A REVIEW ON GLIPIZIDE - ITS DIFFERENT FORMULATIONS

1Sheetal Buddhadev*, 2Sandip Buddhadev

1Assistant Prof., Dept. of Pharmaceutics, Noble Pharmacy College, Junagadh, India
2Associate Prof., Department of Dravyaguna, Government Ayurved College, Junagadh, India

ABSTRACT

The present review describes information regarding drug Glipizide and work done on different types of formulation of glipizide. Glipizide is an oral rapid- and short-acting anti-diabetic drug from the sulfonylurea class. It is classified as a second generation sulfonylurea, which means that it undergoes enterohepatic circulation. Second-generation sulfonylureas are both more potent and have shorter half-lives than the first-generation sulfonylureas. Due to short half life various technology are used to sustain the effect of glipizide. This review includes all available information like Pharmacokinetics, Pharmacodynamics, Pharmacological action and side effects of glipizide. Review also includes different formulations for sustained the effect of glipizide. This review work may be very useful for person working with glipizide.

Key word: Glipizide, Controlled release Drug Delivery System.

INTRODUCTION

Oral Controlled Drug Delivery

An oral drug delivery system providing a uniform drug delivery can only partly satisfy therapeutic and biopharmaceutical needs, as it doesn’t take into account the site specific absorption rates within the gastrointestinal tract (GIT). Therefore there is a need of developing drug delivery system that releases the drug at the right time, at the specific site and with the desired rate. Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve (Fig. 1). Controlled release Drug Delivery System is an attempt to sustain drug blood concentration at relatively constant and effective level in the body by spatial placement or temporal delivery. Thus controlled release drug delivery system (CRDDS) offer various advantages viz. reduce blood level fluctuations, minimize drug accumulation, employ less total drug, improve patient compliance, and minimize local and systemic side effects.

Fig. 1: Plasma level profiles following conventional sustained and controlled release dosing

Sulfonylureas were among the first oral medicines available for the treatment of Type 2 diabetes. They were discovered by accident in France by a researcher who was working on drugs for typhoid fever. Animals that were given sulfonylureas displayed unusual behaviors and were found to have hypoglycemia (low blood glucose). It was quickly recognized that these drugs could be used for the treatment of diabetes. The first sulfonylurea became available in 1955. Despite the many new diabetes therapies that have been discovered over the past 50 years, metformin and sulfonylureas are still two of the initial choices for treatment. Medicines in the sulfonylurea class include chlorpropamide, glyburide, glipizide and glini nepiride. Sulfonylureas have gone through several steps of development and are categorized as first, second, or third
generation drugs. The main difference between the generations is how well they bind to the sulfonylurea receptor, with each progressive generation binding more tightly and thus requiring a lower dose to bring about the same amount of insulin secretion.(1-8)

Glipizide is an oral hypoglycaemic agent, which is a com-monly prescribed drug for the treatment of patients with type II diabetes. It is used adjunct to diet to the manage-ment of type II (non-insulin dependent) diabetes mellitus in patients whose hyperglycemias cannot be controlled by diet and exercise alone. Glipizide stimulates insulin secre-tion from the $\beta$ cells of pancreatic islets tissue, increases the concentration of insulin in the pancreatic vein and may increase the number of insulin receptors. Glipizide is a weak acid ($pKa = 5.9$) which is practically insoluble in water and acidic solutions but as per the Bio-pharmaceutical Classification System (BCS) it has lower solubility and higher permeability (class II). The oral ab-sorption is uniform, rapid and complete with a bioavail-ability of nearly 100% and an elimination half-life of 2–4 h. Glipizide is an effective oral antidiabetic, 100 times more potent than tolbutamide in evoking pancreatic se-cretion of insulin and have a short biological half-life (3.4 ± 0.7 h) and is rapidly eliminated, so requiring it to be administered in 2 to 3 doses of 2.5 to 10 mg per day. Hence sustained release formulations is needed for glipizide for better control of blood glucose levels to pre-vent hypoglycemia and enhance clinical efficiency, to reduce G.I disturbances and to enhance patient compli-ance.

Several approaches have been used to sustained release of glipizide like Mucoadhesive approch, Gastro retentive approach, Bilayer tablet, Sustained release matrix tablet etc. This approch are helpful to to lengthen the stay of glipizide in its absorption area.(9-15)

**GLIPIZIDE (16-21)**

**Physiochemical properties**

**Structure**

![Glipizide Structure](image)

- **Synonyms:** Glipizidum [Latin], Glydiazinamide
- **IUPAC Name:** N-[2-(4-[(cyclohexylcarbamoyl)amino]sulfonyl)phenyl]ethyl]-5-methylpyrazine-2-carboxamide
- **Molecular formula:** $C_{21}H_{27}N_5O_4S$
- **Molecular weight:** 445.535 g/mole
- **State:** Whitish powder
- **Melting point:** 208-209°C

**Properties**

- **BCS class:** Class – II
- **log $p$:** 2.5
- **$pKa$:** 5.9

**Pharmacodynamics** Glipizide, a second-generation sulfonylurea, is used with diet to lower blood glucose in patients with diabetes mellitus type II. In human, glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets.

**PHARMACOKINETICS**

- **Absorption** Gastrointestinal absorption is uniform, rapid, and essentially complete.
- **Bioavailability** 90%
- **Protein binding** 98-99%

**Metabolism:** Hepatic. The major metabolites of glipizide are products of aromatic hydroxylation and have no hypoglycemic activity. A minor metabolite which accounts for less than 2% of a dose, an acetyl amino ethyl benzene derivatives is reported to have 1/10 to 1/3 as much hypoglycemic activities as the parent compound.

**Route of elimination:** The primary metabolites are inactive hydroxylation products and polar conjugates and are excreted mainly in the urine.

- **Half-life:** 2 - 5 hr
- **Dose:** Initial dose: 5 mg orally once a day. Maintenance dose: 5 to 20 mg (sustained-release) orally in 1 or 2 divided doses. (Orally)

**Category** Hypoglycemic Agents
Mechanism of action: Sulfonylureas likely bind to ATP-sensitive potassium-channel receptors on the pancreatic cell surface, reducing potassium conductance and causing depolarization of the membrane. Depolarization stimulates calcium ion influx through voltage-sensitive calcium channels, raising intracellular concentrations of calcium ions, which induces the secretion, or exocytosis, of insulin.

Solubility: Being a weak acid, glipizide is better absorbed from basic medium; however, at very low pH levels, the solubility of glipizide is: Water solubility 37.2 (mg/L) Simulated gastric fluid (pH 1.2) 1.08 (gm/ml) Phosphate Buffer (pH 7.4) 2.41 (gm/ml)

Contraindications:
1) Known hypersensitivity to glipizide or any ingredient in the formulation.
2) Diabetes mellitus complicated by acidosis, ketosis, or coma; use of insulin is necessary.
3) Monotherapy for type 1 diabetes mellitus.

Drugs will affect Glipizide: Probenecid, aspirin or other salicylates, a blood thinner like warfarin, Sulpha drugs, insulin or other oral diabetes medications

Special precautions: Hypoglycemia reported infrequently; usually mild; especially geriatric patients, malnourished patients, and those with adrenal, pituitary, epatic, or renal insufficiency. Concurrent illness possible loss of glycemic control during periods of stress (e.g., fever of any cause, trauma, infection, surgery) GI disease use extended-release tablets with caution may occur in patients with severe preexisting GI narrowing, since obstruction may occur.

Side effects: With conventional tablets, nausea, anorexia, vomiting, pyrosis, gastralgia, diarrhea, and constipation. With extended-release tablets, asthenia, headache, pain, dizziness, nervousness, tremor, diarrhea, hypoglycemia, and flatulence.

Drug interaction: Potential pharmacokinetic interaction with other protein-bound drugs. Use with caution with protein-bound drugs.

Marketed Glipizide powder
Formulation Glucotrol XL 2.5, 5, 10 mg 24 Hour tablet Glucotrol xl 2.5, 5, 10 mg tablet
Brand names of combination products Metaglip® (containing Glipizide, Metformin)

TECHNOLOGIES DEVELOPED FOR GLIPIZIDE

A) SOLUBILITY ENHANCEMENT APPROACH Enhanced solubility study of Glipizide using different solubilization techniques
In this method, comparative study on effect of solubility of glipizide by using different solubilization techniques like solid dispersion, hydrotrophy and micellar solubilization was carried out. Solid dispersion of glipizide was prepared by solvent evaporation method; PEG (Polyethylene glycol) 4000, mannitol and urea were used as carriers. Hydrotropic studies were carried out using different hydrotropic agents (sodium acetate, sodium benzoate and salicylate) and Micellar solubilization was carried out using different surfactant solutions (sodium lauryl sulphate, tween 80 and cetrimide). The solubility enhancement of glipizide by different solubilization technique was observed in decreasing order as hydrotropic solubilization > solid dispersion > micellar solubilization. It was observed that the solubility increased with the increase in the concentration of hydrotropic agents and amongst the various hydrotropic agents used the solubility was enhanced greatest to 55 folds with sodium salicylate. This increase may be attributed due to aggregation of the hydrotropic molecules and inclusion of one of these aggregates at high concentration probably by reacting to form an associated product as a result of hydrogen bonding.

Solid dispersion of glipizide for solubility and dissolution rate enhancement
In this work researcher had formulated solid dispersion of glipizide using melting fusion and solvent vaporization method. Drug and carriers like Eudragit E-100, Croscarmellose and Sodium Starch Glycolate in different ratios like 1:1, 1:2, 1:3 and 1:4 were used for formulating solid dispersions. The solid dispersions were evaluated for practical yield and in vitro dissolution. It was concluded that 1:4 ratio of drug: SSG shows better in vitro dissolution rate compared to the pure drug and marketed preparation. Further the solid dispersion with highest release rate was formulated in tablet dosage form. The angle of repose, bulk density, tapped density, carr’s index and hausner ratio were calculated for the micrometric characterization of the powder blend. The tablets were further studied for different pharmacopeial and non pharmacopeial evaluation test. Similarity factor F2 was 52 and difference factor F1 was 14 for glipizide was found to be within the standards. The in vitro release from the formulation was observed three times increased from the glipizide API.

B. SUSTAINED RELEASE APPROCHE

Sustained release matrix tablets of Glipizide using HPMC
The aim of researcher investigation was to enhance the solubility of glipizide (BCS Class II). Glipizide is an oral antidiabetic agent with relatively short elimination half life. Inclusion complex of Glipizide with β-
cyclohexedrine was prepared by kneading method and evaluated for its in-vitro release. Phase solubility studies were performed according to method reported by Higuchi and Connors which was classified as AL type characterized by apparent 1:1 stability constant. The Glipizide & Beta Cycloexedrine found to be compatible which was observed from FTIR spectra of Glipizide β- CD Complex. The dissolution study of Glipizide β CD complex shows significant increase in the drug release than pure drug. Matrix Glipizide β - CD complex tablet complex equivalent to 10 mg Glipizide were prepared by using Hydroxy propyl methyl cellulose (HPMC), Carbopoly methyl cellulose sodium (NaCMC) and Microcrystalline cellulose (MCC). The tablets were evaluated for various tests like hardness, friability, disintegration and in-vitro dissolution studies.

**Sustained release matrix tablets of Glipizide using HPMC and sodium CMC**

The Glipizide matrix tablet were prepared using different hydrophilic polymers (HPMC different grades and sodium CMC) in various proportions as release retarding agent to prolong the drug release and to improve the patient compliance. The matrix tablets were prepared by direct compression method. The prepared matrix tablets subjected to thickness, friability, swelling, dissolution, drug content and drug index and in vitro release studies. The in vitro dissolution study shows that F18 formulation is releases the drug in a controlled manner for 12 hours. Among all the formulations, formulation F18 which contains combination of HPMC K100 & E15 releases the drugs which follow Zero order kinetics via, swelling, diffusion.

**Stability studies** were carried out for optimized formulation F18 according to ICH guidelines. Stability studies (40±2°C/75±5% RH) for 3 months indicated that Glipizide was stable in matrix tablets.

**Sustained release glipizide matrix tablet of glipizide using HPMC K100CR, Eudragit L-100**

Sustained release glipizide matrix tablet prepared using HPMC K100CR, Eudragit L-100 polymers. Matrix tablets of Glipizide were prepared by direct compression method. All the prepared formulations were tested for Physical parameters like Hardness, Thickness, Friability, Weight variation and drug content were found to be within the Pharmacopeias limits. The drug content of all the formulations was determined and was found to be within the permissible limit. Release profile was studied using USP type II dissolution apparatus. Formulation F3 was considered as best formulation among all the nine formulations as it showed controlled the drug release for desired period of time (10 hrs). The stability studies were carried out on the optimized formulation i.e. F3 at 40°C/75 RH for three months to assess their long term stability and results indicated that irrespective of the concentration of polymer, these formulations remained stable for three months. Formulation F3 having Swellable polymer as HPMC K100CR showing better drug release profile than non-Swellable polymer Eudragit L-100. Hence the Swellable polymer HPMC k100 CR is better suitable for sustained release delivery. Thus the results suggest the developed sustained-release tablets of Glipizide performed therapeutically better than conventional dosage forms, leading to improved bioavailability, therapeutic efficacy with better patient compliance.

**Sustained Release Matrix Tablet of Glipizide using HPMC, Ethyl cellulose, , Guar gum, Eudragit RS 100, and Xanthan gum**

The present aims to develop sustained release matrix tablet of Glipizide employing synthetic and natural matrix forming polymers. Matrix tablet of Glipizide was prepared by wet granulation method using different hydrophilic and hy-drophobic polymers like Hydroxyl Propyl Methyl Cellulose, Ethyl cellulose, Guar gum, Eudragit RS 100, and Xanthan gum. Starch was used as a granulating agent. The FTIR spectra of the glipizide and different polymers alone and in combination show the compatibility of the drug and excipients. Formulation was optimized on the basis of in-vitro drug release in pH 7.4 phosphate buffer. The formulation of drug: eudragit RS 100 and xanthan gum shows better in-vitro dissolution rate, compared to the other. The optimized formulation studied for different pharmacopoeial and non-pharmacopoeial evaluation tests. Similarity factor f2 was 51 for glipizide was found to be within the standards.

**Glipizide sustained release tablets using hydrophilic polymers and hydrophobic polymers**

Sustained release tablet formulation of glipizide was prepared by employing two hydrophobic polymers (ethyl cellulose and ethylene vinyl acetate copolymer) and two natural hydrophobic polymers resins obaltan resin and olopolphon). Different batches of glipizide sustained release tablets were prepared by using lactose and dicalcium phosphate as diluents by wet granulation technique. The prepared tablets were evaluated for various parameters. In vitro drug release study was carried out and compared with the commercial Glynase XL tablets. The independent model method, Lin Ju and Liaw's difference factor (f1) and similarity factor (f2) were used to compare various dissolution profiles. The dissolution profiles of an ideal formulation (SR F3) containing obaltan resin and lactose as diluent was found to be comparable with the reference product. The kinetics of drug release was best explained by Korsmeyer and peappas model and the mechanism of drug release from these tablets was by non-fickian diffusion mechanism. The ideal formulation (SR F3) was stable when it was stored at 4±2°C, 27±2°C and 45±2°C for 6 months. In conclusion, SR formulation of Glipizide could be developed employing obaltan resin as rate-controlling matrix former and lactose as diluent.

**Glipizide sustained release Microspheres**

The aim of the investigation was to formulate and evaluate Eudragit microspheres for controlled release of glipizide. The microspheres were produced by emulsion solvent evaporation method, using the Eudragit RS100, Eudragit RL100 and also by their combination. Further, the prepared microspheres were characterized for the micromeric properties, drug loading as well as Fourier transform infrared spectroscopy (FTIR) and scanning electron microscopy. In vitro release study was performed in phosphate buffer (pH 7.4). The microspheres were free flowing in nature. The mean particle size ranged from 112 to 132 mm and the entrapment efficiencies ranged from 43.27 to 61.99%. The entrapment efficiency was found to be dependent on concentration of polymer used for formulation. The FTIR confirmed stable structure of glipizide in the drug-loaded microspheres. The DSC revealed the uniform dispersion of drug and polymer. Scanning electron
microscopy revealed the surface morphology. The mechanism of drug release from the microsphere was found to be non-fickian type.

Sustained Release Microspheres of Glipizide Prepared by the Emulsion Solvent Diffusion-Evaporation Method\textsuperscript{30}

The objective of the researcher investigation was to reduce dosing frequency and improve patient compliance by designing and systematically evaluating sustained release microspheres of glipizide. Glipizide microspheres were formulated by using the emulsion solvent diffusion-evaporation technique by using the modified ethanol-dichloromethane co-solvent system. The polymer mixture of ethyl cellulose and Eudragit® S100 was used in different ratios (1:0, 1:1, 2:3, 1:4 and 0:1) to formulate batches F1 to F5. The resulting microspheres were evaluated for particle size, densities, flow properties, morphology, recovery yield, drug content, and in vitro drug release behavior. The formulated microspheres were discrete, spherical with relatively smooth surface, and with good flow properties. Among different formulations, the fabricated microspheres of batch F3 had shown the optimum percent drug encapsulation of microspheres and the sustained release of the Glipizide for about 12 h. Release pattern of Glipizide from microspheres of batch F3 followed Korsmeyers-peppas model and zero-order release kinetic model. The value of ‘n’ was found to be 0.960, which indicates that the drug release was followed by anomalous (non-fickian) diffusion. The data obtained thus suggest that a microparticulate system can be successfully designed for sustained delivery of Glipizide and to improve dosage form characteristics for easy formulation.

C. FAST DISSOLVING APPROACH

Fast dissolving tablets of glipizide using crospovidone and croscarmellose sodium\textsuperscript{31}

In the present work, fast dissolving tablets of glipizide were prepared by direct compression method with a view to enhance patient compliance. Two superdisintegrants viz, crospovidone and croscarmellose sodium (4%, 5%, 6%) with different binders viz, pvp k-30 and pregelatinized starch (3%) were used. The prepared batches of tablets were evaluated for hardness, friability, weight variation, disintegration, wetting time, drug content and in vitro dissolution studies. Based on the results the formulation F3, 1:2 (Avicel PH-102: PVP K30) was selected as optimized formulation. The fabricated microspheres were discrete, spherical with relatively smooth surface, and with good flow properties. Among different formulations, the fabricated microspheres of batch F3 had shown the optimum percent drug encapsulation of microspheres and the sustained release of the Glipizide for about 12 h. Release pattern of Glipizide from microspheres of batch F3 followed Korsmeyers-peppas model and zero-order release kinetic model. The value of ‘n’ was found to be 0.960, which indicates that the drug release was followed by anomalous (non-fickian) diffusion. The data obtained thus suggest that a microparticulate system can be successfully designed for sustained delivery of Glipizide and to improve dosage form characteristics for easy formulation.

Immediate release glipizide liquisolid tablets using Avicel PH-102 and Aerosil 200\textsuperscript{32}

In this method immediate release glipizide liquisolid tablets was prepared using Avicel PH-102 and Aerosil 200 as the carrier and coating material respectively to increase dissolution rate of poorly soluble glipizide. This study also aims to evaluate treated Gellan gum as disintegrant in the preparation of liquisolid tablets. The solubility of glipizide was increased by use of liquisolid technique. The glipizide liquisolid tablets were evaluated for characteristics like drug content, friability, hardness, disintegration time, thermal analysis, X-ray diffraction (XRD) study and dissolution rates. The dissolution patterns of glipizide liquisolid tablets, carried out according to USP paddle method, and were compared with their commercial counterparts. The results obtained shows that all glipizide liquisolid tablets exhibits higher dissolution rates than those of marketed glipizide tablets. Dissolution rates increases with increasing concentration of liquid vehicles and maximum drug release achieved by formulations containing Polyethylene glycol 400 (PEG 400) as a liquid vehicle.

Fast dissolving glipizide tablet using husk of \textit{Planta\textit{go ovata} as a superdisintegrant\textsuperscript{33}

The objective of the study was to develop fast-dissolving tablets (FDTs) of glipizide. The husk of \textit{Plantago ovata} and pregelatinized husk of \textit{P. ovata} were used as disintegrating agents. Microcrystalline cellulose was used as binder and starch (soluble) was used as bulk-forming agent. The powder blends were evaluated for angle of repose, compressibility index and Hausner ratio. The tablet blends were converted into tablets by using direct compression method. The tablets were evaluated for disintegration test, hardness test, friability test, drug entrapment efficiency, content uniformity tests and drug release study. Formulations, which contained pregelatinized husk of \textit{P. ovata} as a superdisintegrant, showed faster disintegration, higher percentage friability and lesser hardness than those formulations containing husk of \textit{P. ovata} as a superdisintegrant. Drug entrapment efficiency was found to be uniform among different batches of the tablets and ranged from 97.53±0.52 to 99.72±0.45. The results of content uniformity test of all the batches were found in the official range. The batches containing husk of \textit{P. ovata} as a superdisintegrant released 15%–27% of glipizide per minute and those containing pregelatinized husk of \textit{P. ovata} as a superdisintegrant released more than 95% of the drug within a minute. These results revealed that pregelatinized husk of \textit{P. ovata} can be used as a superdisintegrant for obtaining FDTs.

D. MUCOADHESIVE APPROACH

Mucoadhesive buccal tablets of glipizide\textsuperscript{34}

The aim of study was to prepare and characterize mucoadhesive buccal tablets of glipizide using different Mucoadhesive polymers such as Carbopol 940, Sodium alginate and HPMC K15M in combination. Twenty one formulation were developed with different concentration of mucoadhesive polymers in each formulation. The formulated buccal tablets were tested for surface pH, in vitro drug release and moisture absorption. The prepared tablets were evaluated for bioadhesive strength, ex vivo residence time and drug permeation through porcine buccal mucosa. In vitro bioadhesive strength, ex vivo residence time and in vitro release
A transdermal delivery system for glipizide was determined in natural human saliva; it was found that both glipizide and buccal tablets were stable in human saliva.

**Microcapsules of glipizide Na CMC, Methylcellulose, Carbopol and HPMC**

Large spherical microcapsules of glipizide with a coat consisting of alginate and a mucoadhesive polymer (sodium CMC, methylcellulose, Carbopol, or HPMC) could be prepared by an orifice-ionic gelation process. The microcapsules exhibited good mucoadhesive properties in an in vitro test. Glipizide release from these muco-adhesive microcapsules was slow and extended over longer periods of time and depended on composition of the coat. Drug release was diffusion controlled and followed zero-order kinetics after a lag period of 1 hour. In the in vivo evaluation, alginate-Carbopol microcapsules could sustain the hypoglycemic effect of glipizide over a 14-hour period. These mucoadhesive microcapsules are, thus, suitable for oral controlled release of glipizide.

**Mucoadhesive film of glipizide using HPMC and PEG 400**

Glipizide was formulated in a mucoadhesive film that could be retained in the stomach for prolonged intervals. Polymeric films were designed with various compositions of hydroxypropyl cellulose and polyethylene glycol 400 (PEG 400). Properties of the mucoadhesive film such as tensile strength, percentage elongation, swelling index, moisture content, pH and viscosity of polymeric dispersion, film thickness, content uniformity and mucoadhesion in a simulated gastric environment were characterized. In addition, percentage drug retained in stomach mucosa was estimated using a simulated dynamic stomach system as a function of time. Increase in hydroxypropyl cellulose concentration resulted in a higher tensile strength and elongation at break, while increase in concentration of PEG 400 was reflected in a decrease in tensile strength and increase of elongation at break. Glipizide/hydroxypropyl cellulose/PEG 400 (2.5:1:0.5) (GF5) was found to be the optimal composition for a novel mucoadhesive stomach formulation that showed good peelability, relatively high swelling index, moderate tensile strength, and stayed on rat stomach mucosa up to 8 h.

**Mucoadhesive Glipizide Microspheres**

Mucoadhesive microspheres of glipizide were prepared by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. Results of preliminary trials indicate that volume of cross-linking agent, time for cross-linking, polymer-to-drug ratio, and speed of rotation affected characteristics of microspheres. Microspheres were discrete, spherical, and free flowing. The microspheres exhibited good mucoadhesive property in the in vitro wash-off test and also showed a high percentage drug entrapment efficiency. A 3^3 full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio (X1), and stirring speed (X2) on dependent variables percentage mucoadhesion, t_{50}, drug entrapment efficiency, and swelling index. The best batch exhibited a high drug entrapment efficiency of 75% and a swelling index of 1.42; percentage mucoadhesion after 1 hour was 78%. The drug release was also sustained for more than 12 hours. The polymer-to-drug ratio had a more significant effect on the dependent variables. In vivo testing of the mucoadhesive microspheres to albino Wistar rats demonstrated significant hypoglycemic effect of glipizide.

**E. TRANSDERMAL APPROACH**

A transdermal delivery system for glipizide was developed. In this method, first inclusion complexes of the drug in beta-cyclodextrin (beta-CyD), dimethyl-beta-cyclodextrin (DM-beta-CyD), hydroxypropyl-beta-cyclodextrin (HP-beta-CyD), and hydroxypropyl-gamma-cyclodextrin (HP-gamma-CyD) were prepared. Several percutaneous formulations of the drug and the prepared complexes in different bases [o/w emulsion, polyethylene glycol, carboxymethyl cellulose and Carbopol] were developed. Release studies revealed an improved release of the drug from formulations containing glipizide-CyD complexes. Ex vivo permeation studies through full thickness rat abdominal skin were conducted, whereby the effect of several conventional penetration enhancers (propylene glycol [PG], oleic acid, urea, dimethyl sulfoxide, menthol, limonene and cineole) was monitored. Highest flux was obtained from ointments prepared with Carbopol gel base containing a combination of PG and oleic acid as well as ointments prepared in the same base utilizing glipizide-DM-beta-CyD complex and urea. In vivo studies on diabetic male Wistar rats revealed a marked therapeutic efficacy sustained for about 48 hours. In this respect, two formulations showed best biological performance. In the first formulation, the drug was incorporated in Carbopol gel base in the presence of 20% PG together with 15% oleic acid. The second was prepared by incorporating glipizide-DM-beta-CyD complex in Carbopol gel base in presence of 15% urea. The glucose tolerance test showed suppression of hyperglycaemia induced in glucose-loaded rats. The above-mentioned results might shed a strong beam of light on the feasibility of using glipizide in a transdermal delivery system for treatment of type 2 diabetes with the aim of improving both patient compliance and pathophysiology of the disease.

**F. BILAYER APPROACH**

Bilayer tablet of glipizide was prepared by using different grades of HPMC like, HPMC K-100, HPMC K-50 and Ethyl Cellulose along with other excipients by wet granulation process. The aim of present study is to formulate glipizide sustained release (SR) and immediate release (IR) bilayer matrix tablet by different concentration of Hydroxypropyl methylcellulose (HPMC) and Ethyl Cellulose (EC) to control the release pattern. The sustained release layer of glipizide was prepared by using different grades of HPMC.
technique. The immediate release layer of glipizide was prepared by Lactose and Sodium starch glycolate by wet granulation Method. The powders were evaluated for their flow properties and the finished tablets were evaluated for their physical parameters. The both immediate release and sustained release layers of glipizide were characterized by FT-IR and in vitro dissolution studies. The drug release study of glipizide was evaluated using USP-II paddle type dissolution apparatus. The release rate of glipizide in immediate release layer was studied for 3 h in pH 7.4 phosphate buffer media and that of glipizide in sustained release layer was studied for 10 h in pH 7.4 phosphate buffer media. From the six batches F5 batch showed good release behaviour 91.92% of drug is released over 10 hours and R2 value is 0.977 in zero-order kinetics.

Zero order release glipizide bilayer matrix tablets

The aim of the present investigation was to develop controlled zero-order release glipizide bilayered matrix tablets using different grades of hydroxy propyl methyl cellulose (HPMC) as novel release modifier along with xanthan gum (XG), guar gum (GG), and karaya gum (KG) as release retardants. Bilayered matrix tablets of glipizide were prepared by wet granulation method. The release rate were modulated by varying concentration of different types of rate controlling material as well as in a combination of two different rate controlling material. After evaluation of physical properties of tablets, the in vitro release study was performed in phosphate buffer pH 7.4 upto 12 hrs. The effect of polymer concentration and polymer blend concentration were studied. All precompressional parameters were found to be within acceptable standard limits. It was observed that bilayer matrix tablets contained polymer blend of HPMC/Ethyl cellulose were successfully sustained the release of drug upto 12 hrs. The release data were fit into different kinetic models (zero order, first order, and Korsmeyer–Peppas powers law equation). The DSC and FTIR studies demonstrated that there was no interaction between polymers and drug. Stability studies were carried out according ICH guidelines. Stability studies (40±2°C/75±5% RH) for 6 months indicated that glipizide was stable in matrix tablets. All above polymers can be successfully used to achieve desired zero order drug release.

Fixed dose combination of glipizide and metformin hydrochloride by steam granulation technique

The main objective of the investigation was to design and development of the fixed dose combination of Glipizide and Metformin Hydrochloride in-lay tablets prepared by steam granulation technique. The tablets were evaluated for hardness, friability, thickness, % drug content and in vitro release studies. In-lay tablet comprises of glipizide immediate release layer formulated with neem gum as disintegrating agent and metformin hydrochloride for sustained release formulated with HPMC K4M and gums such as xanthum gum and guar gum in which SR layer surrounded by glipizide immediate release granules. The drug-excipient compatibility studies were conducted by FT-IR studies. The mechanism of drug release from glipizide IR layer follows first order kinetics and zero order kinetic observed for metformin hydrochloride SR layer and the stability studies were performed as per ICH guide lines for formulated P9 and results obtained found to be stable.

Floating bilayer tablet of Glipizide and Lisinopril

The purpose of the study is to prepare Bilayer floating tablets containing Glipizide as sustained release and Lisinopril as immediate release which can be used to treat both the diseases concomitantly. Sustained layer were prepared by direct compression method using the release retarding polymer HPMC K4 M & HPMC K100M. A 3x Full factorial design was used for optimization of polymers. The quantity of HPMC K4 M (X1) and HPMC K100M (X2) were selected as independent variables and Floating Duration, Percentage drug release at 8 h (Q8h)and Percentage drug release at 20 h (Q20h) were selected as dependent variables. Tablets were evaluated. The formulations (FT4) showed release of Lisinopril within 30 min followed by sustained release of glipizide in sustained manner in up to 12 hours and Atenelol immediate release F5 formulation showed 100.6% drug release with in 30 min. Dissolution of all the tablets prepared followed zero order kinetics with coefficient of determination (R2) value is 0.965. Plots of percent release versus square root of time were found to be linear with R2 0.9877 with all the tablets prepared indicating that the drug release from these tablets was diffusion controlled. FTIR studies were performed on drug and the optimized formulation using Shimadzu FTIR as a result no interactions were observed in drug-excipients.

CONCLUSION

Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes (non-insulin dependent diabetes mellitus). One of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drug. Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drug with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects. Glipizide, an anti diabetic drug has poor water solubility there by facing problems in their
formulations in absorption leads to poor bioavailability. As it is an anti diabetic drug it has to be absorbed rapidly. So enhancement of the solubility of drug is important. Solid dispersions are one the most successful strategic approach to improve drug release of poorly soluble drugs. In this review, effect of solubility of glipizide by using different solubilization techniques like solid dispersion, hydrotropy and micellar solubilization was discussed.

As Glipizide has short biological half-life (3.4±0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg per day. This review contain information on work done on sustained release tablets of glipizide by various techniques and different polymers like HPMC K4, sodium CMC, HPMC K100 CR, Eudragit L-100, Ethyl cellulose, Guar gum, Eudragit RS 100 and Xanthan gum as well as ethyl cellulose and ethylene vinyl acetate copolymer. Review also contains information on Eudragit microspheres for controlled release of glipizide. The microspheres were produced by emulsion solvent evaporation method as well as emulsion solvent diffusion method. Thus, the development of controlled release dosage forms would clearly be advantageous.

Review contain information of work done on fast dissolving tablets of glipizide using Crospovidone, cross carmellose sodium, Avicel PH-102, Aerosil 200 as well as Plantago ovata as a super disintegrant. Finally from it, it was concluded that the superdisintegrant based fast dissolving tablets of Glipizide would providing quick onset of action without need of water for swallowing or administration.

This review also include formulation and characterization of Mucoadhesive Buccal tablet, Microcapsules, Microspheres as well as Films of glipizide using mucoadhesive polymers like Hydroxy propylmethylcellulose, Carbopol-934P, Eudragit RL-100 and Sodium carboxymethylcellulose as etc. Due to short half life, Buccal mucoadhesive dosage form of glipizide proved effective for improving and enhancing bioavailability in a controlled release fashion.

The transdermal drug delivery system is mainly suited for the drugs that preferably undergo hepatic first pass metabolism alongwith the short elimination half life of less than five hours. This review also contains information on Glipizide transdermal patches.

Bilayer tablet concept has long been utilized to develop sustained released formulation. Such tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustaining layer. This review include bilayer tablet of Glipizide, Fixed dose combination of glipizide and metformin hydrochloride, Floating Bilayer tablet of glipizide proved effective for improving and enhancing bioavailability in a controlled release fashion.

As Glipizide has short biological half-life (3.4±0.7 hours) necessitates that it be administered in 2 or 3 doses of 2.5 to 10 mg per day. This review contain information on work done on sustained release tablets of glipizide by various techniques and different polymers like HPMC K4, sodium CMC, HPMC K100 CR, Eudragit L-100, Ethyl cellulose, Guar gum, Eudragit RS 100 and Xanthan gum as well as ethyl cellulose and ethylene vinyl acetate copolymer. Review also contains information on Eudragit microspheres for controlled release of glipizide. The microspheres were produced by emulsion solvent evaporation method as well as emulsion solvent diffusion method. Thus, the development of controlled release dosage forms would clearly be advantageous.

Review contain information of work done on fast dissolving tablets of glipizide using Crospovidone, cross carmellose sodium, Avicel PH-102, Aerosil 200 as well as Plantago ovata as a super disintegrant. Finally from it, it was concluded that the superdisintegrant based fast dissolving tablets of Glipizide would providing quick onset of action without need of water for swallowing or administration.

This review also include formulation and characterization of Mucoadhesive Buccal tablet, Microcapsules, Microspheres as well as Films of glipizide using mucoadhesive polymers like Hydroxy propylmethylcellulose, Carbopol-934P, Eudragit RL-100 and Sodium carboxymethylcellulose as etc. Due to short half life, Buccal mucoadhesive dosage form of glipizide proved effective for improving and enhancing bioavailability in a controlled release fashion.

The transdermal drug delivery system is mainly suited for the drugs that preferably undergo hepatic first pass metabolism alongwith the short elimination half life of less than five hours. This review also contains information on Glipizide transdermal patches.

Bilayer tablet concept has long been utilized to develop sustained released formulation. Such tablet has a fast releasing layer and may contain one (bi-layer), to sustain the drug release. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state as the release from sustaining layer. This review include bilayer tablet of Glipizide, Fixed dose combination of glipizide and metformin hydrochloride, Floating Bilayer tablet of glipizide proved effective for improving and enhancing bioavailability in a controlled release fashion.

This is basically done to improve bioavailability of the drug and better therapeutic compliance. The sustained layer of the drug showed steady state release behaviour over a prolonged duration of time which may reduce dose related side effects.

REFERENCES

3) Brahmanakar Dm, Jaiswal SB, Biopharmaceutics and pharmacokinetics a treatise, 1st Ed, New Delhi, Vallabh Prakashan, 1995; 49- 57,347.
5) N.K Jain, Controlled and Novel Drug Delivery, New Delhi, Vallabh Prakashan, 2002; 150- 200.
16) RX only, Glipizide Tablets for Oral Use, SEP-2006; 1-15.


