Gelucire: An alternative formulation technological tool for both sustained and fast release of drugs in treating diabetes mellitus type II disease

Prashant Upadhyay¹*, Jayanta Kumar Pandit² and Arun Kumar Wahi ²

¹Department of Pharmaceutics, College of Pharmacy, IFTM, Moradabad-244001, (U.P)-India
²Department of Pharmaceutics, I.T-B.H.U. Varanasi-221010, (U.P)-India

Received 2 August 2012; revised 20 March 2013; accepted 6 August 2013

Gelucire is the family of vehicle derived from mixtures of mono-, di- and tri-glycerides with PEG esters of fatty acids. They have a wide variety of application in pharmaceutical formulations. These are used in the preparation of fast release and sustained release formulations. In order to increase the bioavailability of 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 includes density control delivery system, which float on gastric fluid and an asset to treat Diabetes type II. Gastro retentive solid dispersion could be achieved of poorly soluble drug Glibenclamide with the help of polyethylene glycol and Gelucire 50/13. On the other hand sustained release gastroretentive multiparticulates of metformin hydrochloride could be achieved using Gelucire 39/01 and 43/01 grades. Further both formulations can be explored individual as well as in combination for improved bioavailability by their pharmacokinetic and pharmacodynamic evaluation in wistar rats.

Key words: Gelucire, Gastro retentive multiparticulates, Metformin, Glibenclamide, Solid dispersion.

Introduction

Diabetes is one of the major causes of death and disability in the world. The global figure of people with diabetes is set to rise from the current estimate of 150 million to 220 million in 2010 and 300 million in 2025. Most cases will be of type II diabetes, due to sedentary lifestyle and obesity¹.

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 emptying. Rapid gastrointestinal transit could result in incomplete drug release from the orally administered dosage form above the absorption zone leading to diminished efficacy².

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 fluid³-⁶.

Recently, much attention has been focused on the use of fats and fatty acid as carriers in drug delivery systems⁷,⁸,⁹. The use of amphiphilic lipid glyceryl monooleate for the design of floating matrix system¹⁰. 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°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. Owing to their extreme hydrophilicity and low density, Gelucire 50/13 may be considered an appropriate carrier for designing fast release floating drug delivery system¹¹. 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 are considered as appropriate carriers for designing sustained release floating drug delivery system¹²,¹³,¹⁴.
Gastric floating drug delivery system (GFDDS) is particularly useful for drugs that are primarily absorbed in the duodenum and upper jejunum segments 15. The GFDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug 6.

Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestine. Lipids are considered as alternative to polymers in the design of controlled drug delivery systems due to their advantages like (a) low melt viscosity, thereby obviating the need of organic solvents for solubilization, (b) the absence of toxic impurities such as residual monomers catalyst and initiators, and (c) the potential biocompatibility and biodegradability and prevention of gastric irritation by forming a coat around the drug 7.

A plethora of antidiabetic drugs are used, of which Glibenclamide and Metformin hydrochloride is a very widely accepted combination of drugs 16. The rationale of Combinations of the Sulfonylureas and the Biguanides is 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 i.e. Glucomide Liphra- Glibenclamide & Metformin (2.5 mg) (500 mg), Glibomet Guidotti-Glibenclamide & Metformin (2.5 mg) (400 mg), Suguan M Hoechst - Glibenclamide & Metformin (2.5 mg) (400 mg) and Bi-Euglucon M Boehringer M-Glibenclamide & Metformin (2.5 mg) (400 mg) 17.

The ability of lipid-based formulations to facilitate gastrointestinal absorption of many poorly soluble drug candidates has been thoroughly documented in the published literature. However, a considerable gap exists between our knowledge of this technology and the know-how required for its application. This commentary provides a comprehensive summary of the development, characterization, and utilization of oral lipid-based formulations, from both physicochemical and biopharmaceutical perspectives. The characteristics of currently available lipid excipients are reviewed in context of their application to the basic lipid-based formulation modalities 7. Development of new drug entities is posing real challenge to formulators, particularly due to their poor aqueous solubility which in turn is also a major factor responsible for their poor oral bioavailability. Lipids as carriers, in their various forms, have the potential of providing endless opportunities in the area of drug delivery due to their ability to enhance gastrointestinal solubilization and absorption via selective lymphatic uptake of poorly bioavailable drugs. These properties can be harvested to improve the therapeutic efficacy of the drugs with low bioavailability, as well as to reduce their effective dose requirement 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
dispersions and recent advances related to the area of solid dosage forms. In this review, it is intended to discuss the formulations, thus avoiding drug recrystallization and hence improving drug wettability, bioavailability, and oral bioavailability of poorly water-soluble drugs. By reducing drug particle size to the absolute minimum, the solubility of Glibenclamide. Solid dispersions are utilized in a limited number of researches to increase the solubility of Glibenclamide. Solid dispersions of glibenclamide (poorly water-soluble drug) is an important aspect of formulation development. Although there is a 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. Solid dispersions of glibenclamide (poorly water-soluble drug) and polyglycolized glycerides (Gelucire®) with the aid of silicon dioxide (Aerosil® 200); as an adsorbent, were prepared by spray drying technique. Solid dispersions and spray dried glibenclamide in comparison with pure glibenclamide and corresponding physical mixtures were initially characterized and then subjected to ageing study up to 3 months. Initial characterization of Solid dispersions and spray dried glibenclamide by DSC and XRPD showed that glibenclamide was present in its amorphous form (AGBM). Glibenclamide is a second-generation orally administered sulphonylurea derivative with potent hypoglycemic activity. Use of low melting point excipients like polyethylene glycols (PEG) and polyglycolized glycerides have been used widely as excipients in solid dispersions. These excipients have shown to cause faster drug dissolution by improving wettability of the drug particles, significant reduction in particle size during the formation of solid dispersions or the inherently higher rate of dissolution of the soluble component of solid dispersions, which would pull along the more insoluble but finely mixed drug into the dissolution medium. The polyglycolized glycol esters like Gelucires® are reported to reduce erratic bioavailability of poorly water soluble drugs. The use of nimodipine–polyethylene glycol solid dispersions, for the development of effervescent controlled release floating tablet formulations. The physical state of the dispersed nimodipine in the polymer matrix was characterized by differential scanning calorimetry, powder X-ray diffraction, FT-IR spectroscopy and polarized light microscopy. The purpose of the current study review could be utilized to examine the solid-state properties of the solid dispersion system of Glibenclamide using various grades of PEGs and Gelucire 50/13 prepared
at different ratios. The methods of characterization can be achieved through using different tools as FTIR, Differential scanning calorimetry, Powder X-ray diffractometry. Moreover, solubility and dissolution rate study to be performed to qualify the solid dispersions comparing with the drug alone or as physical mixtures.

On the other hand, Metformin hydrochloride is an oral antidiabetic drug. Continued efforts to develop metformin oral dosage form for achieving an optimal therapy is needed. These efforts mainly focus on controlled/slow release of the drug including the sophisticated gastroretentive system. Metformin is an antidiabetic agent of biguanide group and used in the management of type II diabetes mellitus (non insulin dependent, NIDDM). Metformin acts by decreasing hepatic glucose production, intestinal absorption of glucose and improves insulin sensitivity. Metformin has elimination half-life of 6.5 h. In spite of its favorable clinical response and lack of significant drawbacks, chronic therapy with metformin suffers from certain specific problems of which the most prominent are the high dose (1.5–2.0 g/day), low bioavailability (60%), and high incidence of gastrointestinal (GI) side effects (30% cases). There have been contradictory reports on the utilization of metformin hydrochloride in single unit gastroretentive dosage form. However, bioavailability of this drug has been found to reduce further with control release dosage form probably due to the fact that passage of the control release single unit dosage form of the drug is faster than its release and most of the drug releases at the colon, where metformin is poorly absorbed. Therefore, it is desirable as per current review to improve bioavailability by formulating metformin hydrochloride in sustained release gastro retentive multiparticulates using Gelucire in order to optimize the pharmacokinetics and pharmacodynamics of the drug. Metformin HCl ranges from 0.5–2.5 gm per day divided in two or three doses taken with meals. The low bioavailability (50-60%) and short plasma half-life (1.7–4.5 hrs) of metformin hydrochloride make the development of sustained-release forms desirable. However, drug absorption is limited to the upper gastrointestinal (GI) tract, thus requiring suitable delivery systems providing complete release during stomach-to-jejunum transit. Metformin hydrochloride is a highly water-soluble antihyperglycaemic agent used in the treatment of type II non-insulin-dependent diabetes mellitus. Gastric-retentive swelling tablets of metformin showed only a 15% increase of bioavailability with respect to the immediate-release tablets.

The present short review suggest the possibility of Gelucire application to achieve formulation of gastro retentive solid dispersion of poorly soluble drug Glibenclamide with the help of polyethylene glycol and Gelucire 50/13. On the other hand sustained release gastroretentive multiparticulates of metformin hydrochloride could be achieved using Gelucire 39/01 and 43/01 grades. Further both formulations can be explored individual as well as in combination for improved bioavailability by their pharmacokinetic and pharmacodynamic evaluation in wistar rats.

Acknowledgement
Authors are thankful to Department of Pharmaceutics, College of Pharmacy, IFTM, Moradabad-244001 (Uttar Pradesh) India for providing all research facility to carry out research work at the institution and to Gautam Buddh Technical University, Lucknow (Uttar Pradesh) India.

References


