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REVIEW ARTICLE

An Overview of Solubility Enhancement Techniques

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ABSTARCT
Solubility enhancement of Glibenclamide, a poorly water-soluble drug, utilizing beta cyclodextrin (β-CD). Glibenclamide is commonly used for the treatment of type 2 diabetes, but its low solubility poses challenges in formulation and drug delivery. β-CD, a cyclic oligosaccharide, has gained significant attention as a solubilizing agent due to its ability to form inclusion complexes with hydrophobic drugs. Various techniques including physical mixing, co-grinding, kneading, and freeze-drying have been explored to prepare Glibenclamide-β-CD inclusion complexes. The characterization, solubility enhancement mechanisms, and potential applications of these complexes in improving the bioavailability and therapeutic efficacy of Glibenclamide.
Keywords: *Solubility enhancement, glibenclamide, βcyclodextrin, bioavailability.*

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INTRODUCTION

Solubility is the property of substance in a particular solvent. In quantitative terms, it is the concentration of dissolved solute in a saturated solution at a specific temperature. In qualitative terms it means continuous interaction of two or more compounds to form single phase/ clear homogeneous molecular dispersion. It is measured as the maximum amount of solute dissolved in a solvent at equilibrium. The resulting solution is called a saturated solution. Drug solubility is the maximum concentration of the drug/solute dissolved in the solvent under the specific condition of temperature, pH, and pressure. The drug solubility in a saturated solution is a static property whereas the drug dissolution rate is a dynamic property that relates more closely to the bioavailability rate. The solubility of a drug is described in various descriptive terms which are based on the amount of drug dissolved in the solvent and discussed in Table No 1.

Table No. 1: Solubility in terms of Parts of Solute

S. No	Solubility	Parts of solvent needed to dissolve one part of solute
1.	Very soluble	under1- 2
2.	Freely soluble	1to10
3.	Soluble	10 to 30
4.	Spraringly soluble	30 to 100
5.	Slightly soluble	100 to1000
6.	Very slightly soluble	1000 to 10000
7.	Practically insolvable	>10000

BIOPHARMACEUTICS CLASSIFICATION SYSTEM

It was developed by the US Food and Drug Administration (FDA) and is used to divide drugs into four types based on solubility and permeability **(Table No. 2)**. As per this classification, Class II and Class IV experience low solubility, with dissolution acting as the rate-limiting step for drug absorption.

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 within 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 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, and due to this reason, a correlation between In vivo bioavailability and invitro dissolution rate may be observed.

e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine

Class III - High Solubility, Low Permeability

In this class 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 gastric 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.

Table No. 2: BCS Classification of Drug

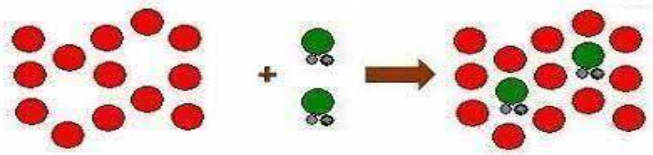
Class	Solubility	Permeability	Drugs
I	High	High	β-blockers- Propranolol, Metoprolol
II	Low	High	NSAID`S- Ketoprofen, Carbamazepine
III	High	Low	β-blockers-Aatenolol, H_2 antagonist-Ranitidine
IV	Low	Low	Diuretics- Hydrochlorothiazide, Frusemide

PROCESS OF SOLUBILIZATION

The process of solubilization involves the breaking of inter-ionic or intermolecular bonds in the solute, the separation of the molecules of the solvent to provide space in the solvent for the solute, interaction between the solvent and the solute molecule or ion.

Step 1: Holes opens in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3: The freed solid molecule is integrated into the hole in the solvent

Figure No. 1: Process of Solubilization

IMPORTANCE OF SOLUBILITY

Most of the dosage form are significantly impacted by solubility. Solubility is the one of the most crucial factors used in reaching the necessary drug to the systemic circulation and is used to get necessary pharmacological response. Poorly water-soluble medicines need high doses after oral delivery to reach therapeutic plasma levels. Low aqueous solubility is the main issue with creating novel chemical entities and genetic materials. As water is the most widely used solvent, any chemical that must be absorbed should in form of aqueous solution at the absorption site. The majority of drugs have low solubility in water and are either weakly basic or moderately acidic.

TECHNIQUES FOR SOLUBILITY ENHANCEMENT

Various techniques are used to improve the solubility of poorly soluble drug. There are some traditional and novel techniques to increase the solubility are mentioned in **Figure No. 2**.

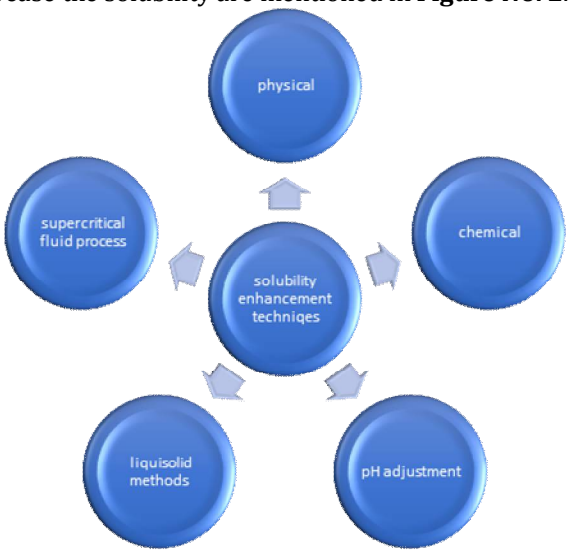


Figure No. 2: Classification of Solubility Enhancement Techniques

PHYSICAL MODIFICATION

Particle size reduction like micronization and nano suspension, drug dispersion in carriers like eutectic mixtures, solid dispersions, solid solutions and cryogenic techniques are the some of the methods under this class which can be used for solubility enhancement.

Particle Size Reduction

The drug's solubility and particle size are very important to get better solubility of the drug. By lowering particle size, more surface area is created, which enhances the drug's ability to dissolve. For poorly soluble medicines, bioavailability is frequently correlated with drug particle size. Colloid milling, jet milling, and other milling processes are used to reduce particle size.

Micronization: This process is used to accelerate the drug dissolution rate by reducing the particle size and by enhancing the particle surface area. These procedures were used to increase the bioavailability, digestive absorption, and therapeutic effectiveness of certain drugs like progesterone, fenofibrate, griseofulvin, and spironolactone.

Nanosuspension: Drugs that are poorly soluble and insoluble in water and oils are treated using this method. Nanosuspension is a biphasic system made up of nanoparticles suspended in water. Particle size distribution of solid particles in nano suspension is typically less than one micron. Nano size medication particles are stabilised by surfactant. They can be used to formulate parenteral, pulmonary ,oral and tropical dosage forms use. The preparation of nanosuspension can be done in a number of ways, including Nanocrystals, Nanopore, and Nano edge. solubility of some drugs like buparvaquone, atovaquone, amphotericin & paclitaxel, and tarazepide were enhanced by this method..

Drug Dispersion in Carrier

Solid Solution: In a solid solution, the two components crystallize together in a homogeneous one phase system. The particle size of the drug in the solid solution is reduced to its molecular size responsible for increase in dissolution rate. On the extend of miscibility of two components, solid solution is classified as continuous and discontinuous. In continuous solid solution, the two components are miscible in the solid state in all proportions. In discontinuous solid solutions, the solubility of each of the components in the

other component is limited. It produces a significantly higher rate of dissolution than a simple intestinal system.

Solid Dispersion (SD): Solid dispersion is a helpful pharmaceutical approach for increasing the rate of medication dissolution, absorption, and therapeutic efficacy is solid dispersion. The phrase "solid dispersion" describes a collection of solid products that typically includes a hydrophilic matrix and a hydrophobic medication. Polyvinyl pyrrolidone, plasdone-S630, surfactant and polyethylene glycols are often utilised hydrophilic carriers. The solid dispersions (SDs) depict one of the most interesting approaches since it presents a reduced particle size, improved wettability and solubility, high porosity, and enhanced drug stability. It can be defined as a dispersion of one or more active moiety in a suitable inert carrier or matrix in a solid-state. . Examples include Docusate sodium, Myrj-52, Tween-80, Sodium lauryl sulphate, and Pluronic-F68. To increase the solubility, this procedure was used with halofantrine, celecoxib, and ritonavir.

Fusion process: In this process, carrier is heated to its melting point, and the drug is absorbed into the matrix while the mixture is constantly stirred. The mixture is then cooled to spread the drug throughout the matrix.

Solvent evaporation method: The carrier and active component are dissolved in a suitable organic solvent. A solid residue is created by the solvent evaporating at a high temperature and vacuum. Chloroform, ethanol, or a combination of dichloromethane and ethanol are typical solvents.

Solubilisation by Surfactants

Microemulsion: A microemulsion is an isotropic translucent system that is optically clear, transparent, thermodynamically stable. It contains a combination of oil, surfactant, and hydrophilic solvent to dissolve drugs that are poorly soluble in water. Surfactant was selected basing on its HLB value and non-toxicity. The formulations self-emulsify when they come into contact with water, creating a transparent emulsion of tiny, homogenous oil droplets that contain the solubilized, weakly soluble drug. Microemulsions have been used to add proteins for oral, parenteral, and intravenous delivery as well as to increase the solubility of several drugs that are almost insoluble in water. The formulation works best is an oil-in-water (o/w), which aims to increase solubility by converting molecules with low water solubility into those with high solubility in the oil phase.

Complexation

Cyclodextrins have been complexed with drugs to increase their water solubility and stability. The most popular -cyclodextrin derivatives with better water solubility are employed in medicinal formulations. In addition to their use in enhancing solubility, CDs can also be used as stabilisers and agents that increase membrane permeability. The permeability through biological membranes is improved by the presence of cyclodextrins.

CHEMICAL MODIFICATION

Solubility enhancement of insoluble drugs can also be achieved by chemical modification like Hydrotropy, Co-Solvency, Nanotechnology and Salt Formation.

Hydrotrophy

In the solubilization process known as hydrotropy, a significant amount of a second solute (hydrotrope) is added to a insoluble solute to increase its solubility in water. It directly affects solubility through a process called complexation, which involves weak interaction between weakly soluble drug and hydrotropic agents such sodium alginate, sodium acetate, sodium benzoate, and urea. The hydrotropic agents are non-micelle-forming substances, either liquids or solids, organic or inorganic, capable of insoluble solubilizing compounds. Hydrotropic salts usually consist of two essential parts, anionic group, and a hydrophobic aromatic ring or ring system. The anionic group is involved in bringing about high aqueous solubility, which is a prerequisite for a hydrotropic substance.

Co-Solvency

It is also known as “Solvent blending”. It enhances the solubility of a poorly water-soluble drug by the addition of water-miscible solvent in which drug has good solubility by reducing the interfacial tension between the aqueous solution and hydrophobic solute. Poorly soluble compounds which are lipophilic or highly crystalline that have a high solubility in the solvent mixture may be suited to a co-solvent approach. It has found its main use in parenteral dosage forms because of the low toxicity of many co-solvents, and the relatively greater ability of co-solvents to solubilize nonpolar drugs. Commonly used cosolvents Glycerol, propylene glycol, PEG 400, Dimethyl Sulfoxide, Dimethyl Acetamide, Ethanol, n-octanol are the commonly used cosolvents.

Nanotechnology

Nanotechnology is the study and use of materials and structures at the nanoscale level of about 100 nanometers (nm) or less. As these products have a very small effective surface area it increases the dissolution and oral bioavailability.

Salt Formation

Salt formation approaches have widely been utilized to increase solubility, and therefore, the dissolution rate of a drug and dissolution can be improved. Salt is created when a drug is ionised. The ability of a chemical to create suitable salts depends on how basic or acidic it is and how soluble it is in water as a function of pH. It modifies the drug's stability, bioavailability, purity, and manufacturability using a variety of techniques, including physiochemical characteristics. This method has wide rage of applications in solid dosage forms and in parenteral and other liquid dose forms. 54 of the 101 approved salts of basic pharmaceuticals were made using hydrochloric acid, demonstrating that this salt form is the most prevalent. For many years, salt manufacturing has been utilised to increase the solubility of drug candidates with limited solubility. Examples are theophylline, barbiturates, and aspirin.

pH ADJUSTMENT

pH adjustment is the simplest and most commonly used method to increase the solubility of ionisable drugs. It works on the principle that natural changes in pH value within the GI tract influence the bioavailability drug. When utilising this approach to increase the solubility, the buffer capacity of the selected pH must be taken into account. The solubility of a drug is increased by alkaline excipients which raise the pH of the environment inside the dosage form. It can also be applied to poorly soluble crystalline and lipophilic compounds.

SUPERCRITICAL FLUID PROCESS

Supercritical fluids (SCFs) can dissolve non-volatile solvents near the critical point of carbon dioxide. A SCF is a single phase above its critical temperature and pressure. It is a secure, economical, and environmentally friendly process. The low working conditions (temperature and pressure) of SCFs make them attractive for pharmacological research. SCFs, which are intermediate between pure liquid and pure gas, have characteristics that are helpful to increase the solubility of products. Common supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene, propane, n-pentane, ethanol, ammonia, and water.

LIQUISOLID METHODS

Both absorption and adsorption happen when a drug dissolved in a liquid vehicle is added to a carrier material with a porous surface and fibres inside, like cellulose. Specifically, the liquid first absorbs into the interior of the particles and is captured by its internal structure, and once this process reaches saturation, the liquid adsorbs on to the internal and external surfaces of the porous carrier particles. A liquid drug can be transformed into a dry, non-adherent, free-flowing, compressible powder by mixing it with specific powder excipients, like the carrier and coating material. Silica powders, both microcrystalline and amorphous, and cellulose are used as coating materials.

SOLUBILITY ENHANCED DRUGS[29-30]

The following are the some of the reported ist of drugs whose solubility was enhanced by suitable methods

Table No. 3: List of Solubility Enhanced Drugs

Drug	Polymer	Method
Fenofibrate	PEG6000, Poloxamer 407	Melt evaporation, Lyophillization
Glipizide	PEG6000, mannitol, PVPK30	Fusion (melt) method Solvent evaporation method
Griseofulvin, Progesterone, Spironolactone Diosmin, and Fenofibrate	(Povidone, PVP), polyethylene glycols (PEGs), and PlasdoneS63031-32	Reducing particle size
celecoxib, halofantrine, and ritonavir	Poly Vinyl Pyrrolidone (Povidone, PVP), Poly Ethylene Glycols (PEGs), PlasdoneS630. Surfactants like Tween-80, docusate sodium, Myrj-52, Pluronic-F68, and sodium lauryl sulphate (SLS)31-32	Solid dispersion
Flurbiprofen	HPC	Solvent evaporation method
efavirenz	PEG 6000	Solvent evaporation method
chlordiazepoxide	PVP K 30	Co -precipitaton

CARRIERS FOR SOLUBILITY ENHANCEMEN

Carriers, which are soluble and dissolve in water at a fast rate, are widely used in pharmaceutical formulations to enhance solubility and dissolution of drugs. Various carriers are used for solubility enhancement listed mentioned in the table 4.

Table No. 4: List of carriers used for solubility enhancement.

Category	Examples of carrier
Polymeric materials	Povidone (PVP), Poly Ethylene Glycol (PEG), Cyclodextrin, Hydroxypropyl Methyl Cellulose, mMethyl Cellulose, Hydroxy Ethyl Cellulose, Hydroxy Propyl Cellulose.
Acid	Citric acid, Succinic acid.
Miscellaneous	Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride
Hydrotrops	Urea, Sodium acetate, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium-o-hydroxy benzoate.
Sugars	Dextrose, Sucrose, Galactose, Sorbitol, Maltose, Mannitol, Lactose.
Surfactants	Deoxycholic acid, Tweens, Spans, Polyoxyethylene stearate, Poloxamer
Insoluble or enteric polymer	Eudragit L100, Eudragit S100, Eudragit RL, Eudragit RS, Hydroxy propyl methyl cellulose phthalate

CONCLUSION

The solubility of the drug is the most important factor that decides the formulation of the drug as well as therapeutic efficacy of the drug for quantitative analysis. Dissolution of drugs is the rate determining step for oral absorption of the poorly water-soluble drugs and solubility is also the fundamental requirement for the formulation and development of different dosage forms of different drugs. The choice of any method for increasing solubility is determined by the drug's nature and properties, such as physical nature, chemical nature, pharmacokinetic and so on. With the use of various technical procedures, such as those mentioned above, it is now possible to enhance the solubility of poorly soluble drugs.

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