WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 7, 669-692. Review Article ISSN 2277– 7105

A REVIEW: FACTORS AFFECTING DISSOLUTION OF BCS CLASS II DRUG

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Article Received on
26 March 2019,

Revised on 16 April 2019,
Accepted on 06 May 2019,

DOI: 10.20959/wjpr20197-15025

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ABSTRACT

Pharmaceutical products exists in the form of different dosage forms such as oral solid dosage form, oral semi-solid dosage form, oral liquid dosage form, injectable, etc. Solid dosage form contributes to more than 40% of the pharmaceutical products primary reasons for preference being ease of administration, ease to identify and relatively acceptable taste. Pharmaceutical solid dosage form on administration undergo dissolution in biological media, followed by absorption of the drug entity into the systemic circulation. Two drug products containing the same active substance are considered bioequivalent if their bioavailability (rate and extent of drug absorption) after administration in the same molar dose lie within acceptable predefined limits. The insufficient dissolution rate of the drug is the limiting factor in the oral bioavailability of poorly water soluble compounds. The purpose of this review article is to provide overview of dissolution and describe the factors affecting dissolution of BCS class II drug.

KEYWORDS: Oral solid dosage form, Dissolution, solubility, BCS class II drug, poor water solubility.

INTRODUCTION

Dissolution is defined as the process by which a solid substance enters in the solvent to yield a solution. Dissolution can also be defined as a process by which a solid substance dissolves.

Drug dissolution mainly of the oral solid dosage form depend on two steps:

1) Release of the drug from the dosage form,

2) Subsequent solubilization of drug particles in physiological fluid.

Dissolution process of solid oral dosage form is illustrated below:

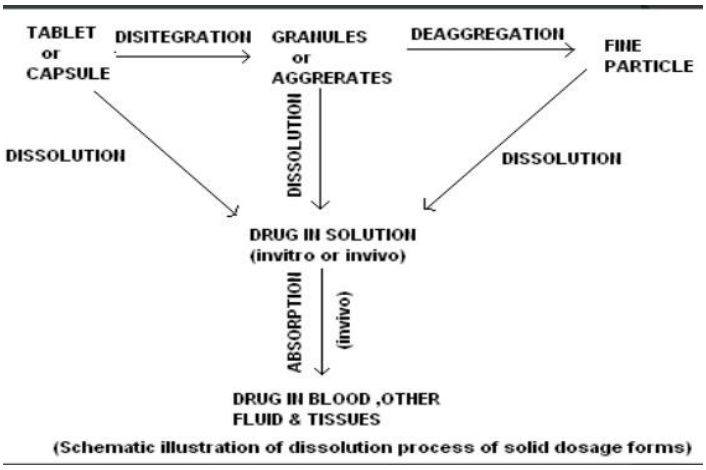

Figure 1: Illustration of dissolution process.

Different dissolution apparatus mentioned in pharmacopeia are tabulated in the following table 1.

Table 1: Dissolution apparatus mentioned in pharmacopeia.

	I.P	USP	B.P.	E.P.
Type 1	Paddle apparatus	Basket apparatus	Basket apparatus	Basket apparatus
Type 2	Basket apparatus	Paddle apparatus	Paddle apparatus	Paddle apparatus
Type 3	Reciprocating cylinder	Reciprocating cylinder	Reciprocating cylinder	Reciprocating cylinder
Type 4	Flow through cell apparatus	Flow through cell apparatus	Flow through cell apparatus	Flow through cell apparatus
Type 5		Paddle over disk		
Type 6		Cylinder		
Type 7		Reciprocating holder		

Biopharmaceutical classification system (BCS) is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance. The BCS categorizes drug substances into one of four BCS classes as follows:

Class I: high solubility, high permeability

Class II: low solubility, high permeability

Class III: high solubility, low permeability

Class IV: low solubility, low permeability

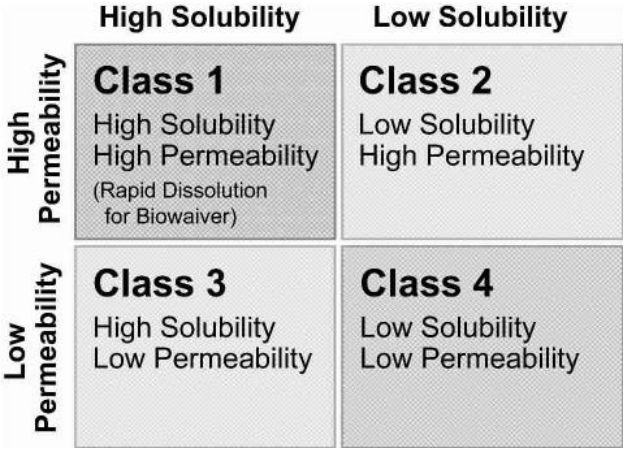

Figure 2: BCS classification.

Characteristics of the drugs under BCS

Class I: In-vivo these drugs behave like an oral solution having fast dissolution and rapid bioavailability. Since the dissolution and absorption of class I drugs is very fast, bioavailability and bioequivalence are unnecessary for the products of such drugs. These drugs are good candidates for controlled drug delivery if they qualify pharmacokinetically and pharmacodynamically for the purpose. Gastric emptying is often the rate governing parameter in this case.

Class II: Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability. These drugs exhibit variable bioavailability and need enhancement in the dissolution rate by different methods for improvement in bioavailability. These are also suitable for controlled release development.

Class III: Permeation through the intestinal membrane forms the rate-determining step for these drugs. Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form. For example, the various ranitidine products having different dissolution profiles produce superimposable plasma concentration versus time profile in-vivo. These drugs generally exhibit low bioavailability and permeability enhancement is generally required. These drugs are problematic for controlled release development.

Class IV: Drugs of this class exhibit poor and variable bioavailability. The overall bioavailability is governed by several factors such as rate of dissolution, intestinal permeability, gastric emptying, and so on. These drugs are generally not suitable for oral drug

delivery or else some special drug delivery technologies such as nanosuspensions will be needed.

In this review article we will be considering only BCS class II drug. For poorly water soluble drugs, mainly categorized as class II in BCS classification system (low solubility and high permeability), the dissolution is the rate determining step in the absorption process.

As the process of dissolution is a rate limiting process for undertaking further absorption into the body. So, it has become a major difficulty in case of poorly water soluble drugs that have low solubility and high permeability i.e., BCS class II drugs, it is possible to enhance their dissolution rate and bioavailability. Many attempts and approaches were initiated on the improvement of dissolution rate of poorly soluble drugs.

Factors influencing dissolution rate from solid oral dosage form

1. Environmental factors during dissolution
   - Intensity of agitation.
   - Concentration gradient.
   - Composition of dissolution media.
   - Temperature of dissolution media.

2. Factors relating to the physicochemical properties of the drug
   - Factors affecting solubility.
   - Factors affecting surface area available for dissolution.

3. Factors related to the composition and method of manufacture.
4. Environmental factors involved with dosage form.
   - Humidity during manufacturing
   - Storage condition for dosage forms
   - Age of dosage form.
5. Factors related to the dissolution testing device.

1. Environmental factors during dissolution

- **Intensity of agitation**

Degree of agitation, or the stirring condition is one of the most important variable to consider in dissolution. From various theories of dissolution it is apparent that agitation can markedly effect diffusion controlled dissolution, because the diffusion layer thickness is inversely

proportional to the agitation speed. However, for pharmacopeia products the monograph mentions the agitation speed while for most of the products other than pharmacopeia are mentioned in official site of USFDA.

➢ **Concentration gradient**

It is the concentration difference between the solubility of the drug in the dissolution medium and the average concentration in the bulk fluid. Higher the concentration gradient between the soluble drug and bulk fluid rapid is the dissolution.

➢ **Composition of dissolution media**

Selection of proper dissolution medium for dissolution testing depends on the solubility of the drug. Factors such as dissolved gasses, media pH and viscosity of the medium been shown to be significantly influential as far as dissolution rate is concerned.

- Dissolved gases: At any given temperature and pressure, a portion of the gas is dissolved in the liquid. The dissolved gas can alter the pH of the dissolution medium e.g. distilled water pH is 6; deareated distilled water pH 7.2 the difference in the pH is due to the dissolved gases in the liquid. With change in temperature the gases may release in the form of bubbles which will alter the dissolution pattern of the drug.
- Media pH: Dissolution rates of the drug product can be influenced by the pH of the dissolution medium. Dissolution of drug in different pH is based on the solubility of the drug in respective pH. Numerous studies have examined the effects of changes in the pH of the dissolution media over the range of pH 2 to 7.
- Viscosity: Dissolution rate is inversely proportional to viscosity of dissolution media especially in diffusion controlled dissolution process. However viscosity will have very little effect on interfacial controlled dissolution process.

➢ **Temperature of dissolution media.**

Pharmacopeia specifies that the dissolution medium must be held at 37± 0.5°C. All standard commercial water bath meet the pharmacopeia requirement. Since the drug solubility is temperature dependent, temperature control during dissolution process is crucial. Stokes' equation explains the temperature dependency of a dissolved molecule and diffusion coefficient:

$$D = \frac{kT}{6\pi\eta r}$$

Where *k* is the Boltzmann constant and the denominator expresses the strokes force for a spherical molecule, η is the viscosity and r is the radius of the molecule.

2. Factors relating to the physicochemical properties of the drug

➢ Factors affecting solubility

The solubility depends on the physical form of the solid, the nature and composition of solvent medium as well as temperature and pressure of system.

- **Particle size:** The size of the solid particle influences the solubility because as a particle becomes smaller, the surface area to volume ratio increases. The larger surface area allows a greater interaction with the solvent. According to Nernst – Brunner theory, dissolution rate is directly proportional to the surface area of the drug. Surface area increases with the decrease in particle size which will result in increased dissolution of the drug. This effect is observed when micronized drug is used for formulation where higher dissolutions are observed. The effective surface area i.e. the surface area available to the dissolution fluid should be increased in order to increase the dissolution of the drug. Drug solubility and surface area can be correlated by the Ostwald – Freundlich equation:

$$\text{Ln } Cs = \frac{2M\gamma}{\rho RT} \frac{1}{r} = \frac{\alpha}{r}$$

Where Cs is the solubility of the drug, M the molecular weight, ρ the density, γ the interfacial tension of the solid, T the temperature, R the gas constant and r the radius of the particle.

- **Temperature:** Temperature will affect solubility. If the solution process absorbs energy then the solubility will be increased as the temperature is increased. If the solution process releases energy then the solubility will decrease with increasing temperature. Generally, an increase in the temperature of the solution increases the solubility of a solid solute. A few solid solutes are less soluble in warm solutions. For all gases, solubility decreases as the temperature of the solution increases.

- **Pressure:** For gaseous solutes, an increase in pressure increases solubility and a decrease in pressure decrease the solubility. For solids and liquid solutes, changes in pressure have practically no effect on solubility.

- **Nature of the solute and solvent:** While only 1 gram of lead (II) chloride can be dissolved in 100 grams of water at room temperature, 200 grams of zinc chloride can be dissolved. The great difference in the solubilities of these two substances is the result of differences in their nature.

- **Molecular size:** The larger the molecule or the higher its molecular weight the less soluble the substance. Larger molecules are more difficult to surround with solvent molecules in order to solvate the substance. In the case of organic compounds the amount of carbon branching will increase the solubility since more branching will reduce the size (or volume) of the molecule and make it easier to solvate the molecules with solvent.

- **Polarity:** Generally non-polar solute molecules will dissolve in non-polar solvents and polar solute molecules will dissolve in polar solvents. The polar solute molecules have a positive and a negative end to the molecule. If the solvent molecule is also polar, then positive ends of solvent molecules will attract negative ends of solute molecules. This is a type of intermolecular force known as dipole-dipole interaction.

- **Polymorphs:** A solid has a rigid form and a definite shape. The shape or habit of a crystal of a given substance may vary but the angles between the faces are always constant. A crystal is made up of atoms, ions, or molecules in a regular geometric arrangement or lattice constantly repeated in three dimensions. This repeating pattern is known as the unit cell. The capacity for a substance to crystallize in more than one crystalline form is polymorphism. The polymorphic forms of drugs have shown to influence changes in the solubilizing characteristics and thus the dissolution rate of the drug substance. Numerous reports have shown that polymorphism and the states of hydration, salvation, and/or complexation markedly influence the dissolution characteristics of the drug. Polymorphic forms of drugs have shown to influence changes in the solubilisation characteristics and thus the dissolution rate of the drug substance. Different polymorphs of the same drug have difference in solubility which intern effects the dissolution of a particular polymorph.

- **Solid-Phase Characteristics:** The solid-phase characteristics of drugs, such as amorphicity and crystallinity, have been shown to have a significant effect or the dissolution rate. studies have demonstrated that the amorphous form of a drug usually exhibits greater solubility and higher dissolution rate as compared to that exhibited by the

crystalline form, Piccolo and Saks3. showed that the dissolution rate of amorphous erythromycin estolate is markedly lower than the crystalline form of erythromycin estolate, as exemplified.

- **Coprecipitation and/or Complexation:** Numerous reports have shown that polymorphism and the states of hydration, salvation, and/or complexation markedly influence the dissolution characteristics of the drug.

- **Surfactant:** The drugs that are practically insoluble in aqueous medium are of increasing therapeutic interest, particularly due to the problem associated with their bioavailability when administered orally. It is often suggested that drugs with low solubilities when incorporated with surfactants can enhance their dissolution rate. Numerous articles addressing the effects of surfactants on the dissolution rate of such drug have been reported in literature. Surfactants reduce interfacial tension and increase the solubility of the drug dissolution. Additionally the method of incorporation of the surfactant in the drug product formulation can marked influence the dissolution characteristic of the relatively hydrophobic drug.

➢ **Factors affecting surface area available for dissolution**

- Particle size: In most instances, reduction in particle size of drugs contained in tablets or capsules will enhance dissolution and intern absorption. Gastrointestinal fluids have good wetting properties, so that reduction in particle size will increase the effective surface area of the drug.
- Manufacturing variable: Process used for manufacturing may influence dissolution of the product. Wet granulation using aqueous solution has shown to improve dissolution rate of poorly soluble drugs. Order of addition of drug and excipients can also influence the dissolution rate of the drug. e.g. disintegrant like croscarmellose sodium should be added both intragranularly and extragranularly to have better dissolution results.

3. Factors related to the composition and method of manufacture

A variety of factors concerning the formulation of a drug product can directly influence the dissolution rate of the active ingredient contained within it. Once these factors are completely characterized, one can use this information to achieve custom-tailored drug dissolution profiles. This information is then employed in the development of optimally effective dosage forms.

- **Excipients and Additives**

Most solid dosage forms incorporate more than one excipient for various purposes together with the active ingredient in the formulation. It has been shown that the dissolution rate of a pure drug can be altered significantly when mixed with various adjuncts. These adjuncts include diluents, binders, lubricants, granulating agents, disintegrants, and so on. In the following discussion we address the influence of excipients on the rate of dissolution of the active ingredient from a dosage form.

- **Particle Size**

Several investigators have concluded that in most instances, reduction in particle size of drugs contained in tablets or capsules will enhance dissolution and absorption. This can most likely be attributed to the procedures employed in tablet production: that is, mixing the drug with usually hydrophilic diluents and subsequent granulation will result in a more hydrophilic surface, even for originally hydrophobic drug particles. Investigators have extensively evaluated the effect of particle size on the dissolution rate of drug from granules and tablets.

- **Granulating agent and binder**

It has been reported by several investigators that binder and granulating agent incorporated in tablet formulation and other solid dosage forms can markedly influence the dissolution characteristics of the drug from the dosage form. Solvong and finholt have shown that Phenobarbital tablet granulated with gelatin solution provide a faster dissolution rate in human gastric juice than do those prepared using sodium carboxy methylcellulose or polyethylene glycol 6000 as binder.

- **Disintegrating Agents**

Several reports have been published in the literature demonstrating the effect of various disintegrating agents on the dissolution rate of tablets. It must be noted that the type and amount of disintegrating agent employed in the formulation significantly controls the overall rate of dissolution of the dosage form.

- **Lubricants**

Lubricants that are commonly incorporated in the formulation of solid dosage forms fall predominantly in the class of hydrophobic compounds. Consequently, the nature, quality, and quantity of the lubricant added can affect the dissolution rate.

The effects of various lubricants on the dissolution rate of salicylic acid tablets were studied by Levy and Gumtow. They concluded that magnesium stearate, a hydrophobic lubricant, tends to retard the dissolution rate of salicylic acid tablets, whereas sodium lauryl sulfate enhances dissolution, due to its hydrophilic character combined with surface activity, which increases the microenvironment pH surrounding the weak acid and increases wetting and better solvent penetration into the tablets.

- **Interfacial tension between drug and dissolution medium**

The properties of the interface between the drug and the dissolution medium can become a deciding factor as far as dissolution rate is concerned. The characteristics can be modified by the addition of agent that act at the interface.

- **Surfactant**

The drugs that are practically insoluble in aqueous medium (<0.01%) are of increasing therapeutic interest, particularly due to the problems associated with their bioavaibility when administered orally. Drugs with low solubilities when incorporated with surfactants can enhance their dissolution rate.

4. Environmental factors involved with dosage form.

- **Humidity during manufacturing**

Moisture has been shown to influence the dissolution of many drugs from the solid oral dosage forms. The environmental conditions to which the dosage forms are exposed, moisture content in particular, should be rigorously assessed if reproducible and reliable dissolution data are to be obtained. Additionally, humidity during manufacturing of the dosage form should be carefully controlled to guarantee the quality of product from batch to batch.

- **Storage condition for dosage forms**

Dosage forms should be stored in the optimum pack and condition to ensure stability and optimum dissolution at any point of time during shelf life of the product.

- **Age of dosage form**

Aging of the dosage form can affect the dissolution of the drug. Example tablets granulated with acacia exhibited decrease in the dissolution rate during 1 year of aging at room temperature.

5. Factor related to the dissolution testing device

➢ **Eccentricity of Agitating (Stirring) Element**

The current official compendium specifies that the stirring shaft must rotate smoothly without significant wobble. The lerrd significant gives the experimenter full right to ensure that such wobble does not significantly affect the dissolution rate. Additionally, USP XX/NF XV states that the axis of rotation of the stirring shaft must not deviate > 2 mm from the axis of the stirring vessel. This implies that this specification permits eccentricity up to ±2 nun but that such eccentricity must not significantly affect the dissolution rate. This is certainly an excessive amount.

➢ **Vibration**

The speed of the rotational device selected by official compendium is 100 rpm. Other speeds are specified for certain drugs. Precise speed control is best obtained with a synchronous motor that locks into line frequency. Such motors are not only more rugged but are far from reliable. Periodic variations in rpm might result in possible disturbance in rotational acceleration. This phenomenon, present in almost all rotational devices, is commonly referred to as torsional vibration, Such vibration indicates a variation in the velocity of rotation for short periods of time. There average velocity was well within ±4% of the specified rate.)

Vibration is a common variable introduced into a dissolution system due to various causes. It can effect change in the flow patterns of the dissolution medium. Additionally, it can introduce unwanted energy to the dynamic system. Both effects may result in significant changes in dissolution rate.

➢ **Agitation Intensity**

It can be stated with a significant amount of certainty that the degree of agitation, or the stirring conditions, is one of the most important variables to consider in dissolution. Given the background on the various theories of dissolution, it is apparent that agitation conditions can markedly affect diffusion-controlled dissolution, because the thickness of the diffusion layer is inversely proportional to agitation speed. Wurster and Taylor39 employed the empiritical relationship.

$K=a(N)b$

Where N is the agitation rate, K the reaction (dissolution) rate, and a and b arc constants. For diffusion-controlled processes, b = I. Dissolution that is interfacial-reaction-rate-controlled will be independent of agitation intensity and thus b=0.

- **Flow Pattern Disturbances**

For dissolution-rate data to be reproducible and reliable, the flow pattern should be consistent from test to test. The geometry and alignment of the stir-ring device, external vibration, and rotational speed are some of the factors that can influence flow patterns. In 1978, DRTL conducted an extensive examination of these factors and their influence on dissolution testingl0. They concluded that the geometry of the rotating paddle and/or basket, the flask dimensions, and the sampling positions can all introduce various types of flow patterns that can alter the dissolution characteristics of the drug product. Cox at al. further suggested that variations in smoothness of the round-bottomed flask can make significant differences in flow patterns as well. The influence on flow patterns of the vertical distance of the basket or paddle from the lowest point of the bottom of the round-bottomed flask should also be considered. The official compendium specifies this distance to be 2.5 cm (±2 mm).

- **Sampling Probes, Position, and Filters**

Large probe can affect the hydrodynamics of the system and therefore the dissolution rate of some dosage forms, causing results that differ from those obtained by manual sampling. USP/NF states that samples should be removed at approximately half the distance from the bottom of the basket or paddle to the surface of the dissolution medium and not closer than 1 cm to the side of the flask. The choice of a filter should be preceded by an investigation of the adsorption characteristics of the drug and the particular filter material.

- **Temperature**

USP/NF specifics that the dissolution medium must be held at 37°C (±0.5°). Although most commercial water baths can meet this standard of performance, failure to meet this requirement is not uncommon, It is often assumed that the water-bath temperature and the flask temperature are the same. Plastic flasks have a heat transfer coefficient approximately 3.5 times less than that of glass M. As the temperature difference between the bath and the flask's medium is lowered, the amount of heat transferred into the flasks is reduced. It is vital to cover the flasks at least during dissolution testing.

Since the drug solubility is temperature dependent, its careful control during the dissolution process is crucial. The effect of temperature variations of the dissolution medium depends mainly on the temperature-solubility curves of the drug and excipients in the formulation. Stokes' equation explains the temperature dependency of a dissolved molecule and diffusion coefficient:

$$D = \frac{kT}{6\pi\eta r}$$

Where, k is the Boltzmann constant and the denominator expresses the Stokes force for a spherical molecule, n is the viscosity, and r is the radius of the molecule.

- **Dissolution Medium**

The constituents, nature, and overall characteristics of the dissolution medium have a significant bearing on the dissolution performance of a drug substance. Also, selection of the proper dissolution medium for dissolution testing depends on the solubility of the drug as well as on economics and practicality. Factors such as dissolved gases, media pH, and viscosity of the medium have been shown to be significantly influential as far as dissolution rate is concerned.

- **Viscosity**

Dissolution rate decrease with increase viscosity of the dissolution medium; especially in the case of diffusion controlled dissolution process. Viscosity has very little effect on interfacial controlled dissolution process.

- **Sorption**

The relative density of the tablets was found to decrease, resulting in increased disintegration time with increase in water sorption-rate constants.

- **Detection Errors**

Analytical methods be checked carefully for each dissolution system. Extreme care must also be exercised when laboratory methods are introduced into quality control to ensure that no part of the equipment interferes with sensitive determinations.

Bioavailability: "Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action". The bioavailability of a drug is controlled by three principal factors. These variants are

namely, Rate and extent of release of the drug from the dosage form Subsequent absorption from the solution state.

According to BCS, a drug on the basis of these solubility and permeability characteristics can be classified in one of the four possible categories as indicated in Figure 2.

A Class II drug will typically exhibit dissolution rate limited absorption and a Class IV drug will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research focus on improving the oral bioavailability of an API. These are: Enhancing solubility and dissolution rate of poorly water-soluble drugs Enhancing permeability of poorly permeable drugs.

Various techniques that can be used for solubility enhancement of BCS Class II drugs are discussed below.

- **Solubility Enhancement of BCS Class II Drugs**

The solubility of a solute is the maximum quantity of solute that can dissolve in a certain quantity of solvent or quantity of solution at a specified temperature. Various techniques are available to improve the solubility of poorly soluble drugs. These techniques can be categorized in three basic approaches:

1. Traditional Techniques 2. Newer and Novel Techniques 3. Solid Dispersion Technique

1. Traditional techniques

Traditional techniques includes use of co-solvents, Hydrotropy, Micronization, Change in dielectric constant of solvent, amorphous forms, chemical modification of drug, use of surfactants, inclusion complex or clathrates, alteration of pH of solvent, use of hydrates or solvates, use of soluble prodrugs, application of ultrasonic waves, functional polymer technology, controlled precipitation technology, evaporative precipitation in aqueous solution, use of precipitation inhibitors, solvent deposition, precipitation, selective adsorption on insoluble carriers.

- **Use of Co-Solvents**

The addition of a water-miscible or partially miscible organic solvent is a common and an effective way to increase the solubility of a nonpolar drug. This process is known as cosolvency and the solvents used in combination to increase the solubility of the drugs are known as cosolvents. The cosolvent system works by reducing the interfacial tension

between the predominately aqueous solution and the hydrophobic solute. It is also commonly referred to as solvent blending. Cosolvents such as ethanol, propylene glycol, glycerin, sorbitol and polyoxyethylene glycols can be used. Ternary diagrams are used to visualize where maximum solubility occurs when more than one solvent is used.

- **Hydrotropy Method**

Hydrotropy is a solubilization process whereby addition of large amounts of a second solute (Hydrotropic agents) results in an increase in the aqueous solubility of another solute. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water results in "salting in" of non-electrolytes called "hydrotropic salts" a phenomenon known as "Hydrotropism". The solubility of rofecoxib was enhanced by using hydrotropes such as urea and nicotinamide.

- **Micronization**

The particle size reduction technique enhance the solubility and dissolution rate of poorly water soluble drugs due to the enormous surface that is generated. The process involves reducing the size of the solid drug particle to 1 to 10 microns commonly by spray drying or by use of air attrition methods such as fluid energy mill, jet mill, rotor stator colloid mill etc. The process is also called as "Micromilling". Micronization is not suitable for drugs having a high dose number because it does not change the saturation solubility of the drug. Micronization of drug is not preferred because micronized product has the tendency of agglomeration, which leads to decreased effective surface area for dissolution.

- **Change in dielectric constant of solvent**:

The addition of a cosolvent can increase solubility of hydrophobic molecules by reducing the dielectric constant of the solvent. Due to hydrogen bonding, water is a good solvent for polar molecules and has a high dielectric constant. The dielectric constant is a measure of the effect a substance on the energy needed to separate two oppositely charged bodies. The energy required to separate two oppositely charged bodies is inversely proportional to the dielectric constant of the medium.

- **Amorphous forms**

In amorphous forms atoms or molecules are randomly placed and have higher thermodynamic energy than corresponding crystalline forms. Solubility as well as dissolution rates are generally greater.

- **Chemical modification of drug**

By the addition of polar groups like carboxylic acids, ketones and amines, solubility is increased by increasing hydrogen bonding and the interaction with water.

- **Use of Surfactants**

Surfactants are amphiphilic in nature having a polar end (the circular head) and non-polar end (the tail). When a surfactant such as tween-80, sodium lauryl sulphate is placed in water, it will form micelles. A non polar drug will partition into the hydrophobic core of the micelle and the polar tail will solubilize the complex. This has been illustrated by solubilization and wetting effects of bile salts on the dissolution of steroids.

- **Inclusion complex/clathrates**

Considerable increase in solubility and dissolution of the drug has been achieved by the use of cyclodextrins. These complexes can be prepared with ß-cyclodextrin (ß-CD) and HP-ß-CD; the required quantity of ß-CD is weighed and water added to get tough consistency. To the mass, weighed quantity of the drug is added. The mixture is kneaded in a glass mortar for one hour and then completely dried in hot air oven at 60ºC for 2 hours. The dried mass is sieved through mesh no.12.

- **Alteration of pH of solvents**

The pH of solvent when reduced causes solubility enhancement. A combined effect of pH and complexation on solubilization is also synergistic in nature. It was attempted to enhance dissolution of gliclazide using pH change approach.

- **Use of Hydrates or Solvates**

A crystalline compound may contain either a stoichiometric or non-stoichiometric adducts, such as inclusions, involve entrapped solvent molecules within the crystal lattice. A stoichiometric adducts, commonly referred to as “Solvate”, and is a molecular complex that has incorporated the crystallizing solvent molecules into specific sites within the crystal lattice. When the incorporated solvent is water, the complex is called as “Hydrate”. A

compound not containing any water within its crystal structure is termed "Anhydrous". Aqueous solubilities of anhydrous forms are higher than the hydrate forms.

- **Use of Soluble Prodrugs**

The physicochemical properties of the drugs are improved by bio-reversible chemical alteration. The most common prodrug strategy involves the incorporation of polar or ionizable moiety into the parent compound to improve aqueous solubility. The pro-drug approach has been successfully used to improve the water solubility of corticosteroids, vitamins and benzodiazepines. Enhancement of rate of dissolution of allopurinol was successfully achieved by prodrug formation.

- **Application of Ultrasonic Waves**

Solubility can be increased by the use of ultrasonic vibrators. An oscillator of high frequency (100-500 KHz) is used and the device is known as "Pohlman whistle".

- **Functional Polymer Technology**

Functional polymers enhance the dissolution rate of poorly soluble drugs by avoiding the lattice energy of the drug crystal, which is the main barrier to rapid dissolution in aqueous media. These polymers are ion exchange materials which contain basic or acidic groups that interact with the ionizable molecules of the surrounding medium and exchange their mobile ions of equal charge with surrounding medium reversibly and stoichiometrically. The resultant complex, known as, "Resinate", can be formulated as a suspension, dry powder or tablet. The resins are insoluble and not absorbed into the body and the drug is released from resinate on exposure to the physiological fluids.

- **Controlled Precipitation Technology**

In this process, the drug is dissolved in a water miscible organic solvent and then dissolved into aqueous medium containing stabilizers (HPMC, cellulose ethers, gelatin). The solvent dissolves in water and causes precipitation of the drug in the form of micro-crystals. The stabilizers control particle growth and enhance the dissolution rate of poorly soluble drug due to large surface area hydrophilized by the adsorbed stabilizer. For e.g. nanomorph, a patented technology by Solids for controlled crystallization of drugs.

- **Evaporative Precipitation in Aqueous Solution (EPAS)**

The EPAS process utilizes rapid phase separation to nucleate and grow nanoparticles and microparticles of lipophilic drugs. The drug is first dissolved in a low boiling point organic solvent. This solution is pumped through a tube where it is heated under pressure to a temperature above the solvents boiling point and then sprayed through a fine atomizing nozzle into a heated aqueous solution. Surfactants are added to the organic solution and aqueous solution to optimize particle formation and solubilization. The solubility of danazol was enhanced by this technique.

- **Use of Precipitation Inhibitors**

A significant increase in free drug concentration above equilibrium solubility results in supersaturation, which can lead to drug precipitation or crystallization. This can be prevented by use of inert polymers such HPMC, PVP, PVA, PEG etc. which act by one or more of the following mechanisms.

Increase the viscosity of crystallization medium thereby reducing the crystallization rate of drugs. Provide a stearic barrier to drug molecules and inhibit crystallization through specific intermolecular interaction on growing crystal surfaces. Adsorb onto faces of host crystals, reduce the crystal growth rate of the host and produce smaller crystals.

- **Solvent Deposition**

In this method, the poorly aqueous soluble drugs is dissolved in an organic solvent like alcohol and deposited on a inert, hydrophilic, solid matrix such as starch or microcrystalline cellulose followed by evaporation of solvent. Enhancement of dissolution rate of piroxicam using liquisolid compacts is an example illustrating this technology. The dissolution rate of a poorly soluble drug indomethacin was enhanced using liquid solid compacts.

- **Precipitation**

In this method, the poorly aqueous soluble drug is dissolved in a suitable organic solvent followed by its rapid mixing with a non-solvent to effect precipitation of drug in nanosize particles. The product so prepared is also called as “Hydrosol”. Hydrosols are colloidal aqueous suspensions containing drug nanoparticles of poorly water-soluble drugs for intravenous administration. They are prepared by a precipitation process as the drug solution is mixed with a relatively high volume of water (96–98% water after mixing) in the presence of stabilizing agents such as poloxamer and modified gelatins, which act as “short term

stabilizers". After precipitation, the amorphous hydrosol is stable for approximately 60 min because of the stabilizers and the high amount of non-solvent. After this time, the drug crystallizes. Because the clouding correlates with the particle size, crystallization and particle growth can be observed by a steep increase of absorbance at a wavelength where the drug substance does not absorb. Thus, for durable stabilizing the amorphous nanosized drug, the hydrosol is immediately spray dried with excipients such as lactose or mannitol before crystallization occurs. Before use, the preparations are reconstituted with water. Hydrosols contain the drug in a particle size of approximately 200 nm and are thus suitable for parenteral application. An example is cyclosporin, which can be formed as a hydrosol (ratio drug: gelatin = 1: 20).

2. Newer and novel techniques

Newer and novel drug delivery technologies developed in recent years for solubility enhancement of insoluble drugs are Size reduction technologies, Nanoparticle Technology, Nanocrystal Technology, Nanosuspension Cryogenic Technology, Supercritical Technology, Lipid based delivery system, Microemulsion Technology, Self Dispersing Lipid Formulation (SDLF), Micellar technologies, Mixed Micelle, Polymeric Micelle, Porous Microparticle technology.

- **Size Reduction Technologies**

Nanoformulations are one of the more complex formulations. Not only must the drug particles be rendered into nanosized but they must also be stabilized and formulated rigorously to retain the nature and properties of the nanoparticles.

- **Lipid based delivery system**

Lipid-based formulations have been shown to enhance oral absorption of lipophilic drugs.

- **Self Dispersing Lipid Formulation (SDLF)**

The SDLFs contain oil and a surfactant mixture into which the drug is incorporated. They emulsify when mixed with aqueous environment.

- **Micellar Technologies**

Mixed Micelles In general, amphiphilic, ionic, anionic or ampholytic molecules, which are able to decrease the surface tension of a solvent, arrange in micelles above a certain critical concentration. Micelle formation can only occur above a certain solute concentration, the

critical micellar concentration (CMC), and at solution temperatures above the critical micellar temperature (CMT).

- **Polymeric Micelles**

Amphiphilic polymers assemble into nanoscopic supramolecular core-shell structures, termed polymeric micelles. The block copolymers used for formation of polymeric micelles are Pluronics®, poly (ethylene glycol) (PEG)-phospholipid conjugates, PEG-b-poly (ester), and PEG-bpoly (Lamino acids).

- **Porous Microparticle Technology**

The poorly water soluble drug is embedded in microparticles having a porous, water soluble, sponge like matrix. When mixed with water, the matrix dissolves, wetting the drug and leaving a suspension of rapidly dissolving drug particles. This is the core technology applied as HDDS™ (Hydrophobic Drug Delivery System).

3. Solid dispersion system

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" (31). 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 matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles.

Types of Solid Dispersion System

Based on their molecular arrangement, six different types of solid dispersions can be distinguished.

- **Simple Eutectic Mixture**

When a mixture of A and B with composition E is cooled, A and B crystallize out simultaneously, whereas when other compositions are cooled, one of the components starts to crystallize out before the other. Solid eutectic mixtures are usually prepared by rapid cooling of a co-melt of the two compounds in order to obtain a physical mixture of very fine crystals of the two components. When a mixture with composition E, consisting of a slightly soluble drug and an inert, highly water soluble carrier, is dissolved in an aqueous medium, the carrier will dissolve rapidly, releasing very fine crystals of the drug. The large surface area of the

resulting suspension should result in an enhanced dissolution rate and thereby improved bioavailability.

- **Solid Solution Continuous Solid Solution**

In a continuous solid solution, the components are miscible in all proportions. Theoretically, this means that the bonding strength between the two components is stronger than the bonding strength between the molecules of each of the individual components.

- **Discontinuous Solid Solution**

In the case of discontinuous solid solutions, the solubility of each of the components in the other component is limited. Below a certain temperature, the mutual solubilities of the two components start to decrease. It has been suggested by Goldberg that the term `solid solution' should only be applied when the mutual solubility of the two components exceeds 5%. Whether or not a given solid solution can be utilized as a dosage form strategy will depend not only on the mutual solubilities of the two components but also on the dose of the drug component. The upper limit for the mass of a tablet or capsule is about 1 g.

- **Substitutional Crystalline Solid Solution:**

Classical solid solutions have a crystalline structure, in which the solute molecules can either substitute for solvent molecules in the crystal lattice or into the interstices between the solvent molecules. Substitution is only possible when the size of the solute molecules differs by less than 15% or so from that of the solvent molecules.

- **Interstitial Crystalline Solid Solution**

In interstitial solid solutions, the dissolved molecules occupy the interstitial spaces between the solvent molecules in the crystal lattice. To occupy interstitial space, the solute molecules should have a molecular diameter that is no greater than 0.59 of the solvent molecule's molecular diameter. Furthermore, the volume of the solute molecules should be less than 20% of the solvent.

- **Amorphous Solid Solution**

In an amorphous solid solution, the solute molecules are dispersed molecularly but irregularly within the amorphous solvent. Using griseofulvin in citric acid, it was the first attempt to report the formation of an amorphous solid solution to improve a drug's dissolution properties. Other carriers that were used in early studies included urea and sugars such as

sucrose, dextrose and galactose. More recently, organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives have been utilized for this purpose.

- **Glass Solution and Glass Suspension**

A glass solution is a homogenous, glassy system in which a solute dissolves in a glassy solvent. The glassy or vitreous state is usually obtained by an abrupt quenching of the melt. It is characterized by transparency and brittleness below the glass transition temperature (Tg). On heating, it softens progressively and continuously without a sharp melting point.

CONCLUSION

A drug administered in solution form immediately available for absorption and efficiently absorbed than the same amount of drug administered in a tablet or capsule form. Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate determining step for oral absorption of the poorly water soluble drugs, which can subsequently affect the in vivo absorption of drug. Currently only 8% of new drug candidates have both high solubility and permeability. Because of solubility problem of many drugs the bioavailability of them gets affected and hence solubility enhancement becomes necessary. It is now possible that to increase the solubility of poorly soluble drugs with the help of various techniques as mentioned above.

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