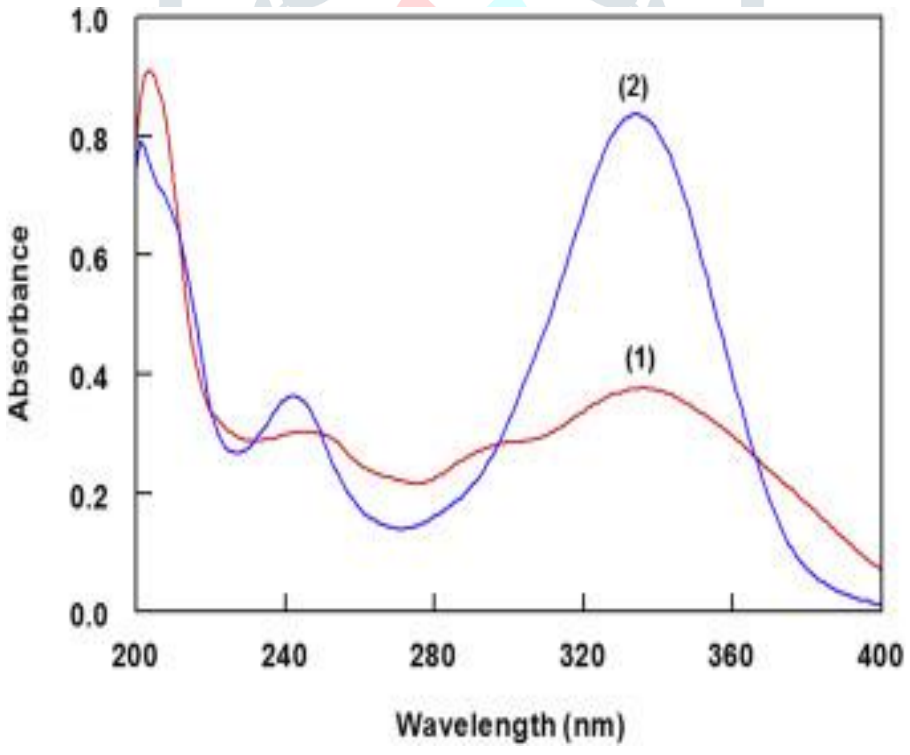
Class IV- Low Solubility, Low Permeability

Those compounds have a poor bioavailability usually they are not well absorbed over the intestinal mucosa and a high variability is expected with very poor oral bioavailability. These compounds are not only difficult to dissolve but once dissolved, often show incomplete permeability across the GI mucosa. These drugs tend to be extremely tricky to formulate and can exhibit very large inter subject and intra subject variability.

Ultraviolet Spectroscopy:

Determination of Maximum Wavelength (λmax):

a. **In Methanol:** Drug (10 mg) was accurately weighed and transferred to 100 ml volumetric flask, volume was made up to the mark with methanol to obtain strength 100 µg/ml. It was used as a standard stock solution. This stock solution was further diluted suitably to give a concentration of 10 µg/ml. The UV spectrums were recorded in the range 200-400 nm by using UV-Visible double beam spectrophotometer (Shimadzu 2450). The wavelength of maximum absorption (λmzax) was determined.



Conclusion

Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs and solubility is the basic requirement for the absorption of the drug from GIT. The various techniques described above alone or in combination can be used to enhance the solubility of the drugs.

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