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Studies on Formulation and optimization of Gastro Retentive multi-Particulates of Glibenclamide and Metformin hydrochloride for the treatment of Type II Diabetes mellitus using Gelucire: A Review.

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Abstract:
In order to increase the bioavailability of poorly soluble drug as well as highly soluble drug, the residence time of the orally administered dosage form in the upper GIT needs to be prolonged. Gelucire are used as carrier for designing low density floating drug delivery system. Glibenclamide is a low dose, poorly soluble drug with possible content uniformity problems and dissolution rate-limited bioavailability while Metformin HCl ranges from 0.5-2.5 gm per day divided in two or three doses taken with meals. Plasma half life is 1.7 –4.5 hrs and absolute bioavailability is 50-60%. There has been contradictory report on the utilization of metformin HCl in single unit gastroretentive dosage form.
Keywords: Gelucire, Glibenclamide, Metformin hydrochloride, Floating Multiparticulates, Hot melt techniques.

Introduction:

Oral ingestion is the predominant and most preferable route for drug delivery because of their systematic effects such as patient acceptance, convenience in administration, and cost effective manufacturing process. In the human body the residence time of orally administered dosage form in the stomach is generally short due to rapid gastric empting. Rapid gastro intestinal transit could result in incomplete drug release from the orally administered dosage form above the absorption zone leading to diminished efficacy.[1]

In order to increase the bioavailability of such drugs, the residence time of the orally administered dosage form in the upper GIT needs to be prolonged. The main approaches to prolonging the gastric residence time of pharmaceutical dosage forms include bioadhesive drug delivery system, which adhere to mucosal surface; devices that rapidly increase in size once they are in stomach to retard the passage through the pylorus; and density control delivery system, which float on gastric fluid.[2,3,4,5]

Recently, much attention has been focused on the use of fats and fatty acid as carriers in drug delivery systems. Kumar et al. [6] demonstrated the use of amphiphilic lipid glyceryl monooleate for the design of floating matrix system. Gelucire is the family of vehicle derived from mixtures of mono-, di- and tri-glycerides with PEG esters of fatty acids. These are available with range of properties depending on their HLB and melting point range (33- 65^{0}C). They have a wide variety of application in pharmaceutical formulations. These are used in the preparation of fast release and sustained release formulations. Gelucire containing only PEG esters are generally used in the preparation of fast release formulation. Gelucire containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 39/01, 43/01) are used in the preparation of sustained release formulation. Owing to their extreme hydrophobicity and low density, Gelucire 39/01and 43/01 may be considered an appropriate carrier for designing sustained release floating drug delivery system. [7]

Glibenclamide, an oral hypoglycemic of the sulphonyl urea group and Metformin hydrochloride, antidiabetic agent of biguanide group, are used in the management of type 2 diabetes mellitus (non insulin dependent, NIDDM). Glibenclamide works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells and increasing the release of insulin upto serum glucose level by triggering an increase in intracellular calcium into the β cells of pancreas. Metformin acts by

decreasing hepatic glucose production, intestinal absorption of glucose and improves insulin sensitivity.

Glibenclamide is a low dose, poorly soluble drug with possible content uniformity problems and dissolution rate-limited bioavailability. The therapeutic dose of Glibenclamide is 5- 15 mg daily, with low bioavailability and half life around 10 hrs while Metformin HCl ranges from 0.5-2.5 gm per day divided in two or three doses taken with meals. Plasma half life is 1.7 –4.5 hrs and absolute bioavailability is 50-60%. There has been contradictory report on the utilization of metformin HCl in single unit gastroretentive dosage form [8, 9], However, bioavailability of drug has been found to reduce further with CR dosage form probably due to the fact that passage of the CR single unit dosage form of the drug is faster than its release and most of the drug releases at the colon, where Metformin HCl is poorly absorbed. [10,11], therefore, it is desirable to improve the earlier studies by formulating Glibenclamide and Metformin HCl in multiparticulate floating system in order to optimize the pharmacokinetic and pharmacodynamic of drug and using them in combination form.

Rationale of Combinations of the Sulfonlyureas and the Biguanides are [12] *:*

Both are major oral antidiabetics. The sulfonylureas, such as Glibenclamide act by stimulating the secretion of insulin. Their targets are insulin-producing pancreatic β cells and the biguanides, such as Metformin, inhibit glycogenesis and increase the peripheral use of glucose. The biguanides can only be active in the presence of endogenous insulin. Since the introduction of the various antidiabetic medicaments, doctors prescribe in particular oral treatments of diabetes which combine these various products, that forces patients to take these combinations of medicaments several times per day. Unavoidably, low compliance is then observed on the part of the patients, who are often elderly persons. Under these conditions, oral treatments do not have the expected effects and the patients suffer serious complications. Thus, compliance is a fundamental parameter for the efficacy of the treatment (prevention of serious disorders caused by hyperglycemia and survival of the patient). By improving compliance, dosage errors and their deleterious effects would be limited. Since sulfonylureas are capable of stimulating insulin release, but are not capable of acting on insulin resistance, and biguanides are able to act on insulin resistance, whereas they are not able to stimulate insulin secretion, the therapeutical rationale suggest the use of combined formulations of medicaments capable of finding a remedy for both the deficiency in insulin secretion and the insulin-resistance condition. At present 4 combinations are marketed which use a combination of metformin with glibenclamide.

1.Glucomide Lipha- Glibenclamide & Metformin (2.5 mg) (500 mg)

2.Glibomet Guidotti-Glibenclamide & Metformin (2.5 mg) (400 mg)

3.Suguan M Hoechst -Glibenclamide & Metformin (2.5 mg) (400 mg)

4. Bi-Euglucon M Boehringer M - Glibenclamide & Metformin (2.5 mg) (400 mg)

Solubility Enhancement techniques for Glibenclamide:

Solubility enhancement of poorly aqueous soluble drug is an important aspect of formulation development. Although there is plethora of reports of solubility improvement using different techniques, a comparative study of different solubilization approaches are few. Thus, the study generated an important dataset so as to compare effect of various solubilizers on solubility of Glibenclamide. Aqueous solubility of any therapeutically active

substance is a key property as it governs dissolution, absorption and thus the efficacy *in vivo* .Solubilization may be defined as the preparation of a thermodynamically stable solution of a substance that is normally insoluble or very slightly soluble in a given solvent, by the introduction of one or more amphiphilic component(s). Solubilization of poorly aqueous soluble drug forms an important activity in formulation process.

Solubility profile with water-cosolvent systems such as PEG-400 and PEG-600 showed exponential increase in solubility with increase in cosolvent fraction. The increment in solubility was found to be 80-fold and 59-fold for PEG 400 and PEG 600 at 25% cosolvent level.

Solid dispersion technique was selected as it was utilized in a limited number of researches to increase the solubility of Glibenclamide. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent, or solvent-fusion methods. It has been widely used to improve the dissolution rate, solubility and oral absorption of poorly water-soluble drugs. In solid dispersions, the particle size of the drugs was reduced, the wettability and the dispersibility were enhanced; therefore, drug dissolution was improved markedly.

PEG and Gelucire are among the several carriers which have been employed in preparing solid dispersions PEG polymers are widely used for their low melting point, low toxicity, wide drug compatibility and hydropholicity. Gelucire is a family of vehicles derived from the mixtures of mono-, di- and triglycerides with polyethylene glycol (PEG) esters of fatty acids. These are available with a range of properties depending on their hydrophilic– lipophilic balance (HLB) and melting point range (33–65 _C). They have a wide variety of applications in pharmaceutical formulations as the preparation of fast release and sustained release formulations.

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