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GLIPIZIDE (POORLY WATER SOLUBLE DRUG) – ENHANCEMENT OF SOLUBILITY BY VARIOUS SOLUBILIZATION TECHNOLOGY

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ABSTRACT

Glipizide is an oral, rapid and short acting anti diabetic drug. It is classified as a second generation sulfonylurea. It is used for treatment of type-II diabetes mellitus. Its BCS Class-II drug. Due to poor solubility of drug, its bioavailability rate is limited by drug dissolution. Improve the solubility of drug we are using different solubility method such as solid dispersion method, hydrotrophy and micellar solubilization. Solid dispersion, describe as the dispersion of one or more active pharmaceutical ingredient in a carrier at solid state and an efficient technique to increase solubility of poorly water-soluble drug to enhance their bioavailability. Hydrotrophy refers to increasing the water solubility of drug by hydrotrophy agent(Urea, Surfactant, Alkaloids). Micellar solubilization. The use of surfactant to improve the dissolution performance of poorly soluble drug products. Surfactant reduce surface tension and increase the solubility of lipophilic drug in aqueous medium.

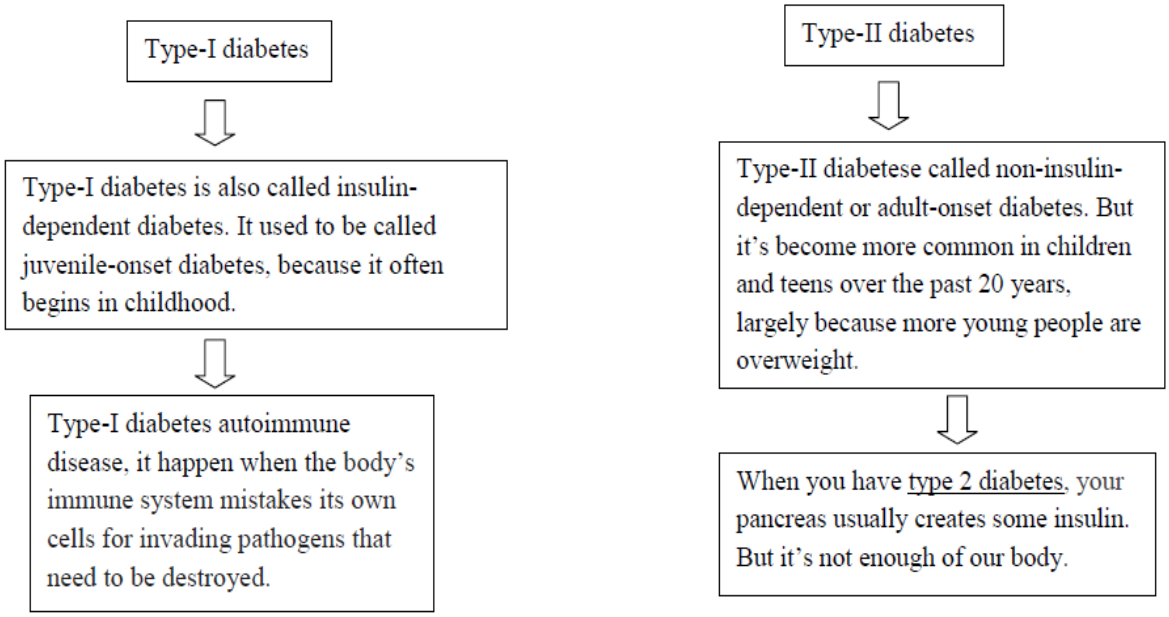
KEYWORDS: Diabetes, Glipizide -drug, BCS Classification**,** Dissolution method.

INTRODUCTION

Diabetes

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentrations (hyperglycemia) caused by insulin deficiency and it is often combined with insulin resistance.

Type of diabetes



Drug- glipizide

Glipizide (GLP) is one of the most regularly prescribed drug for treatment of type-II diabetes. Its BCS (Biopharmaceutical classification of drug) class-II drug. It is an oral hypoglycaemic drug from sulfonylurea group, which means it undergoes entero-hepatic circulation and act by stimulating the release of insulin from the pancreases and hence reducing blood glucose level in human beings. GLP bind to K_{ATP} channels on the cell membrane of Pancreatic β cells of the islets of Langerhans. This leads to increased fusion of insulin granulae with cell membrane, and therefore increased secretion of insulin.

- Chemically, Glipizide (GLP) is a substituted aryl-sulphonylurea.
- Its empirical formula is $C_{21}H_{27}N_5O_4S$
- molecular weight is 445.55 gm
- IUPAC name is 1-cyclohexyl-3-[[p-[2-(5 methylpyrazinecarboxamido) ethyl] phenyl] sulfonylurea].
- It is a weak acid (pK_a = 5.9)
- short biological half-life (3.4±0.7 hr)

Glipizide: is poor water soluble drug and is practically water-insoluble but, its absolute bioavailability is close to 1 and its dissolution is considered to be rate limiting step in its absorption from gastrointestinal tract. GLP face problem of low bioavailability. Various

approaches have been suggested for designing dissolution tests for poorly water-soluble drugs. Such as:-

a) Use of large volumes of dissolution medium,
b) Removal of dissolved drug.
c) Mixed organic aqueous solvents.
d) The inclusion of surfactant.
e) Ph change.

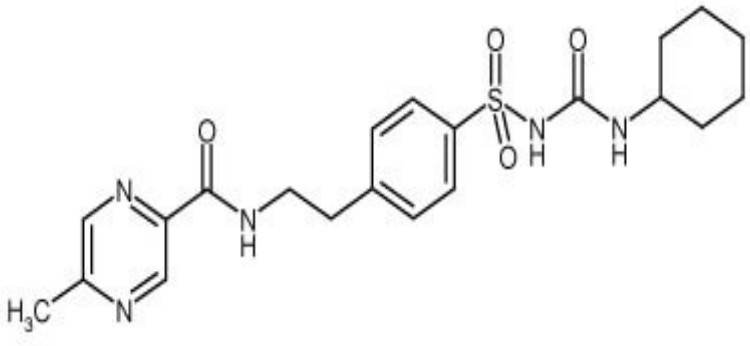


Fig. no. 1: Struture of glipizide.

Biopharmaceutics classification system

The BCS (Biopharmaceutics Classification System)-based biowaiver approach is intended to reduce the need for in vivo bioequivalence studies i.e., it can provide a substitute for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in- vivo performance could be justified by satisfactory in vitro data. The BCS is a scientific approach based on the aqueous solubility and intestinal permeability characteristics of the drug substance(s). The BCS categorizes drug substances into one of four BCS classes as follows:-

Class	Permeability/solubility	Absorption rate control step
Class-I	High/high	Gastric emptying
Class-II	High/low	Dissolution
Class-III	Low/high	Permeability
Class-IV	Case by case	Case by case

Example of some drug as per biopharmaceutics classification system.

Class-I	Class-II	Class-III	Class-IV
Chloroquine	Carbamazepine	Captopril	Ellagic acid
Diltiazem	Troglitazone	Acyclovir	Coenzyme Q10
Metoprolol	Phenytoin	Atenolol	Cyclosporin A
Propranolol	Danazol	Cimetidine	Furosemide
Paracetamol	Nifedipine	Metformin	Taxol
Verapamil	Glibenclamide	Neomycin B	Ritonavir
Theophylline	Ketoconazole	Ranitidine	Saquinavir

Solubilization technology

In 1971 Chiou and Riegelman defined solid dispersion as "A dispesion as "A dispersion of one or more active ingredient in an inert carrier or matrix at solid state prepared by solvent evaporation, melt-solvent method. When exhibit to aqueous media, the carrier is dissolved, the drug is released as fine colloidal particles. This is widely used to increase intrinsic solubility or dissolution and stimulate the bioavailability of drug. Many carriers can be used for solid dispersion method which includes polyethylene glycol, urea, mannitol etc. Novel method used for prepration such as super critical fluid technology, electrospining, spray drying, lyophilization and melt extrusion method.

- **Types of solid despersion**

Solid dispersion solid state

1. Two phase solid system

(a) Eutectic mixture

(b) Crystalline drug amorphous carrier

(c) amorphous drug amorphous carrier

2. Single phase solid system

(a) crystalline

i. Substitutional

ii. Interstitial.

1916, Neuberg in first introduced the concept of hydrotropy.

Hydrotropy may be defined as a phenomenon in which water solubility of poorly water soluble drug may be increased several folds by use of diverse groups of hydrophilic solute called hydrotropes. This method can be conveniently applied to broad range of water insoluble compound. Hydrotropes such as sodium benzoate, sodium acetate, sodium

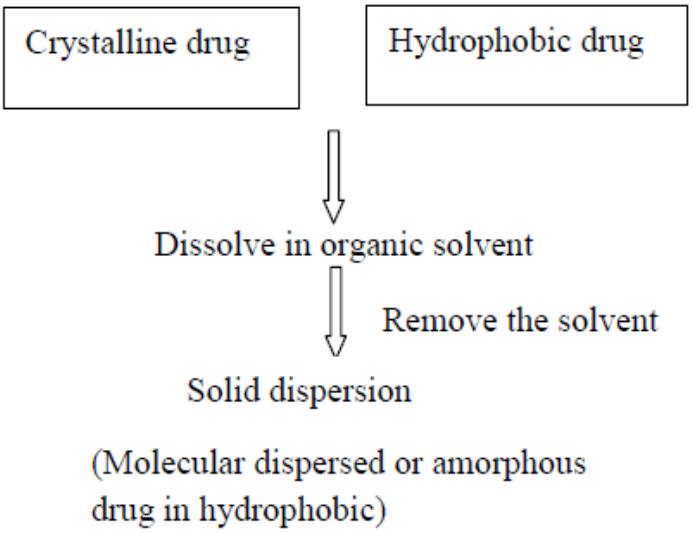
salicylate, nicotinamide, tri-sodium citrate, urea, piperazine, caffeine etc. Hydrotropes used in increase solubility of various drug such as anti-viral, anti-inflammatory, anti-pyretic, anti-tumor, analgesic drug, and xanthine derivatives etc.

Micellar solubilisation is used as an efficient technology for solubilisation of hydrophobic drugs in aqueous environments. Solubilization can be defined as the spontaneous dissolving of a substance by reversible interaction with the micelles of a surfactant in water to form a thermodynamically stable isotropic solution with reduced thermodynamic activity of the solu bilized material. With the dvent of non-ionic surfactant their utility as solubilizing system is increased. The surfactant molecules aggregate and form micelles at particular concentration called critical micelle concentration (cmc) with formation of hydrophobic interior core and hydrophilic external environment. Some example of surfactant used for solubilization lipophilic drug such as, poloxamers, tween 80, brij 54, sodium lauryl sulphate, cremophor EL, cetrimide etc.

Solid dispersion

Method of preparation

(1) Solvent evaporation



Solvent:- solvent to be used for the formulation of solid dispersion should have following

Properties

i. Both drug and carrier should be dissolved.

ii. Toxic solvents should be avoided due to the risk of residual levels after preparation e.g. di-chloromethane, chloroform.

Some solvent to be avoided such as

Class-I

Solvent	Effect
Carbon tetrachloride	Toxic, carcinogenic, environmental hazards.
Benzene	Toxic.
1,1-dichloroethane	Toxic.
1, 1,1,-trichloroetane	Environmental hazards.
1,2- dichloroethane	Toxic.

Class-II (solvent)

Solvent
Chlorobenzene
Methanol
Cyclohexane
Pyridine

(2) Hot melt extrusion

The drug/carrier mix .

⇩ Processed with a twin screw

Drug/carrier mix is simultaneously

⇩ Homogenized and then extruded

Shaped as tablets, granules, pellets, sheet, stick and powder.

The main advantage of hot melt extrusion technique is that the drug carrier mixed only subjected to an elevated temperature for about 1 min, which enables drugs that are slightly thermolabile to be processed.

(3) Spray freeze drying

Dissolve the drug in a solvent at a fixed concentration and carrier in water.

⇩

Mix the solution in a ratio of 40/60 v/v.

⇩

Spray the solution through nozzle at about 10 cm above the liquid nitrogen.

⇩

Hot water is pumped through the jacket of the nozzle in order to avoid freezing of the solution inside the nozzle.

⇩

Finally, transfer the suspension (frozen droplet of the solution in liquid nitrogen) to the lyophilizer.

⇩

Lyophilization procedure is started also all liquid nitrogen evaporated.

Selection of carrier

A carrier should meet the following criteria to be suitable for increasing the dissolution rate of drug.

1) Non-toxic and pharmacological inert.
2) Freely water soluble with intrinsic rapid dissolution properties
3) Heat stable with a low melting point for the melt method

Carrier	Example
First generation	Crystalline carriers:-urea, sugars, organic acids.
Second generation	Fully synthetic polymers:PVP, PEG, HPMC.
Third generation	Poloxamer 80, tween 80, gelucire 44/141.

Advantage

1) Solid dispersion method is usefull to enhance solubility and bioavailability of poorly water soluble drug.
2) To reduce particle size.
3) To avoid undesirable incompatibilities.
4) To stabilize the unstable drug.
5) Improvement of drug release from ointment, creams, and gels.
6) To mask the taste of the drug substance.
7) To prepare rapid disintegration oral tablet.

Hydrotropy

Hydrotropes with an amphiphilic molecular structure posses the ability to increase the solubility of sparingly soluble organic molecules in water. Hydrotropic agent are stated as ionic organic salt which help to increase or decrease the solubility of solute in a given solvent through 'salt in' or 'salt out' effects respectively.

Example of hydrotropic salt

Type		Example
Aromatic anionics		Sodium-benzoate, sodium salicylate, sodium benzene di-sulfonate, sodium cinnamate, N, N-dimethyl benzamide.
Aromatic cationics	Para-aminobenzoic acid hydrochloride, procaine hydrochloride.	
Aliphatic and linear compound	Sodium alkanoate, urea and N,N di-methyl urea.	
Alkaloids	Caffeine nicotinamide, N_1Ndimethylbenzamide.	
Surfactant	Sodium dodecyl sulphate.	

Mechanism of hydrotropic agent:- The increase of solubility of the poorly soluble drug by the hydrotrope is based on the molecular self-association of the hydrotrope and on the association of hydrotrope molecules with the solute. Although hydrotropic agents are widely used in various industrial applications, only periodic details on the mechanism of hydrotrophy is available. Various hypotheses and research efforts are being made to clarify the mechanisms of hydrotrophy. The available present mechanisms can be abridged according to three designs.

(a) Self- aggregation potential.

(b) Structure-breaker and structure- maker.

(c) Ability to from micelle-like structure.

A. Self-aggregation potential:- In hydrotropic solubilization method an electrostatic force of the donor-acceptor molecule plays a key role; hence, they are also termed as a structure-breaker and a structure-maker . Solutes which are capable both of hydrogen donation and acceptance help to increase solubility. Hydrotropic agents, such as urea, exert their solubilizing effect by changing the nature of the solvent, specifically by altering the solvent's ability to participate in structure formation or its ability to engage in structure formation by intermolecular hydrogen bonding.

Structure-breaker hydrotropes are known as chaotropes while structure-maker hydrotropes are known as kosmotropes. Kosmotropes reduce the critical micelle

concentration (CMC) by increasing the hydrophobic interaction which decreases the cloud point. A kosmotrope influences the cloud point in two ways, i. e, it helps to form bigger micelles.

To decrease hydration. In the case of amphiphilic drugs, promazine hydrochloride (PMZ) and promethazine, cyclodextrin act as water structure-makers and reduce cloud point.

B. **Ability to from micelle-like structures:-**This mechanism is based on the self-association of hydrotropes with solutes into a micellar arrangement. They form stably mixed micelles with a solute molecule decreasing the electrostatic repulsion between the head groups. Hydrotropic agents, such as alkyl-benzene sulfonates, lower alkanoates, and alkyl sulphates, exhibit self-association with solutes and form micelles. Aromatic anionic hydrotropic agents, i.e., nicotinamide, increase the solubility of riboflavin by a self-association mechanism. In the case of PMZ, anionic hydrotropic agents, such as sodium salicylate, form stably mixed micelles by decreasing the electrostatic repulsion between the head groups of PMZ.

C. **Fluctuation theory of solutions**:-To determine the mechanism of hydrotropic solubilization some researchers also illustrate the fluctuation theory of solutions (FTS). Fluctuation theory of solutions has recognized two main factors of hydrotrope induced solubilization:-

i. Hydrotrope solute interaction.
ii. Water activity depression.

The former is conquered by hydrotrope solute association while the later is improved by ionic dissociation and hindered by the self-aggregation of the hydrotropes.

Aside from the above-mentioned mechanism, nature and the concentration are the drawing forces for the solubilizing potential of hydrotropes.

An aromatic hydrotropic agent with a planar structure interacts with solute molecules by inducing stacking aggregation mechanisms. In aqueous solutions, caffeine exhibits parallel stacking to solubilize the riboflavin.

At higher concentrations, anionic hydrotropic agents decrease the cloud point while at low concentrations increase the cloud point. Cationic and non-ionic hydrotropes show a sheer rise

in the cloud point of amphiphilic drugs. The extent of the cloud-point variation for using different hydrotropes does variously depend on their nature and structure.

Hydrotropes in high concentrations (0.1-0.8 M) form aggregates and decrease the cloud point of amphiphilic drugs while in lower concentrations they increase the cloud point of amphiphilic drugs. The hydrotropic concentration plays an important role in the solubilization mechanism of drug molecules. Sodium benzoate and sodium salicylate, when employed to enhance the aqueous solubility of nifedipine, illustrated the complexation type of interaction at a low concentration and aggregation at a high concentration.

Hydrotropic solubilization of nimesulide exhibits molecular aggregation at higher hydrotrope concentration and weak ionic interactions at a lower hydrotrope concentration. Dexibuprofen, when combined with hydrotropic agents and investigated by the Differential scanning calorimetry (DSC) and the Infrared (IR) spectroscopy, demonstrated intermolecular interact-tions between the drug and the hydrotropic agents, which increased solubility and dissolution rate of the drug.

Advantage of hydrotropic solubilization method

- It precludes the use of organic solvents and so avoids the problem of residual toxicity, error due to volatility, pollution, cost, e.t.c.
- It is a new, simple, cost-effective, safe, accurate, precise and environmentally friendly method for the analysis of poorly water-soluble drugs by titrimetric and spectrophotometrically precluding the use of organic solvents.
- It only requires mixing the drug with the hydrotrope in water.
- Hydrotropy is suggested to be superior to another solubilization method, such as miscibility, micellar solubilization, co-solvency and salting in, because the solvent character is independent of pH, has high selectivity and does not require emulsification.

Mixed hydrotropy:- mixed hydrotropy solubilization method is the phenomenon to increase solubility of lest soluble drugs using blends of hydrotropic agent, which might give synergistic enhancement effect on solubility ofp poorly water soluble drug, and also reduce the side effect due to the reduction in the concentration of individual hydrotropic agents.

- It can reduce the large total concentration of hydrotropic agents necessary to produce a modest increase in solubility by employing a combination of agents in lower concentration.
- It is a new, simple, cost-effective, safe, accurate, precise and eco-friendly method for the analysis (titrimetric and spectrophotometric) of poorly water-soluble drugs.

Miceller solubilization

The use of surfactants to improve the dissolution of poorly soluble drug products is probably the basic, primary, and the oldest method.

Surfactants reduce surface tension and improve the dissolution of lipophilic drugs in aqueous medium. They are used to stabilize drug suspensions too. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05–0.10% for most surfactants), micelle formation occurs which entrap the drugs within the micelles. This is known as micellization and generally results increase solubility of poorly soluble drugs.

Surfactant improves wetting of solids and increases the rate of disintegration of solid into finer particles too. Commonly used nonionic surfactants include polyoxyethylated castor oil, polyoxyethylated glycerides, polysorbate, lauroyl macroglycerides, and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize microemulsions and suspensions into which drugs are dissolved.

Examples of poorly soluble compounds that use Micellar solubilization are antidiabetic drugs, gliclazide, glyburide, glimepiride, glipizide, repagliniide, pioglitazone, and rosiglitazone.

Application of miceller solubilization

Drug delivery application:- Focused of the following area:-

1. Delivery of antifungal agent.
2. delivery of anti-cancer agent.
3. delivery of imaging agent for diagnostic application.
4. drug delivery to the brain to treat neurodegenerative disease.
5. deliver of polynucleotide therapeutics.

CONCLUSION

In this article we have conclude that glipizide drug used in treatment of type-II diabetes. Glipizide (BCS class-II) is poorly soluble drug.

Improve the solubility of drug we are used various solubilization techniqiue such as solid dispersion, hydrotropy, miceller solubilization.

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