CHAPTER - IV

DRUG PROFILE - GLIPIZIDE
4.1 Structure

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\text{Drug profile – Glipizide}
\]

4.2 Chemical name:
(1-Cyclohexyl-3-[[p-[2-(5-methylpyrazinecarboxamido) ethyl] phenyl] sulfonyl] urea)

4.3 Molecular formula: \( \text{C}_{21}\text{H}_{27}\text{N}_{5}\text{O}_{4}\text{S} \)

4.4 Molecular weight: 445.55

4.5 CAS number: 29094-61-9

4.6 Appearance: Glipizide appears as white to off-white amorphous powder, which is odorless and bitter in taste.

4.7 Solubility: Practically insoluble in water, slightly soluble in ethanol where as soluble in methanol and methylene chloride.

4.8 Literature survey of Glipizide

Glipizide is second generation sulfonyleurea derivative synthesized in 1971 (Ambrogi et al, 1971). It is an oral hypoglycemic agent, used in the treatment of non-insulin dependent diabetes mellitus. This compound appears to be the most potent amongst other sulfonyleurea derivatives (Charles and Shuman, 1983). Rise in immuno-reactive insulin and decrease in blood glucose levels occurs within 30 minutes after ingestion of 5 mg of Glipizide (Norms E, 1979). It is 100 times more potent than Tolbutamide (Brogden et al, 1979).

Sulfonyleureas inhibit the activation of adenosine triphosphate (ATP)-sensitive potassium channels (KATP), leading to depolarization of the cell membrane and an
influx of calcium into the cell, stimulating increased release (but not production) of insulin from the pancreatic beta cell (Bell D.S., 2004).

As a consequence of their mechanism of action (increased insulin secretion) sulfonylureas are associated with hypoglycemia. Mild hypoglycemia is the most commonly occurring adverse event of oral sulfonylurea therapy, affecting 2 to 4% of patients. Glimepiride was associated with a significantly lower cumulative incidence of hypoglycemia (DeFronzo R.A., 1999).

Glipizide is a Biopharmaceutical Classification System (BCS) Class II drug (Shahla and Reza, 2006). It is practically insoluble in water and alcohol, has molecular weight 445.55 and a $pK_a$ of 5.9 (Gidwani et al, 2001). The solubility of Glipizide is minimal at very low pH which causes large variation in oral bioavailability (Ammar et al, 2007).

The drug has a plasma half-life of 3–5 h and needs frequent administration (Tripathi K. D., 2004; Hardman and Limbird, 2001). Recommended therapeutic dose of Glipizide is in the range of 2.5 to 40 mg/day, as single or divided doses (Wahlin-Boll et al, 1980). It is required to be administered 2 to 3 times daily in more than 45% of the patients. The minimum effective concentration for hypoglycemic action is 50ng/ml. The absorption of Glipizide is delayed by concurrent administration of meal. It’s $C_{max}$ in fasting stage is 720 nmol/lit, which is not significantly changed under non-fasting condition. But $T_{max}$ is 120 min under fasting where as it is 160 min after breakfast, which indicates that, the absorption of Glipizide is delayed by presence of food. The AUC in fasting condition is 280 [nmol × h × 1⁻¹] where as 106 [nmol × h × 1⁻¹] under non-fasting, which indicates that the extent of absorption is also significantly affected by food (Wahlin-Boll et al, 1980). Moreover, its oral use is often
associated with severe hypoglycemic and symptoms like nausea, vomiting, heartburn, anorexia and increase in appetite (Mutalik and Udapa, 2006).

The oral therapy with Glipizide is associated with increase in body weight. David and Bell (2004) reported that extended release Glipizide formulation did not increase the weight significantly as compared to immediate release formulation. Grooplc et al (1989) reported that the absorption of Glipizide after oral administration is reduced in hyperglycemic condition, which may be due to its effect on gastric emptying and motility.

Glipizide is conventionally administered as immediate release tablet dosage form by oral route since its discovery. It is also available as extended release tablet by the brand name Glucotrol-XL ® (Pfizer Inc.) containing 2.5 to 20 mg of Glipizide. This extended release tablet is based upon osmotic and hydrostatic pressure system for drug release, which is a complicated and costly technology (Gidwani et al, 2001).

Studies by Berelowitz et al (1994) showed that extended release Glipizide is significantly more effective than immediate release tablet.

Chowdhary and Rao (1994) had developed controlled release microsphere of Glipizide using ethyl cellulose, the hypoglycemic effect of these microspheres was maintained upto 36 h when administered subcutaneously in rabbits. They also developed microcapsules of Glipizide using ethylene vinyl acetate and concluded that the release of Glipizide was controlled for more that 12 h (Chowdhary and Rao, 2003). Thomre et al (1999) designed osmotic delivery system of Glipizide using asymmetric membrane capsule and pH controlling excipients, reported that prolonged release of Glipizide could be obtained with the asymmetric membrane capsule.

Verma and Garg (2004) developed and evaluated osmotically controlled oral drug delivery system of Glipizide. They also studied the drug excipient compatibility for
extended formulation of Glipizide. Thermal and isothermal stress testing techniques were used to assess the compatibility of Glipizide with selected excipients (Verma and Garg, 2005).

According to Doh et al (2003) drug candidates for transdermal delivery should have molecular weight around 200–500 \( \delta \), Glipizide is having molecular weight of 445.5 \( \delta \), fits into the category. The previous studies related to the transdermal drug delivery of Glipizide are discussed in chapter –II (literature review of transdermal anti-diabetic).

4.9 Pharmacokinetic consideration of Glipizide for development of transdermal delivery system.

Pharmacokinetic behavior of drug is very important factor for selection of drug candidate to develop the transdermal delivery system. The pharmacokinetic parameters such as half life, clearance rate, minimum effective plasma level, steady state plasma concentration are the key factors while choosing the drug candidate.

Due to the shorter half life (3-5 h), the steady state level of Glipizide will be achieved faster, which is one of the desirable characteristics for development of transdermal delivery system. Volume of distribution (Vd) and clearance (CL\( _T \)) values are 0.2 L/kg and 0.6 ml/min/kg respectively.

The required flux (Jss) from a transdermal delivery system can be calculated by:

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J_{ss} = CL_T \times C_{pss}
\]

Where \( CL_T \) is total body clearance, \( C_{pss} \) is average effective concentration. The required flux value of Glipizide from the transdermal formulation to achieve the required pharmacological action was calculated to be 184.8 \( \mu \)g/h, which could be achieved by the use of penetration enhancers.
4.10 Rationale for selection of Glipizide for development of transdermal drug delivery system

Glipizide was selected as a candidate because of following reasons.

- The drug has a plasma half-life of 3–5 h and needs frequent oral administration.
- Oral therapy is associated with severe and some time fetal hypoglycemia.
- Its solubility is minimal at very low pH, which causes large variation in oral bioavailability.
- The rate and extent of oral absorption of Glipizide decreases in presence of food.
- It undergoes hepatic first metabolism to about 20-25%.
- Its oral administration causes GI disturbances like nausea, vomiting, heartburn and anorexia.
- The oral therapy with Glipizide associated with increase in body weight.
- The absorption of Glipizide after oral administration is reduced in hyperglycemic condition.

On the basis of the physicochemical, biological and pharmacokinetic parameter it can be concluded that Glipizide may be good candidate for development of transdermal drug delivery system.
4.11 References


David S.H., Bell M.B., Practical considerations and guidelines for dosing sulfonylureas as monotherapy or combination therapy, Clinical Therapeutics, 2004, 26 (11), 1714-1727.


