CHAPTER III

LITERATURE REVIEW OF DRUGS SELECTED
Aceclofenac- A profile

Structure:

\[
\begin{align*}
&\text{Cl} & \text{N} \\
&\text{Cl} & \text{H} \\
&\text{N} & \text{O} \\
&\text{O} & \text{COOH}
\end{align*}
\]

Class: Analgesic, anti-inflammatory.

Chemical Name: \[[[2-[(2, 6-Dichlorophenyl) amino] phenyl] acetyl] oxy] acetic acid.

Molecular Weight: 354.2

Molecular formula: \(C_{16}H_{13}Cl_2NO_4\).

Physical appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, freely soluble in acetone, soluble in alcohol.

Supplied by: Micro Labs, Bangaluru
Dosage: The maximum recommended dose is 200 mg daily in divided dosage. The dose should be reduced in patients with hepatic impairment.

Mechanism of Action:

Aceclofenac is a NSAID and anti-rheumatic drug. It acts by inhibiting the synthesis of inflammatory cytokines interleukins -1\(\beta\) and TNF, and inhibits prostaglandin E2 production. Unique feature of it is, it stimulates glycosaminoglycans synthesis.

Pharmacokinetics:

Absorption: After oral administration, aceclofenac is rapidly absorbed and the bioavailability is almost 100%. Peak plasma concentrations are reached approximately 1.25 to 3 hrs following ingestion. \(T_{\text{max}}\) is delayed with concomitant food intake whereas, the degree of absorption is not influenced.

Distribution: Aceclofenac is highly protein-bound (>99.7%). Aceclofenac penetrates into the synovial fluid, where the concentrations reach approximately 60% of those in plasma. The volume of distribution is approximately 30L.

Elimination: The mean plasma elimination half-life is 4 - 4.3 hrs. Clearance is estimated to 5 liters per hour. Approximately two-thirds of the administered dose is excreted via the urine, mainly as conjugated hydroxyl metabolites. Only 1% of an oral single dose is excreted unchanged. Aceclofenac is probably metabolized
via CYP2C9 to the main metabolite 4-hydroxyaceclofenac whose contribution to the clinical activity probably is negligible.

**Characteristics in patients:** No changes in the pharmacokinetics of aceclofenac have been detected in the elderly. A slower rate of elimination of aceclofenac has been detected in patients with decreased liver function after a single dose of aceclofenac. In a multiple dose study using 100 mg once daily, there was no difference in the pharmacokinetic parameters between subjects with mild to moderate liver cirrhosis and normal subjects. In patients with mild to moderate renal impairment no clinically significant differences in the pharmacokinetics were observed after a single dos

**Precautions:** Aceclofenac should be administered with caution to patient with indicative of gastrointestinal disorder, with a history of peptic ulceration, ulcerative colitis, crohn’s disease, hepatic porphyria, coagulation disorders. Patients suffering from severe hepatic impairment must be monitored.

**Pregnancy:** There is no information on the use of aceclofenac during pregnancy. Aceclofenac should not be administered during pregnancy, unless there are compelling reasons for doing so. The lowest dose should be administered.

**Lactation:** There is no information on the secretion aceclofenac in breast milk. The use of aceclofenac should therefore be avoided during lactation unless the potential benefits to the mother outweigh the possible risk to the children.
**Drug Interactions:** Lithium and Digoxin: Aceclofenac, like other NSAID's may increase plasma concentrations of lithium and digoxin.

Diuretics: Aceclofenac may inhibit the activity of diuretics.

Anticoagulant: Aceclofenac may enhance the activity of anticoagulants.

Quinolones: convulsions may occur.

**Usage:** Aceclofenac is non-steroidal analgesic and anti-inflammatory agent\textsuperscript{1-3} with a good gastrointestinal tolerability profile\textsuperscript{4-11}. Aceclofenac is indicated for the relief of pain and inflammation in both acute and chronic pain like osteoarthritis, rheumatoid arthritis, alkalizing spondylitis, scapulohumeral periarthritis\textsuperscript{12}, dental pain, post-traumatic pain, post surgical pain\textsuperscript{13}, low back pain and gynecological pain, etc.

**Diet:** Reduces bioavailability.

**Storage:** Do not store above 25°C. Protect from light.

**PAST WORK ON ACECLOFENAC FORMULATIONS**

Uma Devi, S. K., et al\textsuperscript{14}. Developed novel colon specific drug delivery systems for aceclofenac using chitosan as a microbially degradable polymeric carrier and to coat the optimized batches with a pH dependent polymeric coating solution containing Eudragit L 100 and S 100 (1:4). Tablets containing four proportions of chitosan were prepared. The tablets were evaluated for physicochemical
properties, drug content, dissolution, water uptake & erosion characteristics, in-vitro drug release studies. Eudragit coated Chitosan tablets prevented release of the aceclofenac in the physiological environment of stomach and small intestine depending on the proportion of chitosan used in the formulation. The dissolution profile and in-vitro release kinetics showed that chitosan tablets were promising for controlled delivery of the drug. The findings of the present study conclusively state that chitosan tablets are promising for colon targeting of aceclofenac to synchronize the chronobiological symptoms for effective treatment of rheumatoid arthritis.

**DR.Umesh, D. Shivhare, et al**\(^{15}\). Studied and developed “once daily” sustained release tablets of aceclofenac by wet granulation using carboxypolymethylene polymer. The drug excipients mixtures were subjected to preformulation studies while the tablets were subjected to physicochemical studies, in vitro drug release, stability studies and validation studies. The physicochemical properties of tablets were found within the limits. Formulation F2 & F9 containing Carbopol 971P and Carbopol 974P were found to release the drug in sustained manner up to 24 hour and were stable under accelerated conditions of temperature for 6 months since there were no significant changes in drug content and physical parameters.

**Srinivas, S., et al**\(^{16}\). Studied and developed optimizing niososomal formulation of aceclofenac in order to improve its bioavailability. In evaluation study the effect of
the varying composition of non ionic surfactant and cholesterol on the properties such as encapsulation efficiency, particle size and drug release were studied. Moreover, the release of the drug was also modified and extended over a period of 72 hrs in all formulations. NSF-3 emerged as the most satisfactory formulation in so far as its properties were concerned. Further, release of the drug from the most satisfactory formulation NSF-6 was evaluated through dialysis membrane to get the idea of drug release. The mechanism of drug release was governed by Peppas model. The present study demonstrated the successful preparation of Aceclofenac niosomes and their evaluation. Hence it was considered to be good niosomal formulation with greater bioavailability.

Tejal Soni., et al\textsuperscript{17}. Developed a meaningful method of dissolution procedure for drug products with limited water solubility has been a challenge to the pharmaceutical industry. Aceclofenac (BCS Class II drug) is a non steroidal anti-inflammatory drug. There is no official dissolution medium available in the literature. In the present study, parameters such as solubility, medium pH, surfactant type, and dissolution behavior of formulations, influence of sink conditions, stability, and discriminatory effect of dissolution testing were studied for the selection of a proper dissolution medium. Results of solubility data revealed that solubility increased with an increase in pH. Sink conditions were exhibited in all media except double-distilled water and 0.1 N HCl. The drug and marketed formulations were stable in the dissolution media used. An agitation
speed of 50 rpm showed a more discriminating drug release profile than 75 rpm. The discriminating dissolution method for aceclofenac formulation is paddle at 50 rpm, 900 ml pH 6.8 phosphate buffer, greater than 80% of the label amount is released over 60 minutes.

Gandhi, S. V., et al\textsuperscript{18}. A new sensitive, simple, rapid and precise method for simultaneous estimation of paracetamol and aceclofenac in combined tablet dosage form has been developed. The method is based on ratio derivative spectrophotometry. The amplitude in first derivative of the ratio spectra at 256 nm and 268 nm (minima) were selected to determine paracetamol and aceclofenac in combined formulation. The method showed good linearity, accuracy and reproducibility. Results of analysis were validated statistically and by recovery studies.

Mallikarjuna, C. Setty., et al\textsuperscript{19}. Prepared aceclofenac fast-dispersible tablets by direct compression method. Effect of superdisintegrants (such as, croscarmellose sodium, sodium starch glycolate and crospovidone) on wetting time, disintegration time, drug content, \textit{and in vitro} release and stability parameters has been studied. Disintegration time and dissolution parameters ($t_{50\%}$ and $t_{80\%}$) decreased with increase in the level of croscarmellose sodium. Where as, disintegration time and dissolution parameters increased with increase in the level of sodium starch glycolate in tablets. However, the disintegration time values did not reflect in the dissolution parameter values of crospovidone tablets and release was dependent on
the aggregate size in the dissolution medium. Stability studies indicated that tablets containing superdisintegrants were sensitive to high humidity conditions. It is concluded that fast-dispersible aceclofenac tablets could be prepared by direct compression using superdisintegrants.

Trivedi Parul., et al\textsuperscript{20}. Formulated and studied microencapsulation of anti-inflammatory drug aceclofenac to provide controlled release and minimizing or eliminating local side effect by avoiding the drug release in the upper gastrointestinal track. The drug was targeted to the colon and their aligned area for their local effect. Aceclofenac was microencapsulated with Eudragit (S 100, RL 100, and RS 100), using an O/W emulsion-solvent evaporation technique. Aceclofenac microspheres were subjected to micromeritic properties, Carr's index, Hausner's ratio, and particle size determination. Microspheres were subjected to drug loading, \textit{in vitro} drug release as well as for scanning electron microscopy. The prepared microspheres were white, free-flowing, and almost spherical in shape. The drug-loaded microspheres show 60-82% drug entrapment. In vitro drug release studies were carried out up to 24 hrs in three different pH media, i.e., 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4). The drug-polymer concentration of dispersed phase influences the particle size and drug release properties. All the formulations at higher pH were followed by the Matrix-Higuchi model.
Maha Nasret, al\textsuperscript{21}. Prepared lipospheres containing aceclofenac intended for topical skin delivery with the aim of exploiting the favorable properties of this carrier system and developing a sustained release formula to overcome the side effects resulting from aceclofenac oral administration. Lipospheres were prepared using different lipid cores and phospholipid coats adopting melt and solvent techniques. Characterization was carried out through photo microscopy, scanning electron microscopy, particle size analysis, DSC, \textit{In vitro} drug release and storage study. The anti-inflammatory effect of liposphere systems was assessed by the rat paw edema technique and compared to the marketed product. Results revealed that liposphere systems were found to possess superior anti-inflammatory activity compared to the marketed product in both lotion and paste consistencies. Liposphere systems proved to be a promising topical system for the delivery of aceclofenac as they possessed the ability to entrap the drug at very high levels and high stability, and to sustain the anti-inflammatory effect of the drug.

Mutalik, S., et al\textsuperscript{22}. Developed and studied once daily sustained release tablets of aceclofenac by direct compression using hydroxyl propyl methyl cellulose K4M (45\%), micro crystalline cellulose (30\%). The tablets exhibited almost similar drug release profile in different distribution media as that of marketed tablet.

Lee, J., et al\textsuperscript{23}. Developed and studied an O/W micro emulsion system to enhance the skin permeability of aceclofenac. Labrafic M1944 cs was chosen as the oil phase and showed a good solubilizing capacity, different formulation with various
values of oil of 6-30% water of 0-80% and the mixture of surfactant and co-surfactant of 14-70%. In vitro Transdermal permeability of aceclofenac from the micro emulsion was evaluated using rat skin. 5% terpenes were added and their effects on the skin permeation were investigated. The results indicated that the micro emulsion system studied in a promising field for the percutaneous delivery of aceclofenac.

**Joshi, V. Y., et al**\(^{24}\). Studied the effect of surfactant system of alkyl polyglycosides and sodium lauryl sulphate in different ratios and aceclofenac as a model drug. The solid dispersions of drug with single and mixed surfactants were prepared with ethanol as a solvent. The mixed surfactant system enhances drug solubilization by many folds in comparison of single surfactant.

**Patil, S. S., and Kasture, P. V**\(^{25}\). Formulated PLA microspheres loaded with aceclofenac and studied the release profile in phosphate buffer pH7.4. Poly-1-lactide was used as polymer, solvent method was used for preparation of microspheres with full factorial design. Drug loading efficiency was 75%. About 95% of drug was released in 9hrs.

**Nyamathulla, S., et al**\(^{26}\). Developed oral controlled release drug delivery systems of aceclofenac using guar gum by wet granulation method, dose of controlled release formulations of aceclofenac was 200 mg. Release of the drug from one formulation followed a biphasic pattern i.e., initial rapid release up to 4 hrs following first order kinetics later slow release up to 24 hrs, following zero order
release. Release of the drug as retarded with increase in polymer concentrations, they concluded that optimized formulation followed zero order release kinetics with erosion mechanism and the preparation was suitable as once daily application.

Gopal Venkatesh Shavi, et al. An enteric-coated multiparticulate drug delivery system of aceclofenac was formulated. The pellet were prepared by using extrusion/spheronization method, and the core pellets were coated with a pH-sensitive poly acrylate copolymer (Eudragit 1100-55) to achieve site-specific drug release. The formulated pellets were characterized. In-vitro dissolution test was used for comparison of drug release profiles of various coated pellets. The study concluded that the formulated multiparticulate dosage forms can be used as an ideal drug delivery system for the aceclofenac.

Dahiya, S., et al. Formulated and developed to characterize Aceclofenac HPβ-CD formulation by differential scanning calorimetry, thermogravimetric analysis, mass spectroscopy, 1H NMR spectroscopy, SEM and in vitro dissolution studies. All the binary system showed superior dissolution and lower dose: solubility ratio as compared to pure aceclofenac. The kneaded product exhibited the best dissolution. Hence, it was suggested that complexation with HPβ-CD may be used as an approach to change the drug from BCS class II to BSC class I without changing its intrinsic permeability.
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DRUG REVIEW

Glipizide—A Profile

Structure

Class: Blood-glucose-lowering drug of the sulfonylurea class.

Description:


Molecular Weight: 445.54.

Molecular Formula: C_{21}H_{27}N_{5}O_{4}S.

Physical Appearance: whitish, odorless powder

Solubility: It is insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide.
**Supplied by:** Micro Labs, Bangaluru

**Dosage**\(^{2-4}\): The maximum recommended dose is 40mg per day in divided dose. The dose should be reduced in patient with hepatic impairment. The recommended starting dose is 5 mg/ day up to 15 mg/day given as a single daily dose. For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 min before breakfast, since rapid absorption is delayed when the drug is taken with food.

**Mechanism of Action:**

Glipizide appears to lower blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. Sulfonylurea’s causes hypoglycemia by provoking a brisk release of insulin from pancrease, reduce gluconeogenesis in liver cells and increase insulin sensitivity in target cell.

**Pharmacokinetics:**

**Absorption:** Glipizide is rapidly and completely absorbed following oral administration in an immediate release dosage form. The absolute bioavailability of Glipizide was 100% after single oral doses in patients with type 2 diabetes. Plasma drug concentrations gradually rises reaching maximum concentrations within 6 to 12 hours after dosing.
Distribution: The mean apparent volume of distribution was approximately 10 liters. Glipizide is 98-99% bound to serum proteins, primarily to albumin.

Elimination: The mean terminal elimination half-life of Glipizide ranged from 2 to 5 hours after single or multiple doses in patients with type 2 diabetes.

Warnings and Precautions:

Hepatic and renal diseases monitor blood and urinary glucose periodically.

Renal and Hepatic Disease: The pharmacokinetics and/or pharmacodynamics of Glipizide may be affected in patients with impaired renal or hepatic function. If hypoglycemia should occur in such patients, it may be prolonged and appropriate management should be instituted.

GI Disease: Markedly reduced GI retention times of the Glipizide extended-release tablets may influence the pharmacokinetic profile and hence the clinical efficacy of the drug.

Hypoglycemia: Renal or hepatic insufficiency may affect the disposition of Glipizide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions.

Pregnancy:

Teratogenic Effects: Pregnancy Category C: Glipizide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Because recent information suggests that abnormal blood-glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood-glucose levels as close to normal as possible.

**Nonteratogenic Effects:** Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. If Glipizide is used during pregnancy, it should be discontinued at least one month before the expected delivery date.

**Drug Interactions:**

The hypoglycemic action of sulfonylurea's may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta-adrenergic blocking agents. When such drugs are administered / withdrawn to a patient receiving Glipizide, the patient should be observed closely for hypoglycemia/hyperglycemia. Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered /withdrawn to a patient receiving Glipizide, the patient should be closely observed for loss of control.
Adverse reaction:

Hypoglycemia is the most common problem. Other non specific side effects are nausea, vomiting, flatulence, diarrhea or constipation, headache, paraesthesia and weight gain. Hypersensitivity reaction like rashes, photosensitivity, purpura transient leucopenia, and rarely agranulocytosis, nervous system—insomnia, paresthesia, anxiety, depression and hypesthesia.


Usage: Glipizide is an oral blood-glucose-lowering drug of the sulphonylurea class.

Storage: Do not store above 25°C. Protect from light.

PAST WORK ON GLIPIZIDE FORMULATIONS

Shelesh Jain., and Swarnlata Saraf. Developed Glipizide (GPZ) loaded biodegradable nanoparticles by using a biodegradable polymer, poly (d, l-lactic-co-glycolic acid) (PLGA) as a sustained release carrier. PLGA nanoparticles (PLGA NPs) were prepared by a modified emulsification solvent evaporation technique. Subsequent study shows no interaction of GPZ with PLGA (FT-IR
study). Various formulation parameters such as stirring speed (300–3000 rpm), drug: polymer ratio (1:4 to 2:1), with addition of surfactants (0.5%, w/v polyvinyl alcohol/polysorbate-80) were studied for particle size, drug loading, and encapsulation efficiency. The drug entrapment efficiency and zeta potential were investigated. The surface morphology was characterized by scanning electron microscopy (SEM). Mean particle size of nanoparticles was altered by changing the drug: polymer ratio and stirring speed. Addition of surfactants showed a promise to increase drug loading, encapsulation efficiency, and decreased particle size. The drug release pattern consisted of two phases releasing about 40% (within first 24 h) followed by a slow releasing phase (up to 90%) within next 48 h. The release data was fitted in various kinetic models (zero-order, first-order, and Higuchi's kinetics) indicated a controlled drug release. Accelerated stability studies (ICH guidelines) revealed that the GPZ-loaded nanoparticles were stable at the end of 6 months. They concluded that, the Controlled release biodegradable nanoparticles can be prepared by selecting the proper processing variables.

Jayvadan, K. Patel., et al. Formulated and systematically evaluated in-vitro and in-vivo performances of mucoadhesive microspheres of Glipizide. Glipizide microspheres containing chitosan 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 high percentage drug entrapment efficiency. A $3^2$ full factorial design was employed to study the effect of independent variables, polymer-to-drug ratio ($X_1$), and stirring speed ($X_2$) on dependent variables percentage mucoadhesion, $t_{80}$, 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.

Chowdary, K.P.R., and Rao, Y.S. Studied to develop, characterize, and evaluate mucoadhesive microcapsules of Glipizide employing various mucoadhesive polymers for prolonged gastrointestinal absorption. Glipizide, an effective antidiabetic that requires controlled release owing to its short biological half-life of $3.4 \pm 0.7$ hours, was used as the core in microencapsulation. The mucoadhesive microcapsules were evaluated by in vitro and in vivo methods for controlled release. Microcapsules containing glipizide were prepared employing sodium alginate in combination with four mucoadhesive polymers sodium CMC, methylcellulose, Carbopol and HPMC—as coat materials. No methods were
reported for microencapsulation by these polymers. An orifice-ionic gelation process that has been extensively used to prepare large alginate beads was employed to prepare the microcapsules. The microcapsules exhibited good mucoadhesive properties in an in vitro test. Glipizide release from these mucoadhesive 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.

Yong Gan., et al⁹. Prepared and studied poorly soluble Glipizide was selected as the model drug to prepare osmotic pump tablets (OPT) inclusion complex by kneading method in order to increase solubility. Polyethylene glycol 4000 (PEG4000) and cellulose acetate (CA) were selected as the coating materials, and acetone-water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push-pull osmotic tablet. The results indicated that glipizide-cyclodextrin inclusion complex OPT had excellent zero-order release characteristics in vitro.
Adel, M.Aly., et al. Studied and formulated enhancement of the dissolution rate and bioavailability of Glipizide-CD inclusion complexes and the effect of various additives on the solubility of GZ-CD complex. A serial concentration of NaCMC, poly-vinylpyrrolidone (PVP), and polyethylene glycol (PEG6000) were added to each formula. Characterization of GZ-CD complexes Differential scanning calorime-try (DSC) In vitro dissolution study and Evaluation of prepared tablets. The results revealed that -CD was more effective as a solubi-lizing complex with GZ than -CD. On the other hand, the effects of several additives, namely NaCMC, PVP, and PEG6000, on the solubility of GZ were studied. NaCMC is the most-enhancing additive compared with PVP or PEG6000. However, no significant difference could be detected between the dissolution of PVP or PEG6000.

Chowdary, K.P.R., and Sundari, G.B. Matrix tablets of Glipizide were formulated using two mucoadhesive polymers namely sodium carboxymethylcellulose and hydroxypropylmethylcellulose and with and without ethylcellulose and the tablets were evaluated. Tablets formulated employing sodium carboxymethylcellulose or hydroxypropylmethylcellulose and with ethylcellulose provided slow release of glipizide over a period of 12 h and were found suitable for maintenance portion of oral controlled release tablets. Glipizide release from these tablets was diffusion controlled and followed zero order kinetics after a lag time of 1 h and up to 90 per cent release. The matrix tablets
exhibited good mucoadhesion in the small intestine for 10 h as evaluated by X-ray studies. Two layered tablet formulations, designed with an immediately releasing layer consisting of glipizide and a super disintegrant (Ac-Di-Sol) and a slow releasing matrix consisting of glipizide in sodium carboxymethylcellulose or hydroxypropylmethylcellulose and ethylcellulose as second layer, gave release close to the theoretical sustained release needed for glipizide based on its pharmacokinetic parameters.

**Gaurav Tiwari, et al**. Glipizide (GPZ) and GPZ-HPC solid dispersion (SD) pellets were developed and characterized for drug release mechanisms from a multi-unit erosion matrix system for controlled release. Solid dispersion with HPC was prepared by coevaporation method and characterized by Fourier transform infra red spectroscopy (FT-IR), scanning electron microscopy (SEM), differential scanning calorimetry (DSC), hot-stage microscopy (HSM), x-ray diffraction (XRD), stability studies. Release rate of GPZ from solid dispersion was measured by the rotating basket method (JP XII). FT-IR study indicated the presence of hydrogen bonding in solid dispersion. SEM confirms the amorphous form in solid dispersion. In DSC melting peak in solid dispersion shifted slightly to lower temperature with respect to drug alone indicated the conversion to amorphous form which was further proved in XRD. HSM have demonstrated the ability of melted HPC to dissolve the crystal of GPZ at increasing temperatures. The release rate of GPZ from solid dispersion granules was markedly larger than that from
GPZ powder, and it was larger with a lower HPC molecular weight. The stability study showed that SD systems were not significantly different during six month of accelerating condition storage.

Mahalaxmi, R., et al\textsuperscript{13}. Developed extended release controlled porosity osmotic pump formulations of model drug Glipizide using a wicking agent and a solubilizing agent. Glipizide osmotic tablets were evaluated for their flow properties, weight variation, hardness, friability and content uniformity. The effect of different formulation variables like level of wicking agent, solubilizing agent, level of pore former and membrane weight gain on \textit{In Vitro} release were studied. Drug release was found to be affected by the level of wicking agent and solubilizing agent in the core. Glipizide release from controlled porosity osmotic pump was directly proportional to the pore former (sorbitol) and inversely proportional to membrane weight gain. Drug release from the developed formulations was independent of pH and agitational intensity and was dependent on osmotic pressure of the release media. The optimized formulation was also found to stable upon stability studies.

Bhosale Ashok, V., et al\textsuperscript{14}. Studied and formulated β-CD complexed controlled release matrix tablet of Glipizide and its \textit{In Vitro} evaluation. The aim of investigation was to enhance the solubility and impart a controlled release in a single formulation. Glipizide was complexed with β-cyclodextrin. Phase solubility studies were performed which was classified as AL type characterized by apparent
1:1 stability constant that had a value 582.48 M⁻¹ in 6.8 phosphate buffer. Inclusion complex of Glipizide with β-cyclodextrin is prepared by kneading and evaluated for its in-vitro release and FTIR spectroscopy studies. Matrix tablet complex equivalent to 10 mg Glipizide were prepared by using increasing concentration of polyethylene oxide and evaluated for various tablet properties and in-vitro dissolution studies. The dissolution study of kneading complex shows significant increase in the drug release from kneading complex than pure drug and physical mixture. The Glipizide & Beta Cyclodextrin found to be compatible from FTIR spectra of kneading complex and Physical mixture. The Dissolution study of various batches from F1- F6 and marketed preparation shows that Glipizide release from tablets containing Poly Ethylene Oxide, at lower concentration % release was more. The formulation F3 having Similar dissolution profile like marketed preparation (GLUCOTROL XL) which having 50 mg of PEO. Finally it can be concluded from the study that molecular complex with β-CD play a vital to obtain a uniform, controlled and complete drug release of a poorly soluble drug from the swellable /erodible matrix tablet.

Gan, Y., et al¹⁵. Prepared and evaluated Cyclodextrin complex osmotic pump tablet delivery for Glipizide. Poorly soluble Glipizide was selected as the model drug to prepare osmotic pump tablets (OPT) with proper accessorial material after it was made an inclusion complex by kneading method in order to increase solubility. Polyethylene glycol 4000 (PEG4000) and cellulose acetate (CA) were
selected as the coating materials, and acetone-water (95:5) co-solvent was employed as the coating medium. The effects of the osmotic promoting agent, diameter of the drug-releasing orifice, coating composition, and coat weight on the drug release profile were investigated. The drug release profile of the optimal formulation was compared with a commercialized push-pull osmotic tablet. The results indicated that Glipizide-cyclodextrin inclusion complex OPT had excellent zero-order release characteristics in vitro.

Shahla Jamzad., and Reza Fassihi\textsuperscript{16}. Developed and studied a new monolithic matrix system to completely deliver Glipizide, a Biopharmaceutics Classification System (BCS) Class II drug in a zero order manner over an extended time period. Two approaches were examined using drug in formulations that contain swellable hydroxypropyl methylcellulose (HPMC) or erodible polyethylene oxide (PEO). The matrices were prepared by dry blending selected ratios of polymers and ingredients using direct compression technique. Dissolution was assessed using modified USP apparatus II. Glucotrol XL push-pull osmotic pump (PPOP) was used as the reference. The interrelationship between matrix hydration, erosion and textural properties were determined and analyzed under the dissolution test conditions. Linear and reproducible release similar to that of Glucotrol XL was achieved for optimized matrices ($\text{	extit{f}}2 > 50$) independent of hydrodynamic conditions. The kinetics of drug delivery was directly related to the synchronization of swelling, erosion and fractional release. HPMC matrices
showed a significantly greater degree of hydration and swelling and stronger
texture property relative to PEO matrices. Results indicate that in the case of low
dose/low soluble drug, total drug release in a zero order manner heavily depends
on the synchronization of erosion and swelling fronts during the entire dissolution
study.

Jolly, M.S., Mayur, G. S., and Raja shree, C. Mashru. Studied to examine a
level A in vitro–in vivo correlation (IVIVC) for Glipizide hydrophilic sustained-
release matrices, with an acceptable internal predictability, in the presence of a
range of formulation/manufacturing changes. The effect of polymeric blends of
ethylcellulose, microcrystalline cellulose, hydroxypropyl methylcellulose, xanthan
gum, guar gum, Starch 1500, and lactose on in vitro release profiles was studied
and fitted to various release kinetics models. Water uptake kinetics with scanning
electron microscopy (SEM) was carried out to support the drug release
mechanism. An IVIVC was established by comparing the pharmacokinetic
parameters of optimized (M-24) and marketed (Glytop-2.5 SR) formulations after
single oral dose studies on white albino rabbits. The matrix M-19 (xanthan: MCC
PH301 at 70:40) and M-24 (xanthan: HPMC K4M: Starch 1500 at 70:25:15)
showed the Glipizide release within the predetermined constraints at all time
points with Korsmeyer–Peppas' and zero-order release mechanism, respectively.
Kopcha model revealed that the xanthan gum is the major excipients responsible
for the diffusion release profile and was further supported by SEM and swelling
studies. A significant level A IVIVC with acceptable limits of prediction errors (below 15%) enables the prediction of in vivo performance from their in vitro release profile. It was concluded that proper selection of rate-controlling polymers with release rate modifier excipients will determine overall release profile, duration and mechanism from directly compressed matrices.

**Patel, R.B., and Patel, M.M.** Studied and developed new osmotic pump tablets of Glipizide (OPT), it was made an inclusion complex with Hydroxypropyl β-Cyclodextrin (HP-β-CD) to increase a solubility and optimize OPT using response surface methodology. The effects of different ratio of drug to HP-β-CD and preparation methods on complex formation were studied. The amount of KCl (X1), amount of HPMC K4M (X2) and amount of plasticizer (PEG 400) in coating composition (X3) were selected as independent variables. The times required for 50% (t50) and 80% (t80) drug release were selected as dependent variables. *In-vitro* drug release profiles of Glipizide from OPT were compared with that of theoretical release profile and statistically analyzed to examine suitability of OPT for once a day administration of Glipizide. Inclusion complex prepared using solvent evaporation method in ratio of 2:1 gave good solubility and dissolution enhancement and hence, selected for further evaluation in OPT. The results was indicated that the X1 (amount of KCl), X2 (Amount of HPMC K4M), and X3 (amount of PEG 400 in coating solvent) all have significant effect on *In-vitro* drug release profile. It is also indicate that the high level of X1 and X3 favors quick
onset of Glipizide release, where as high level of X2 favors prolonged release of Glipizide from OPT with initial low release rate. *In-vitro* drug release profile results indicate that batch F8 showed the highest value among all the batches, and it also shows similarity in t50 and t80 values. The present research works conclude that the inclusion complex increase the solubility of Glipizide and formulating OPT with this inclusion complex gave prolonged drug release for once a day administration of Glipizide.

**Jamjad, S. and Fassihi, R**. Developed a new monolithic matrix system of Glipizide containing Hydroxyl propyl methyl cellulose (HPMC) and erodible polyethylene oxide (PEO) were developed by blending technique. The interrelationship between matrix hydration, erosion and textual properties were determined and analysed under the dissolution test conditions. Linear and reproducible release similar to that of Glucotrol XL was achieved for optimized matrices independent of hydrodynamic conditions. The kinetic of drug release was directly proportional to the synchronization of swelling, erosion and fractional release. HPMC matrices showed a significantly greater degree of hydration and swelling stronger texture property relative to PEO matrices. Drug release followed zero order kinetics.

**Mutalik, S. and Udupa, N**. Developed and studied, membrane-moderate transdermal system of Glipizide using drug containing carbopol gel and ethyl cellulose, as well as Eudragit RS-100, Eudragit RL-100 and ethylene vinyl acetate
as rate controlling membranes and were subsequently evaluated for in vitro and in vivo studies. Variations in drug permeation patterns were observed among the formulation containing different rate controlling membranes. The transdermal system with EVA as rate controlling membrane prevented severe hypoglycemia in the initial hours and it was also effective for chronic application.
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