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MODIFIED-RELEASE DOSAGE SYSTEMS DEVELOPED FOR GLIPIZIDE. A REVIEW

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ABSTRACT: In the last decades, diabetes has become one of the most prevalent health concerns worldwide. Diabetes is a metabolic disease that causes hyperglycemia and is associated with altered insulin production (type 1 diabetes) or with insulin-resistance (type 2 diabetes). The present work aims to point out the relevance of glipizide as an alternative treatment for type 2 diabetes and discuss the different delivery systems developed for this drug. With this in mind, we performed a nonsystematic search in different databases like PubMed, Google Scholar, Science Direct and the FDA's and some other web pages, using key words as search criterion. Because glipizide is a drug with a short elimination half-life, a dosage of two to three tablets per day is needed, depending on the therapeutic requirements of each patient. The as aforementioned has led different research groups to develop new delivery systems for this drug; among them are nanoparticles, nanosuspensions, microspheres, self-emulsifying systems, matrix tablets, osmotic tablets, and gastroretentive systems. The developed systems have been aimed at reducing the dosage frequency of glipizide, expecting to improve therapeutic adherence.

INTRODUCTION: Diabetes (DBT) is a metabolic disease that causes hyperglycemia and is associated with altered insulin production (type 1 diabetes, DBT1) or with insulin resistance (type 2 diabetes, DBT2). Progression of the disease can induce malfunctioning of organs like the heart, kidneys and eyes [1]. DBT is one of the main causes of morbidity and mortality worldwide that affects ca. 463 million adults, of whom 79% live in low- or medium-income countries.

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Of all DBT reported cases, almost 90% belong to DBT2 [2]. Currently, diverse drugs are available for DBT2 treatment; among them is glipizide (GPZ), a drug characterized for having a short elimination half-life (3.4±0.7 h), hence a dosage of two to three tablets per day is needed [3]. The usual initial GPZ dose is of 2.5 to 5 mg per day, but the dose can be increased to reach a maximum effective dose of 10 mg [4].

This work aimed to point out the relevance of GPZ as a therapeutic alternative for the treatment of DBT2 and to investigate different delivery systems developed with this drug. A nonsystematic search was performed in different databases, like PubMed, Google Scholar, Science Direct, using keywords and Boolean operators to obtain specific information on the subject.

We mined documents not older than 10 years; however, there are some exceptions because there is no recent information on clinical assays and metabolism of GPZ.

Diabetes in Mexico: In the last decades, DBT has become one of the most prevalent health concerns worldwide; it is the 7th cause of death worldwide and has caused around 5.2 million deaths. DBT is a risk factor for developing cardiovascular diseases, microvascular complications like nephropathy, retinopathy, neuropathy, and macrovascular complications, including coronary artery disease and peripheral vascular disease [5]. DBT can also cause mood disorders and dementia; all associated morbidities lead to a decreased life quality and premature death. It has been estimated that by 2045, globally, the number of people with DBT will reach 629 million, which is equivalent to 9.9% of the total adult population of the world [6].

About 415 million people worldwide with DBT2 and almost 80% live in countries of low and medium incomes; a significant population (41.1 million) live in Latin America. Mexico is among the 10 leading countries worldwide, with 11.5 million people with this disease [7].

In Mexico, DBT2 is the second cause of death and the first cause of years lost of healthy life. In 2006 and 2016, the national prevalence of the disease was 14.4 and 13.7%, respectively [8]. In the country, DBT2 is related to an increase in the prevalence of obesity and diet changes, represented by higher consumption of refined carbohydrates and sugars [9].

It has been described that, in Mexico, DBT2 is a factor for the appearance of diseases like blindness, chronic kidney failure, and for surgical procedures like non-traumatic amputations; it also increases the risk for myocardial infarction or cerebral infarction [10].

Besides, this disease in one of the main hospitalization causes in the country. In the 2008-2013 period, the Mexican Institute of Social Security (IMSS, for its acronym in Spanish) recorded 411, 302 hospital discharges, of which 68.19% were due to a DBT complication; renal complications were the most frequent ones (23.60%), followed by peripheral circulation alterations (23.11%).

According to the type of DBT, DBT2 presented the largest number of hospital discharges (79.31%) [11]. DBT affects the Mexican health economy importantly; in 2017, the direct costs of DBT in Mexico were estimated to reach 4 billion US dollars (USD) and 5 billion USD for indirect costs12. Likewise, the economic load due to DBT represents more than 2% of Mexico's annual gross domestic product (GDP), and costs are expected to duplicate in the next decade [13].

Glipizide: GPZ **Fig. 1** is a second-generation sulfonylurea developed by Pfizer used as a hypoglycemic agent for the treatment of DBT2; it stimulates pancreatic β cells to release insulin [14] by binding to the specific sulfonylurea receptor, closing the ATP-sensitive potassium channels; consequently, the membrane depolarizes and opens the voltage-dependent calcium channels releasing insulin, which will reduce the blood glucose levels **Fig. 2** [15, 16].

Besides, GPZ can increase insulin sensitivity and diminish hepatic glucose production through indirect extrapancreatic effects related to hepatic glycogen metabolism, gluconeogenesis, and lipogenesis [17, 18].

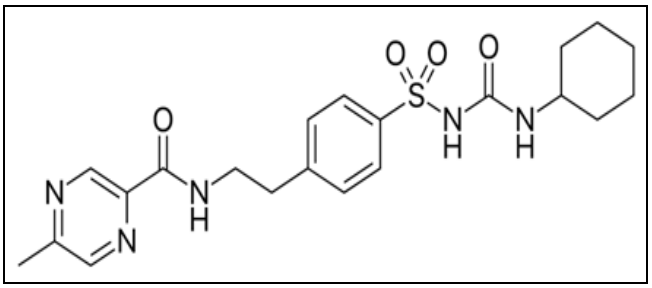

FIG. 1: CHEMICAL STRUCTURE OF GLIPIZIDE

GPZ is a weak acid (pKa 5.9), it is a Biopharmaceutical Classification System (BCS) class II drug [15] and its absorption site is the stomach [19].

Regarding its pharmacokinetics, the maximal plasmatic concentration (C_{max}) is attained 1 to 3 h after administering a sole dose; it binds to plasmatic proteins and has a half-life elimination of 2 to 4 h approximately. Usually, the initial dose is 2.5 to 5 mg daily as a sole dose given 30 min before breakfast; the dose can be adjusted to a maximum of 40 mg per day; however, the maximum effective dose is 10 mg per day [4].

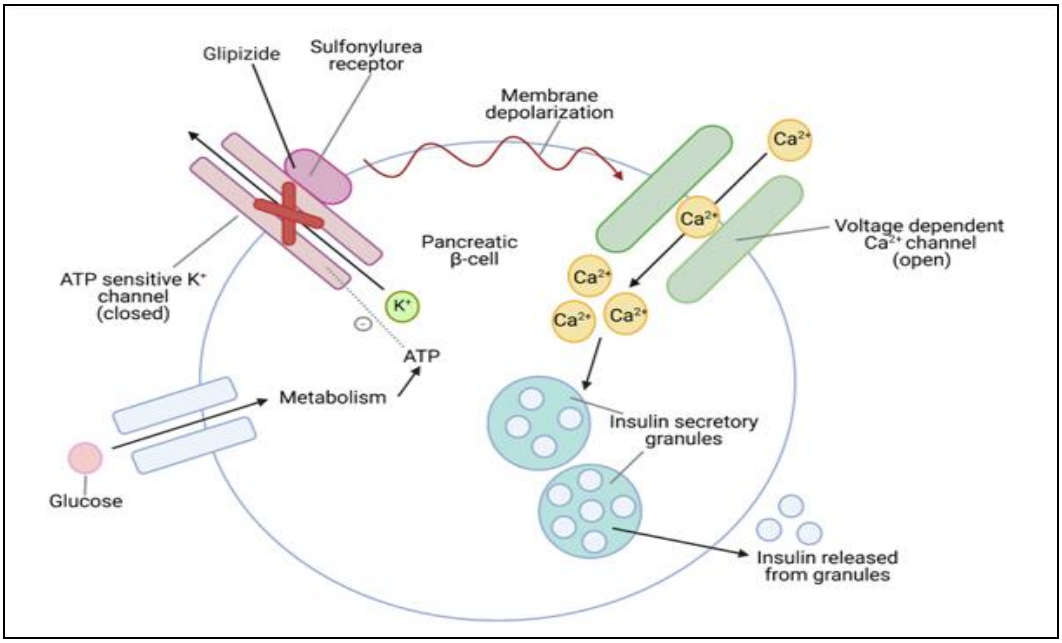

FIG. 2: MECHANISM OF ACTION OF GLIPIZIDE CREATED WITH BIORENDER COM

GPZ is extensively metabolized in the liver by CYP2C9 and CYP3A4 [20,] and its metabolites lack hypoglycemic activity. The main metabolites are 4-trans-hydroxycyclohexyl, 3-cis-hydroxycyclohexyl, and N-(2-acetylamino-ethyl-phenyl-sulfonyl)-N'-cyclohexyl urea (DCDA) derivates; during the first 24 h 3 to 9% of the administered GPZ dose is excreted unaltered by the urine, up to 65% as a 4-trans-hydroxycyclohexyl derivate, approximately 14% as a 3-cis-hydroxycyclohexyl derivate and only between 0.8 and 1.7% as DCDA [21].

The most severe adverse drug reaction (ADR) of this drug consists of hypoglycemic episodes that can induce coma. Other ADRs are nausea, vomiting, cholestatic jaundice, agranulocytosis, aplastic and hemolytic anemias, generalized hypersensitivity reactions, neuromuscular and skeletal anomalies that include tremors, myalgia and paresthesia; ocular and dermatological reactions have also been reported. It should be noted that myalgia and paresthesia occur in less than 3% of people treated with GPZ [22].

Despite the aforementioned, GPZ continues to be a drug of choice for DBT2 treatment; it is the first line of treatment in patients that cannot receive metformin or are not overweight, and the second line when added to metformin treatment. Besides, it is believed that GPZ is a better choice than glyburide (GLY) for patients with a higher risk of hypoglycemia; this is probably due to the accumulation of active metabolites of GLY [23]. In a study performed by Varghese *et al.* (2007), which included 2174 patients that received a hypoglycemic agent (with or without insulin) during 3 months, the authors found that the occurrence of at least one hypoglycemic episode (blood glucose ≤60 mg/dL) for sulfonylurea's in a period of 48 h after receiving the drug was of 13.6% (8/59) forglimepiride, 10.0% (19/190) for GPZ and 19.1% (18/94) for GLY [24]. In contrast to other sulfonylureas, GPZ can be given to patients with kidney failure only if creatinine clearance is equal or higher than 10 mL/min [25].

Pharmaceutical Presentations of Glipizide: GPZ is commercialized in immediate and modified-release tablets. New approaches are being investigated for the administration of this drug that can offer advantages like savings in the manufacturing costs, better release characteristics, and reduction in the frequency of doses, which will be described in the following.

Immediate Release Tablets: Immediate release GPZ tablets (GPZ IR) are administered two or three times per day depending on the patient's requirements; these tablets are available at concentrations of 5 and 10 mg of GPZ. They are manufactured by Pfizer and sold under the trade names of Minodiab® and Glucotrol®. Some of the excipients of this type of formulation are microcrystalline cellulose, corn starch, stearic acid,

lactose monohydrate, and colloidal silicon dioxide [26, 27]. It has been described that the plasmatic GPZ concentrations in this type of formulation are less stable than those of controlled-release tablets and, besides, the therapeutic adherence by patients is lower [28].

Modified Release Tablets: The modified release pharmaceutical dosage forms (MRPDF) are formulations in which the rate and/or site of drug release are different from those of immediate-release administered by the same route. Among the advantages of MRPDF is the reduction in the frequency of doses and reduction of fluctuations in the plasmatic concentrations of the drug, and better therapeutic adherence. Among these dosage forms are the systems of repeated action, prolonged, controlled, sustained, targeted, programmed and pulsatile release systems [29].

Push-pull osmotic Tablets: Controlled release GPZ tablets of 2.5, 5, and 10 mg are found in the market, which are administered once a day and is commercialized under the name of Glucotrol XL®, the trademark of Pfizer for GPZgastrointestina therapeutic system (GPZ GITS). The nucleus is a bilayered tablet, one layer contains the active ingredient (active layer), and the other is pharmacologically inert, but osmotically active (push layer). Among the excipients that constitute the osmotic layer are polyethylene oxide, hypromellose, magnesium stearate, and sodium chloride, aside from the cellulose acetate together with the polyethylene glycol plasticizer that make up a semipermeable membrane.

After manufacturing the nucleus, a semipermeable polymer is used to cover it, and using a laser beam; an orifice is drilled on the side of the active layer to ease the release of the drug. One of the characteristics of the membrane that surrounds the nucleus is that it is permeable to water but not to the drugs or excipients; hence, when the water of the gastrointestinal tract enters the tablet, it induces an increase in the pressure of the osmotic layer and this pushes the layer containing the active ingredient. As a result of this process, the drug is released through the orifice formed with the laser beam **Fig. 3** [30]. These delivery systems have advantages, like attaining zero-order release kinetics; however, the technology for their production is more costly than immediate-release tablets because very specialized equipment is needed to perform the orifice in the tablet [31].

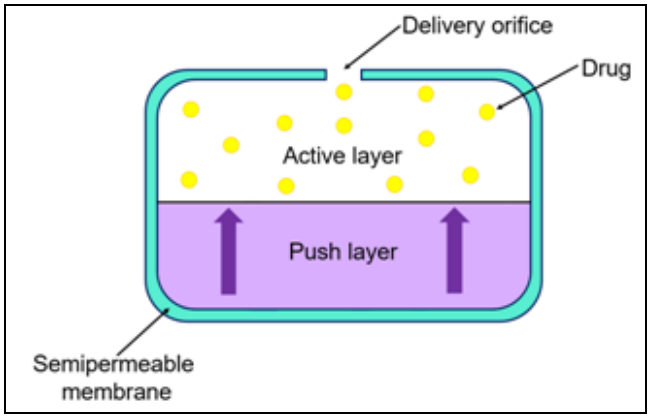

FIG. 3: PUSH-PULL OSMOTIC PUMP

Sustained-Release Tablets: In India, sustained-release tablets with 5 and 10 mg of GPZ are being sold, they are made by different pharmaceutical companies, like USV Private Limited, Emcure Pharmaceuticals Ltd, Orchid Chemicals and Pharmaceuticals Ltd. and are commercialized with the names of Glynase® XL, Bimode® SR and GTrol®, respectively. Likewise, RPG (Acumed) makes tablets with 2.5mg, 5 mg, and 10 mg of GPZ that are commercialized as Glutop®SR; finally, RPG Life Sciences makes tablets with 6.85 mg and 9.35 mg of GPZ that are commercialized as Glytop®SR [32].

Chung *et al.* (2002) performed an open-label, randomized, two-way crossover clinical study in which they compared during 5 days the pharmacokinetic and pharmacodynamic profiles of GPZ controlled-release tablets (GPZ GITS in a 20 mg dose) with GPZ IR (two doses of 10 mg per day, one in the morning and once at night) in 20 male patients with DBT2; they pointed out that during the 5 days of treatment with either GPZ GITS or GPZ IR similar reductions in serum glucose and increases in serum levels of insulin and peptide C were produced; however, the pharmacokinetic profile of the GPZ GITS tablet was significantly different from that of the GPZ IR. The average value of C_{max} of GPZ IR was significantly higher than that of GPZ GITS; however, the mean plasmatic concentration of GPZ at time zero, just before the morning dose (C0) was 80% higher with GPZ GITS, the time to reach maximal plasmatic concentration (t_{max}) was

significantly lower with GPZ IR, besides the area under the curve from time zero (just before de dose) until 24 h after the morning dose (AUC0-24) was lower with GPZ GITS. Hence, the bioavailability of GPZ GITS in relation to GPZ IR was of 81% ± 22%. **Fig. 4** shows that plasmatic concentrations were lower at the end of the dosage intervals for GPZ IR than with GPZ GITS. Authors concluded that therapy with GPZ GITS administered once a day achieves the same degree of glycemic control as the administration twice a day with GPZ IR; besides, the lack of marked peaks in the plasmatic concentrations of GPZ with the controlled release tablets can grant advantages, like lower insulin levels during fasting, which can reduce the sulfonylurea's- associated ADRs like hypoglycemia, increased body weight and changes in plasmatic lipid levels [33].

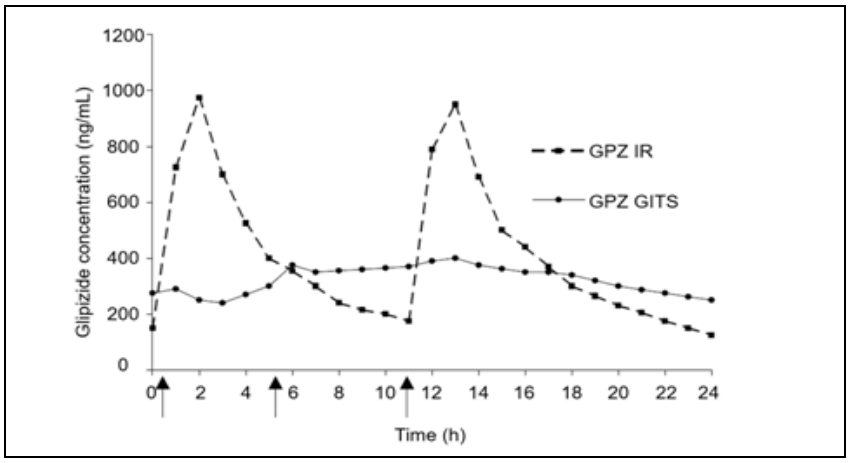

FIG. 4: COMPARISON OF MEAN PLASMATIC CONCENTRATION OF GLIPIZIDE ON THE 5TH DAY OF CONTROLLED RELEASE GPZ TREATMENT (GPZ GITS, 20 MG ONCE A DAY) OR IMMEDIATE-RELEASE GPZ (GPZ IR, 10 MG TWICE DAILY) IN PATIENTS WITH DBT2.↑ = TIME OF DAY OF STANDARDIZED MEALS. GRAPH OBTAINED AND MODIFIED FROM CHUNG *ET AL*., 2002 [33]

Dhawan *et al.* (2006) performed a single-dose clinical assay of four periods and four treatments with a Latin square crossed design, in which 12 healthy male volunteers participated (18-35 years). Here they compared four formulations with 5 mg of GPZ: GPZ IR, GPZ of sustained-release (Glynase XL®), GPZ GITS of controlled release (Glucotrol XL®) and a new formulation developed by the authors (hydrophilic matrix of prolonged-release, HMPR). Results indicated that the effective minimal plasmatic levels of GPZ (50 ng/mL) were maintained for almost 24 h for the three formulations of modified release and for approximately 9 h for the immediate release formulation; plasmatic levels of GPZ were higher with GPZ GITS for a longer time **Fig. 5**.

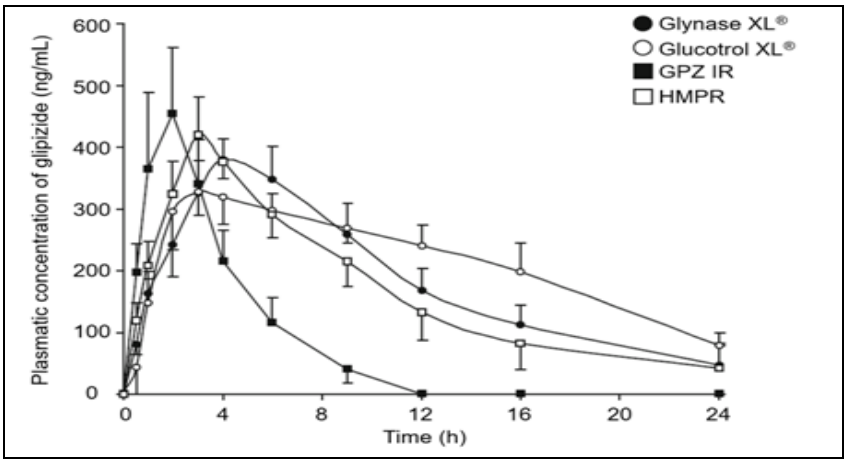

FIG. 5: COMPARISON PROFILE OF MEAN PLASMATIC CONCENTRATION AGAINST TIME OF DIFFERENT GLIPIZIDE FORMULATION IN HEALTHY MALE PATIENTS. GLYNASE XL®=SUSTAINED RELEASE, GLUCOTROL XL®=CONTROLLED RELEASE, GPZ IR= IMMEDIATE RELEASE, AND HMPR=HYDROPHILIC MATRIX OF PROLONGED-RELEASE. GRAPH OBTAINED AND MODIFIED FROM DHAWAN *ET AL*., 2006 [3]

The AUC was higher for Glucotrol XL® followed by Glynase® XL, HMPR, and GPZ IR. The C_{max} was lower for Glucotrol XL® followed by Glynase® XL, HMPR, and GPZ IR. The difference between the t_{max} of GPZ IR and the modified release formulations was statistically significant, but no statistically significant difference was observed between Glucotrol XL® and Glynase® XL. Thet lag was higher for Glucotrol XL®, followed by HMPR and Glynase® XL. The first-order constant for the absorption velocity (ka) was higher for GPZ IR followed by HMPR, Glynase® XL, and Glucotrol XL®. The elimination half-time (t1/2) was not statistically different among formulations. The mean time of residence (MTR) was higher for the modified-release formulations than for GPZ IR. This study concluded that the GPZ modified-release formulations maintained their plasmatic concentrations for approximately 24 h and were higher than those of GPZ IR [34].

Matrix Tablets: Mehsud *et al.* (2016) used the direct compression methodology to make matrix tablets with 5 mg of GPZ. In their formulation, the authors used different grades of ethylcellulose (Ethocel™ Std. 7, 10, 100 premium and Ethocel™ Std. 7, 10, 100 premium FP) and starch, hydroxypropyl methylcellulose (HPMC) K100M and sodium carboxymethylcellulose (CMC-Na) as additional excipients. Results revealed that formulations with different grades of ethylcellulose showed a prolonged release of up to 12 h as compared with the formulation without the polymer; in addition, the release was extended and controlled during 24 h when using Ethocel™ Std. 7 premium. All additional excipients improved the release rate of the drug; however, HPMC K100M showed a slower GPZ release than CMC-Na and starch. Conclusions point out that, with this formulation, the frequency of the dose can be reduced, and consequently, compliance by the patient can be improved [35]. Huang *et al.* (2018) designed GPZ tablets with a hydrophilic matrix; they used HPMC K4M, hydroxypropyl-β-cyclodextrins (HP-β-CD), pH modifiers (magnesium oxide and sodium citrate), spray-dried lactose monohydrate, and magnesium stearate, tablets were made by direct compression. This research pointed out that magnesium oxide is a better pH modifier than sodium citrate; the pH effect on the GPZ release was improved, and the accumulated GPZ release in acid dissolution media increased in 24 h from less than 40% to more than 90%. The drug was released through a Fickian diffusion mechanism [36].

Microspheres: Joshi *et al.* (2013) developed GPZ microspheres through the emulsion solvent evaporation method; they used acrylic and methacrylic acid esters with low content quaternary ammonium groups (Eudragit® RS 100 and Eudragit® RL 100). The obtained microspheres were spherical, with a rugose surface and a 112 to 132 µm size. According to results, when using Eudragit® RL 100combined with Eudragit® RS 100, GPZwas released faster as compared to using Eudragit® RS 100 alone. Likewise, it was found that the release of GPZ from the microspheres occurs through non-Fickian diffusion [19].

In 2019, Sharma and Choudhury developed and evaluated *in vitro* and *in vivo* microspheres with GPZ obtained through a coacervation method. They used ethylcellulose as a polymer and obtained white-colored spherical microspheres. According to the results, the amount of polymer had a direct effect on the morphological and release characteristics. High amounts of ethylcellulose yielded uniformly sized microspheres with smooth surfaces; besides, the GPZ release from the microspheres depended on the thickness of the wall formed by the polymer. The drug was released completely in 10 h. The *in-vivo* evaluation was performed for 7 days in both healthy and hyperglycemia-induced albino male Wistar rats. Animals were divided into four groups; group 1 or control, receiving a saline solution orally; group 2 with streptozotocin-induced DBT2; group 3, receiving orally 5 mg/kg of pure GPZ per day and group 4, receiving orally a number of microspheres equivalent to 5mg/kg of GPZ per day. A 25% reduction in plasma glucose level was considered a significant hypoglycemic effect. The results showed that, with microspheres and with pure GPZ, there was a hypoglycemic effect. Besides, with the microspheres, plasma glucose levels were reduced around 47% and 59.75% to pure GPZ [37].

Nanoparticles: Emami *et al.* (2014) developed modified release GPZ nanoparticles with the ionotropic controlled gelation method using low viscosity sodium alginate and chitosan. The

selection of 150 to 650 nm as the size range of the nanoparticles was for optimization purposes, and the authors indicate that nanoparticles smaller than 1000 nm are better suited for oral administration. The assay pointed out that the developed system can be made easily and economically and escalated; hence, it is feasible at the industrial level. Besides, the developed system is biocompatible, non-toxic, and diminishes the fluctuation in concentration of the drug within the therapeutic window [25].

Kamboj and Verma (2019) developed and evaluated *In-vitro* and *in-vivo* GPZ nanoparticles. They used a non-ionic triblock copolymer, which was soluble in water, constituted by polyoxypropylene and polyoxyethylene units (Pluronic® F127), palmitic acid (PA) polyvinylalcohol. The pentablock copolymer PA-F127 was synthesized by reacting the PA with Pluronic® F127, later to elaborate the nanoparticles through the solvent evaporation method. They evaluated different proportions of GPZ, PA-F127, and maintained constant the amount of polyvinylalcohol; according to morphological features, encapsulation efficiency, and yield percentage, the 1:1 proportion was chosen as optimal. The nanoparticles obtained with this proportion had an average size of 243 nm. Results pointed out that the *in-vitro* release of GPZ was initially abrupt and explosive (burst effect) followed by an extended-release.

The pharmacokinetic evaluation was performed in albino male Wistar rats and comparing the nanoparticles against a GPZ suspension; results showed that the C_{max} of nanoparticles was 2.35-times higher than that of the suspension, the t_{max} was of 6 h for nanoparticles and 4 h for the suspension, the t1/2 was 1.5 times higher for nanoparticles than for the suspension, the $AUC0_{\rightarrow}\infty$of nanoparticles was 3.3-times higher than that of the suspension, and there was a 1.2-times improvement in the mean residence time for nanoparticles. Authors concluded that the oral administration of a dose of nanoparticles equivalent to 1.5 mg/kg of GPZ maintained up to 24 h the therapeutic plasmatic concentrations, suggesting that the issue of administering GPZ two or three times per day can be overcome with the use of nanoparticles [3].

Self-emulsifying systems: A research by Dash *et al.* (2015) developed a solid self-nano emulsifying drug delivery system (S-SNEDDS) of GPZ. They used, as oil, medium-chain triglycerides (Captex®355), polyoxyethylene esters of 12-hydroxystearic acid (Solutol® HS15) as surfactant agent and medium-chain monoglycerides (Imwitor® 988) as a co-surfactant agent. In the optimized formulation, they used the following proportions: Captex®355 (30% w/w), Solutol® HS15 (45% w/w) and Imwitor® 988 (25% w/w). The mean drop size was of 29.4 nm, and the zeta potential of -35.0 mV.

To evaluate the *in vitro* release, a comparison of the four formulations with 5 mg GPZ was performed (liquid SNEDDS, solid SNEDDS, Glucotrol®, and the pure drug).Findings were that the GPZ release percentage in 15 min was 99.65, 97.63, 65.82, and 18.37, respectively, the increase in the release percentage was statistically significant with liquid and solid SNEDDS as compared to Glucotrol® and pure GPZ, suggesting that the increased release percentage of the solid SNEDDS could be attributed to the presence of amorphous GPZ in its inside [38]. On the other hand, Agrawal *et al.* (2015) developed a solid self-emulsifying drug delivery system (S-SEDDS) with 2.5 mg of GPZ, evaluating it *in-vitro* and *in-vivo*.

The chosen oil was biocompatible and contained 53% of phosphatidylcholine in medium-chain caprylic/capric triglycerides (Phosal® 53 MCT), polysorbate 80 as surfactant agent, monoethylic ether of diethylene glycol (Transcutol® P) as cosolvent and porous silicon dioxide (Syloid 244® FP) as adsorbent. *In-vitro* studies in simulated gastric fluid (pH 1.2, without enzyme) and simulated intestinal fluid (pH 6.8, without enzyme) indicated that the S-SEDDS released more than 85% of the drug in 20 min. *In-vivo* studies were performed in male Sprague-Dawley rats treated orally with pure GPZ and S-SEDDS; after 30 min, they received glucose (2g/kg). Results showed that S-SEDDS induced a greater reduction in blood glucose than pure GPZ, but the difference was not statistically significant [39].

Nanosuspensions: In 2020, Raja and Venkataraman developed, with the nano-precipitation method, a 200-mg GPZ nano-

suspension and then evaluated its pharmacokinetics. The materials used were povidone K30, HPMC K15M, anionic copolymers based on methacrylic acid, and methyl methacrylate (Eudragit L100), poloxamer 188, and polyethylene glycol 200. Each polymer at different percentages was assessed in the formulations. The formulation chosen by the authors as the best (2% of Eudragit L100) presented a particle size between 98 and 107 nm, zeta potential of 55.3 mV, and encapsulation percentage of 94.53%. It showed a GPZ release of 99.62% in 12 h, and the release mechanism was through non-Fickian diffusion.

The Pharmacokinetic evaluation was performed in albino Wistar rats; the authors compared the oral administration of 1 mg/kg of body weight of the nanosuspension and pure GPZ, obtaining that the t1/2 was of 1.05 h and 0.63 h for the nanosuspension and the pure drug, respectively. The t_{max} was of 4 h for both cases. The C_{max} was 1.65 ng/mL for the nanosuspension and 0.92 ng/mL for the pure GPZ. The $AUC_{0\rightarrow}t$ was 5.842 µg/mL per hour for the nanosuspension and 3.336 µg/mL per hour for the pure GPZ. Results suggest that the GPZ nanosuspension can be used as an administration system for this drug [40].

Gastroretentive Systems: An alternative to reduce the variability in the release and absorption of the drug and increase the bioavailability in the modified release systems is to prolong the residence time of a drug in the stomach through gastroretentive dosage systems [41]. These systems can be classified into four approaches; swelling, expansion, floating, and bioadhesive and mucoadhesive systems [42]. Some of the advantages of these systems are improved therapeutic efficacy, reduced drug loss, increased solubility and utilization of drugs that act locally in the stomach and duodenum [43]. Low density or floating systems must have a lower density than gastric fluids (1.004 g/cm3); consequently, they float on the gastric content and persist in the stomach while releasing the drug. It is important to point out that floating tablets must fulfill two important characteristics: have a high porosity to promote flotation and resist destruction due to gastric peristalsis [44]. The floating systems can be classified as effervescent and non-effervescent systems. In contrast, the high-density systems must have a higher density than the gastric fluids, approximately 3 g/cm3 to be retained in the stomach folds and of 2.4 to 2.8 g/cm3 to be retained in the folds of the gastric antrum. This type of formulation uses barium sulfate, zinc oxide, titanium oxide, among others, as excipients [45]. For GPZ, different formulations of floating systems have been developed, as will be described in the next paragraphs. A polymer widely used in this type of formulation is HPMC because of its pH-independent gelling property [46].

Non-effervescent Systems: Meka *et al.* (2015) formulated a non-effervescent GPZ floating system and improved the solubility of the drug-using solid dispersion. The formulation incorporated poloxamer 188, which significantly increased GPZ solubility, HPMC and poly (ethylene oxide) (PEO) to provide *in-vitro* floatability and control the drug release crospovidone was used as a swelling agent. Results indicate that the incorporation of solid dispersion in floating tablets is promising because the solubility of scarcely soluble drugs can be improved, and a controlled release can be achieved through gastric retention [47]. Likewise, non-effervescent GPZ floating tablets have been developed through wet granulation and using HPMC K4M and reticulated polyacrylic acid (Carbopol®934) as gel-forming polymers [48].

Effervescent Systems: Effervescent GPZ floating tablets have been formulated through direct compression, using HPMC K15M, HPMC K100M, and reticulated polyacrylic acid polymer (Carbopol® 940P) as gel-forming polymers and sodium bicarbonate and anhydrous citric acid as effervescent agents [42]. Sivabalan *et al.* (2011) elaborated by direct compression floating tablets with 10 mg GPZ. HPMC, ethylcellulose, methylcellulose (MC), microcrystalline cellulose, sodium bicarbonate, and magnesium stearate were used. For the development, a 23 factorial design was used; the chosen factors were: ratio of drug content to total polymer, ratio of polymer mixture (HPMC and MC) to ethylcellulose, and HPMC to MC. The optimized formulation had an *in-vitro* release of 59.25% in 8 h; besides, it showed a controlled GPZ release and a floating time of 16.2 h [49]. Zeel *et al.* (2012) developed floating tablets with 10 mg GPZ, based on an effervescent agent. Tablets were made by direct compression. The used materials were HPMC 5 cps, a reticulated polymer

of polyacrylic acid (Carbopol® 940), sodium bicarbonate, citric acid, povidone K30, microcrystalline cellulose, and magnesium stearate. The best formulation showed a floating lag time of 55 s, floating time of 24 h, and accumulated drug release of 96.62% in 24 h. The diffusion mechanism for GPZ-release was non-Fickian and followed first-order release kinetics [50].

Likewise, Ramabargavi *et al.* (2013) developed, through direct compression, floating tablets with 15 mg GPZ based on a gas-generating agent. They used HPMC 5cps, a reticulated polymer of polyacrylic acid (Carbopol® 940P), sodium bicarbonate, citric oxide, povidone K30, microcrystalline cellulose, and magnesium stearate. The floating lag time was of 45 s, the floating time of 23 h, and the accumulated release of the drug of 98.68% at 24 h. The diffusion mechanism for the drug release was Fickian, showing first-order release kinetics, suggesting that the formulation can be considered for further studies [51].

Singh *et al.* (2013) also formulated tablets with 10 mg GPZ using HPMC K4M and a reticulated polymer of polyacrylic acid (Carbopol® 934P), sodium bicarbonate as a gas-generating agent, microcrystalline cellulose, magnesium stearate, and talc. Tablets were manufactured by direct compression. A central composite design with α=1 was used; HPMC K4M and Carbopol® 934P concentrations were chosen as independent variables; whereas the dependent variables were the total floating time, the floating lag time, and the time to release 50% of GPZ. The optimized formula showed a total flotation time of 15.06 h, a floating lag time of 11.41 s, and the time needed to release 50% of the drug was 4.5 h. Results indicate that Carbopol 934P®is not adequate to improve flotation features but is useful to control the release of drugs like GPZ, whereas HPMC K4M improves flotation [52].

On the other hand, Uddhav *et al*. (2017) designed floating tablets with 10 mg GPZ by direct compression. They used HPMC (K4M, K15M), microcrystalline cellulose, sodium bicarbonate, magnesium stearate, PEG 6000, and talc. Before fabricating the tablets, a solid dispersion was made with PEG 6000 and GPZ (ratio 1:6). A 32 factorial design was used to study the effect of HPMC K4M and HPMC K15M on GPZ release; dependent variables were the percentage of released drug and the floating lag time. According to the results, the optimized formulation showed a floating time greater than 24 h, a floating lag time of 81 s, and a swelling index of 255%. Glynase® XL of 10 mg and the optimized batch were chosen to study the similitude factor. The percentage of released GPZ in 8 h was 61.48% for the optimized formulation and 55.64% for Glynase® XL the similitude factor was 51.58%. The model of best fit for the optimized batch was of zero-order kinetics [53].

Bioadhesive Systems: In 2011, Ranga *et al.* developed a floating and bioadhesive system with 10 mg of GPZ by direct compression. They used HPMC (K4M, K15M, and K100M), a reticulated polymer of polyacrylic acid (Carbopol® 974P), sodium bicarbonate, microcrystalline cellulose, magnesium stearate, and talc. The optimized formula contained HPMC K15M in the same proportion as Carbopol® 974P (50:50). Results showed that the floating lag time was 24 s, the floatability time of 23 h, the swelling index of 101%, and the accumulated GPZ release was 89.9% at 12 h. The force of adhesion was 2.60 dynes, the release kinetics best fitted the Higuchi model. Results indicated that a floating and bioadhesive administration system of drugs offers the advantage of a longer gastric residence time than normal floating drug-delivery systems [54].

CONCLUSION: Glipizide is a second-generation sulfonylurea widely used as a treatment for type 2 diabetes. It is a drug with short half-life elimination; hence it needs to be dosed in two or three tablets per day, depending on the therapeutic requirements of each patient. The aforementioned has led different research groups to develop new delivery systems for this drug: nanoparticles, nanosuspensions, microspheres, self-emulsifying systems, matrix tablets, osmotic tablets, and gastroretentive systems. These systems offer some advantages over immediate release systems. For example, osmotic systems are costly, but they provide zero-order release kinetics. The gastroretentive systems prolong the residence time of the tablet in the stomach, favoring the absorption of glipizide. Finally, the developed systems aim at reducing the frequency of glipizide dosage, which could improve therapeutic adherence by the patient.

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CONFLICTS OF INTEREST: Nil

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