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In Vitro and In Vivo Evaluation of Two Extended Release Preparations of Combination Metformin and Glipizide

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ABSTRACT A system that can deliver multi-drugs at a prolonged rate is very important to the treatment of various chronic diseases such as diabetes, asthma, and heart disease. Two controlled-release systems, which exhibited similar release profiles of metformin and glipizide, i.e., elementary osmotic pump tablets (EOP) and bilayer hydrophilic matrix tablet (BT), were designed. The effects of pH and hydrodynamic conditions on drug release from two formulations were investigated. It was found that both drug releases from EOP were not sensitive to dissolution media pH and hydrodynamics change, while the release of glipizide from BT was influenced by the stirring rate. Moreover, in vivo evaluation was performed, relative to the equivalent dose of conventional metformin tablet and glipizide tablet, by a three-crossover study in six Beagle dogs. Cumulative percent input in vivo was compared to in vitro release profiles. The linear correlations of metformin and glipizide between fraction absorbed in vivo and fraction dissolved in vitro were established for EOP—a true zero-order release formula, whereas only nonlinear correlations were obtained for BT. In conclusion, drug release from EOP was both independent of in vitro and in vivo conditions, where the best sustained release effect was achieved, whereas the in vitro dissolution test employed for BT needed to be further optimized to be biorelevant.

KEYWORDS Elementary osmotic pump, Bilayer matrix tablets, Extended release, In vitro-in vivo correlation, Metformin, Glipizide

INTRODUCTION

Chronic diseases such as diabetes, asthma, and heart disease are often treated using multi-drug therapies, which are vulnerable to incidences of side effects, poor patient compliance, and slow improvement of patients. Though controlled drug delivery systems have been available separately for these drugs, a system that can deliver these drugs at a prolonged rate may ensure improved patient compliance and reduce the problems associated with multi-drug

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therapy. In addition to improved patient compliance, as a once-daily formulation, it could improve the safety profile and activity of drugs exhibiting short biological half-life. Up to now, controlled release of drug from dosage forms could be achieved by various means, ranging from simple matrix tablets to more technologically sophisticated osmotic controlled drug-release systems.

In general, HPMC seems to provide many advantages as a hydrophilic matrix system with excellent processability and many grades to choose for formulation flexibility. However, the oral osmotic pump tablet has more advantages, such as reducing risk of adverse reactions, improving patient compliance, in vivo predictability of release rate based on in vitro data, etc. Although similar in vitro dissolution profiles could be obtained by using completely different controlled release technologies, their in vivo behavior could differ significantly due to different release mechanisms in vivo and physiological factors, such as GI transit time, pH gradient, and hydrodynamics. It has been found that osmotic tablets were not affected by food intake as much as matrix tablets (Schug et al., 2002). Furthermore, the matrix system was usually more subjected to the changes of the stirring rate. So it was generally recognized that in vitro-in vivo correlation was very important to extended release oral dosage forms (U.S. Department of Health and Human Services, 1997).

Metformin and glipizide are oral hypoglycemic agents belonging to the biguanide group and second-generation sulphonylurea, respectively (Carruthers et al., 2000). Generally, they are individually used in the treatment of type II noninsulin dependent diabetes mellitus. Metformin acts by decreasing hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake. Because of its shorter and variable biological half-life of 1.5–4.5 h, it should be repeatedly administered (250 mg twice or thrice a day) to maintain effective plasma concentration. Glipizide lowers glucose concentrations by stimulating the release of insulin from pancreatic β-cells. Glipizide has a similarly biological half-life (2–4 h), depending upon the individual, and the dose is 2.5 mg two to three times a day. The combination of metformin with glipizide is more effective than individual therapy because of the synergism (Katzung, 2001). There were many extended release formulations available on the market for both drugs, such as Glucophage® XR (metformin extended release tablets, Bristol-Myers Squibb Co., USA) and Glucotrol XL® (glipizide controlled release tablet, Pfizer Inc., USA). There were many papers published describing formulation and IVIVC development for these drugs (Balan et al., 2001; Gan et al., 2002; Verma & Garg, 2004).

In this paper, two distinct controlled-release preparations, elementary osmotic pump tablets and bilayer hydrophilic matrix tablets, were employed in formulating combination metformin and glipizide. The in vitro drug dissolution and in vivo drug pharmacokinetics of two formulations were evaluated. Moreover, in vitro dissolution and in vivo absorption correlations of both drugs from two formulations were also investigated.

MATERIALS AND METHODS

Materials

Metformin (Kunsan Shuanghe Pharmaceutical Company, China), glipizide (Shanghai Fifteenth Pharmaceutical Factory, China), HPMC K100M, K15M, and K4M (gift samples from Shanghai Colorcon Coating Technology Limited, China), stearic alcohol (Tianjin Chemical Company, China), lactose (Shenyang Dongxin Chemical Factory, China), cellulose acetate (CA, 54.5–56.0 wt.% acetyl content, Shanghai Chemical, Shanghai, China), polyethylene glycol (PEG) 400, 1500, 4000 (Pudong Gaonan Chemical, Shanghai, China), sodium carbonate (Tianjin Chemical Company, China), conventional metformin tablets (Guangzhou Pharmaceutical Company, Batch 040510), conventional glipizide tablets (Hainan Jinxiao Pharmaceutical Company, Batch 040306). All reagents used were of either HPLC or analytical grade.

Preparation of EOP and BT

Formulations were prepared according to different formulation principles (Table 1). Only formulations that were used later in animal testing were included in this table; other formulations tested in vitro were compositionally similar to the listed formulations.

Granules of the osmotic pump system were prepared by wet granulation method. Metformin, glipizide, PVP, and sodium carbonate were mixed well, 95% alcohol solution was added to make granules by passing through a mesh (1150 μm), and the granules

TABLE 1 Summary of Formulation Composition of Two Controlled-Release Preparations

Ingredients	mg/Tablet
Elementary osmotic pump tablets	
Tablet core	
Metformin	500
Glipizide	5
Sodium carbonate	5
PVP K90	30
Magnesium stearate	3
Coating solution (acetone)	
Cellulose acetate	28
PEG-1500	12
Total tablet weight	583
Bilayer matrix tablets	
Metformin layer	
Metformin hydrochloride	500
HPMC K100M	100
Stearic alcohol	100
Magnesium stearate	3
Glipizide layer	
Glipizide	5
HPMC K4M	80
Lactose	90
Magnesium stearate	1
Total tablet weight	879

were kept at 40°C for 2 hours. After this, the granules were passed though a mesh (1000 μm) and lubricated with magnesium stearate. Granules were compressed by a single-station punching machine (TDP single tablet machine, The First Pharmaceutical Manufacturing of Shanghai, China) with concave punches (diameter, 12 mm). The average hardness of compressed tablets was found to be 80±10 N. Cellulose acetate (CA, 2%, w/v) containing known levels of plasticizer (PEG-1500) was used as a coating solution. An exit port measuring 0.6 mm diameter was mechanically drilled through the membrane.

The bilayer extended release tablets were formulated by using wet granulation technique. Granules of metformin and glipizide were prepared separately. The ingredients (listed in Table 1) were mixed and passed through a mesh (250 μm). A 95% alcohol solution was used as granulating solvent and the wet mass was passed through a mesh (1150 μm). The granules were kept at 40°C for 2 h and dried granules were passed though a mesh (250 μm). Granules were lubricated with magnesium stearate. Granules were compressed by using 19.5/9.5 mm oval shape punches in a single-station punching compression machine. Bilayer tablets were prepared manually by double compression method. First, the die cavity was adjusted for required weight of lower layer and was compressed. Then, the compressed lower layer was again pressed into the die cavity, adjusted for required weight of upper layer and compressed to produce bilayer tablet. The average hardness of tablets was 80±10 N.

In Vitro Dissolution Study

All prototype formulations were evaluated for their in vitro release behavior. The in vitro release test was carried out in USP paddle apparatus by using 500 mL of pH 6.8 phosphate buffer as the medium at 37°C and 50 rpm. Five mL of samples were taken at 1, 2, 3, 4, 6, 8, and 10 h, filtered through 0.45 μm filter membrane. Five mL of fresh dissolution medium was added after each sampling.

The content of metformin was determined at 233 nm by UV (UV spectrophotometer, model UV-9100, Beijing Ruili analysis instrument Co. Beijing, China). The mean calibration curve of metformin (C = 10.952A + 0.1494) was linear between 1.60 and 9.60 μg/mL. The correlation coefficient of calibration curve was 0.9999. The recovery of the 2, 5, and 9.5 μg of metformin per mL was 98.9±0.5%, 99.0±0.7%, and 98.8±0.9%, respectively. The precision of the 2, 5, and 9.5 μg of metformin per mL was 0.61%, 0.40%, and 0.45%, respectively. Stability of metformin in different solvents was good.

The percentage of glipizide was determined at 275 nm by HPLC. Briefly, 20 μL of the filtrate was injected into HPLC, consisting of ODS C_{18}, 250*4.6 mm, 5 μm particle size column. Acetonitrile/methanol/pH 7.0 PBS (5:6:11) was used as the mobile phase and pumped with the help of two LC-10 VP pumps (Shimadzu) at the rate of 1 mL/min. The calibration curve of glipizide (A=50810C+1549.7) was linear between 0.5 and 10 μg/mL. The correlation coefficient of calibration curve was 0.9999. The recovery of the 1, 5, and 10 μg of glipizide per mL was 98.6±0.7%, 99.0±0.5%, and 98.9±0.4%, respectively. The precision of the 1, 5, and 10 μg of glipizide per mL was 0.72%, 0.43%, and 0.66%, respectively. Stability of glipizide in different solvents was good. The retention time, tailing factor, and theoretical plates were 7.1 min, 1.01, and 4200, respectively.

In Vivo Evaluation

In vivo evaluation of osmotic pump tablet and bilayer tablet were performed relative to the equivalent dose of conventional metformin tablet and glipizide tablet, by a three-crossover design in six Beagle dogs. Six Beagle dogs were open-label and fasting 12 h. Five-milliliter samples of blood were collected predose and at the following times postdose: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 14, and 24 h. Samples were immediately centrifuged at 3500 rpm for 10 min. The plasma was separated and frozen at −20°C for use. Mean concentrations in plasma vs. time data were evaluated using 3P97 Professional (Chinese pharmacological association software). The deconvolution procedure was used to obtain in vivo input profiles of metformin and glipizide from bilayer tablet and EOP. The deconvolution of bilayer tablet and EOP data was attempted using the data of the immediate release tablets as the reference treatment.

Determination of metformin in blood samples: 0.2 mL plasma was vortex-mixed with 0.5 mL methanol for 3 min and centrifuged at 3500 rpm for 10 min. The organic layer was analyzed at 233 nm using a reversed-phase HPLC system. Briefly, 20 μL of the filtrate was injected into HPLC, consisting of ODS C_{18}, 250*4.6 mm, 5 μm particle size column. Methanol/0.02 $mol \cdot l^{-1}$ ammonium phosphate monobasic aqueous solution (50:50, consisting of 0.1% sodium lauryl sulfate) was used as the mobile phase and pumped with the help of two LC-10 VP pumps (Shimadzu) at the rate of 1 mL/min. The calibration curve of glipizide was linear between 0.5 and 20 μg/mL and the correlation coefficient of calibration curve was 0.9934. The detection limit was 0.2 μg per mL. The recovery of the 0.5, 5, and 20 μg of metformin per mL was 99.1±0.8%, 98.0±0.6%, and 98.8±0.4%, respectively. The precision of the 1, 5, and 10 μg of metformin per mL was 0.87%, 0.56%, and 0.76%, respectively.

Determination of glipizide in blood samples: 0.5 mL plasma was acidified with 200 μL 0.5 M HCl and vortex-mixed 1 min. Acidified plasma was vortex-mixed with 3 mL benzene for 5 min and centrifuged at 3500 rpm for 10 min. The organic layer was dried at 40°C under a stream of nitrogen and the residue was dissolved in 100 μL methanol. Briefly, 20 μL of the filtrate was injected into HPLC, consisting of ODS C_{18}, 250*4.6 mm, 5 μm particle size column. The mobile phase was acetonitrile/methanol/H_2O (35:10:55) at the rate of 1 mL/min. The calibration curve of glipizide was linear between 20 and 600 ng/mL and the correlation coefficient of calibration curve was 0.9952. The detection limit was 8 ng per mL. The recovery of the 20, 100, and 600 ng of glipizide per mL was 98.4±0.8%, 99.0±0.5%, and 99.1±0.4%, respectively. The precision of the 20, 100, and 600 ng of glipizide per mL was 0.79%, 0.86%, and 0.87%, respectively.

RESULTS AND DISCUSSIONS

Metformin has an absorption window and exhibits saturation in absorption. Oral absorption of metformin is confined to the upper part of the intestine, i.e., the duodenum, jejunum and, to a lesser extent, ileum (Scheen, 1996; Vidon et al., 1988). Metformin is a class 3 (high solubility–low permeability) Biopharmaceutical Classification System (BCS) drug with pKa 11.5. Glipizide is a class 2 (low solubility–high permeability) BCS compound and has no absorption window. Ideally, the extended release dosage forms should be designed considering that the drug is having absorption windows and exhibits saturation in absorption. If the drug has an absorption window, the long time release is undesirable, otherwise it would lead to reduction of bioavailability.

Formulations and In Vitro Release Study

Formulation Design

In general, both highly and poorly water-soluble drugs are not good candidates for osmotic delivery. However, metformin hydrochloride is highly soluble and high dose (500 mg), while glipizide is water insoluble and low dose (5 mg). It was a great challenge to the pharmacists how to design a formulation containing both drugs. In our previous study, it was found that the solubility of glipizide increased in the higher pH media. So sodium carbonate was chosen as a solubilizer for glipizide to modulate the microenvironment pH within the core during the dissolution process. From Figs. 1 and 2 it can be seen that glipizide release without sodium carbonate from osmotic pump was incomplete. Incorporation of sodium carbonate that modulated the solubility of glipizide within the core controlled the release of glipizide from the

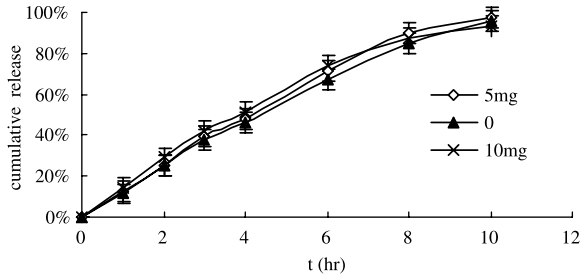

FIGURE 1 **Influence of Sodium Carbonate on Metformin Release Profiles from EOP (n=6).**

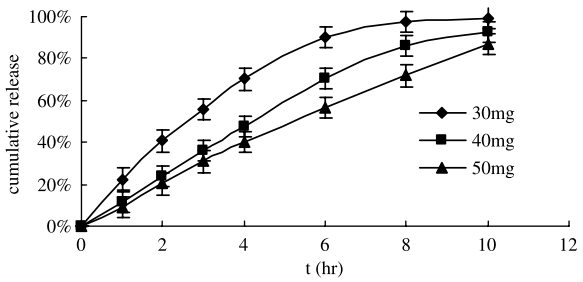

FIGURE 3 **Influence of Different Coating Levels on Metformin Release Profiles from EOP (n=6).**

osmotic systems (Fig. 1). However, sodium carbonate had no influence on the release of metformin (Fig. 2). On the other hand, high-dose metformin was difficult to formulate into a tablet dosage form due to its poor compressibility and compactibility Matharu et al., 2003. The way to overcome the difficulty was to utilize PVP K90 as a binder to prepare the tablet core. Cellulose acetate (CA) was used as semipermeable membrane and polyethylene glycol 1500 (PEG-1500) was employed as plasticizer for controlling membrane porosity.

Unlike matrix systems, the osmotic system had the potential to deliver drugs in a zero-order fashion as long as orifice diameter was optimized, and exhibited true zero-order release as indicated by the linear release profiles between 0 and 8 h. When the osmotic system was subjected to different levels of coating (30 mg, 40 mg, and 50 mg), a gradual decrease in the release rates were observed as a function of coating levels (Figs. 3 and 4).

For bilayer matrix tablet, stearic alcohol was essential because metformin had poor compressibility and compactibility. Strictly speaking, the compressibility of a material was its ability to reduce in volume as a result of an applied pressure. In contrast, compactibility was the ability of a material to produce a cohesive mass (compact or compressed tablet). In the

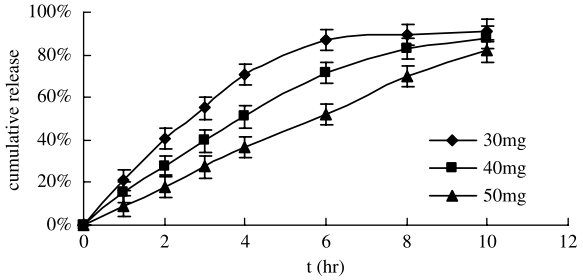

FIGURE 4 **Influence of Different Coating Levels on Glipizide Release Profiles from EOP (n=6).**

process of compressing the granules into the tablets, stearic alcohol melted because of its low melting point and formed a solid bridge to improve the physical properties of the tablets. From Figs. 5, 6, it can be seen that the viscosity of HPMC had only little influence on metformin release, while it has much effect on glipizide release. The main reason was that metformin had high dose (500 mg) and was highly soluble, while glipizide had low dose and low solubility. The higher viscosity of polymer was used, the slower rate of polymer hydration/erosion was produced.

To evaluate the performance of the optimal formulations, release profiles were compared with the marketed extended release formulations. Figures 7

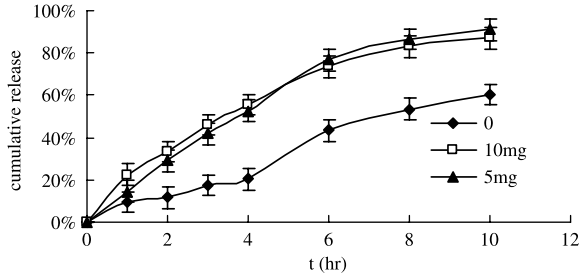

FIGURE 2 **Influence of Sodium Carbonate on Glipizide Release Profiles from EOP (n=6).**

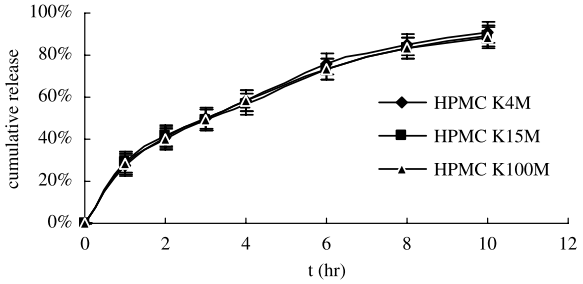

FIGURE 5 **Influence of the Viscosity of HPMC on Metformin Release Profiles from BT (n=6).**

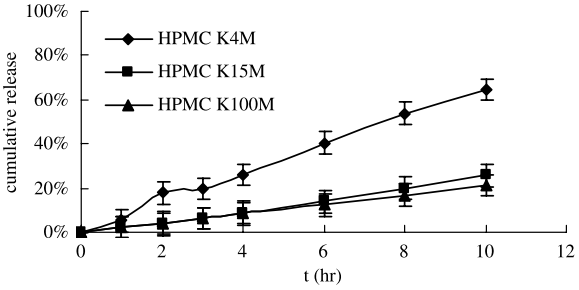

FIGURE 6 **Influence of the Viscosity of HPMC on Glipizide Release Profiles from BT (n=6).**

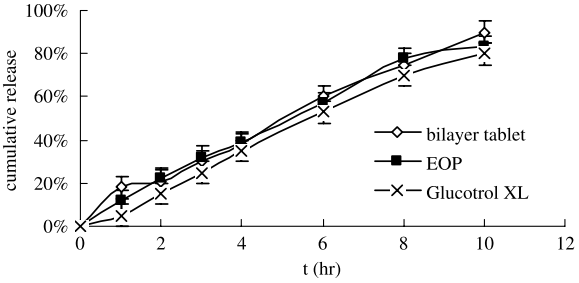

FIGURE 8 **Glipizide Release Profiles of Bilayer Tablet, EOP in Comparison with Glucotrol XL (Pfizer Inc., USA) (n=6).**

and 8 show that release profiles of bilayer tablet, EOP, and marketed formulations were similar.

Evaluation of Formulation

In order to simulate the environmental conditions in the human gastrointestinal tract, in vitro drug release tests of the optimal formulations were conducted in 0.1 N HCl (pH 1.1) for the first 2 hours followed by pH 6.8 phosphate buffer for 8 hours. Figure 9 shows that the release profiles of bilayer tablet and EOP were similar.

To study the effect of stirring rate on the drug release profiles, dissolution tests of the optimal formulations were carried out at stirring rates of 50, 100, and 150 rpm. Figures 10 and 11 show that an increase in the rate of stirring did not significantly affect the release rate of drug. Thus, the mobility of the gastrointestinal tract might scarcely affect the drug release of the EOP.

However, when the effect of hydrodynamics was evaluated using bilayer tablets as shown in Figures 12 and 13, it was found that the release of glipizide was significantly faster with the increase of the stirring rate. It indicated that the effect of hydrodynamic change due to stirring rates (50–150 rpm) had a significant

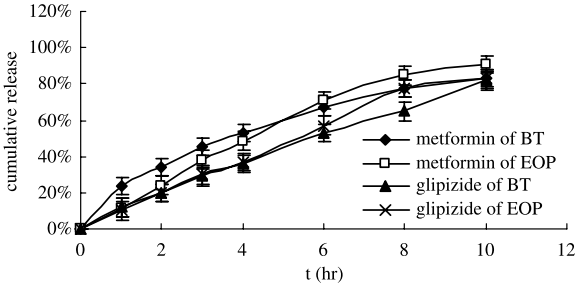

FIGURE 9 **In vitro Release of Metformin and Glipizide from Bilayer Tablet (BT) and Elementary Osmotic Pump (EOP), Using 0.1 N HCl (0–2 hr) and pH 6.8 Phosphate Buffer (2–10 hr) as Medium (n=6).**

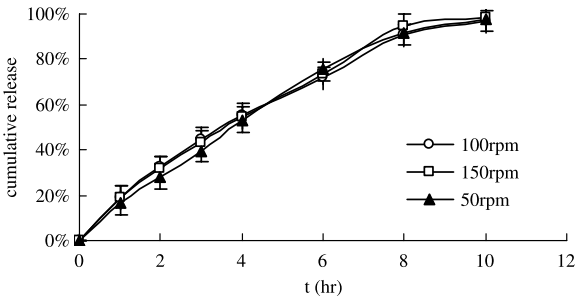

FIGURE 10 **Influence of the Stirring Rate on Metformin Release Profiles from EOP (n=6).**

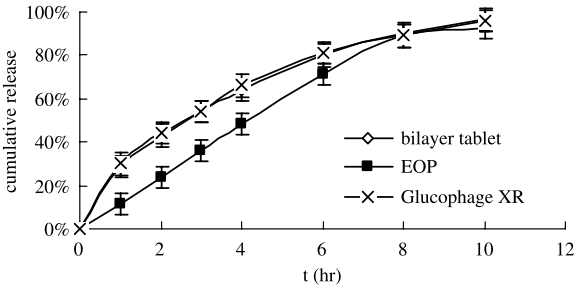

FIGURE 7 **Metformin Release Profiles of Bilayer Tablet, EOP in Comparison with Glucophage XR (Bristol-Myers Squibb Co., USA) (n=6).**

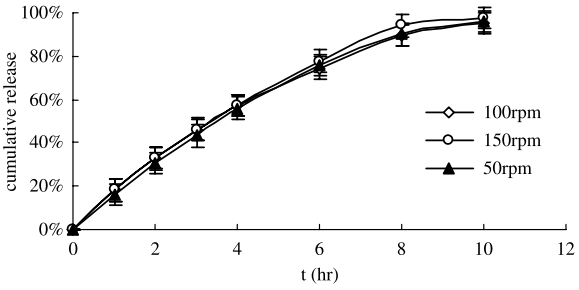

FIGURE 11 **Influence of the Stirring Rate on Glipizide Release Profiles from EOP (n=6).**

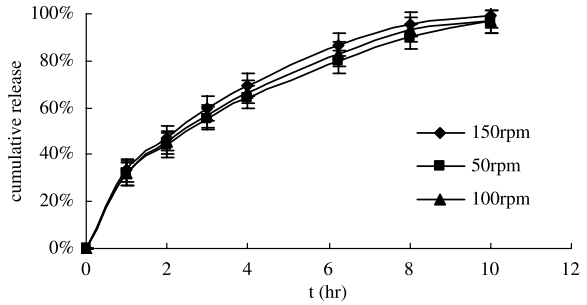

FIGURE 12 **Influence of the Stirring Rate on Metformin Release Profiles from BT (n=6).**

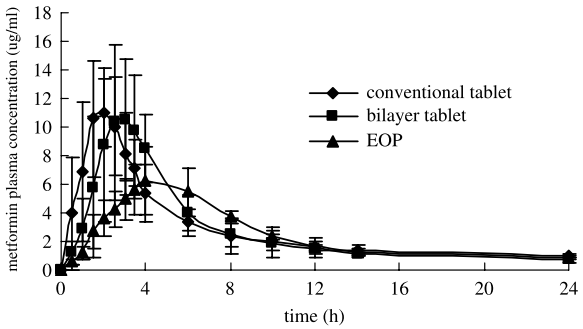

FIGURE 14 **In Vivo Pharmacokinetic Profiles of Metformin in Beagle Dogs of Two Controlled Release Formulations (n=6).**

impact on the erosion of the hydrogel of the layer of glipizide. Potentially, matrix tablets might be more variable when tested in vivo, compared to the osmotic pump, which was later confirmed by the in vivo study (Figs. 12 and 13).

Release Mechanism

For osmotic tablets, when the tablets come in contact with the aqueous environment of the GI tract, the osmotic core imbibed water from the surrounding medium via the semipermeable membrane and formed a saturated solution of metformin inside the device. At the same time, due to sodium carbonate-modulated pH within the core, the solubility of glipizide was improved and the glipizide solution was formed. As the membrane was nonextensible, the increase in volume caused by the imbibition of water lead to the development of hydrostatic pressure inside the tablet. Metformin not only acted as one of the active ingredients but also as the osmotic agent. This pressure was relieved by the flow of saturated solution out of the device through the delivery. This process continued at a constant rate until the entire solid agent inside the tablet had been dissolved, and only a solution-filled coating membrane was left. The residual dissolved agents continued to be delivered at a declined rate until the osmotic pressures inside and outside the tablet were equal.

For bilayer tablets, it could be seen that the data of metformin obtained from in vitro release was best fitted with Higuchi kinetics ($r=0.9984$), while the release of glipizide in vitro was found to follow zero kinetics ($r=0.9986$). Highly water-soluble metformin released primarily by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble glipizide was released predominantly by erosion mechanism.

In Vivo Evaluation

Concentration-time profiles of metformin and glipizide in blood after oral administration of two controlled released formulations are shown in Figs. 14 and 15. Measurable levels of metformin and glipzide were present in two of the three dogs at the last sample time point, 24 h post doses. The osmotic tablet generated at a nearly constant blood level of metformin and glipizide. The sustained plasma level was due to the constant drug release pattern from osmotic tablets in vivo. This was a preliminary

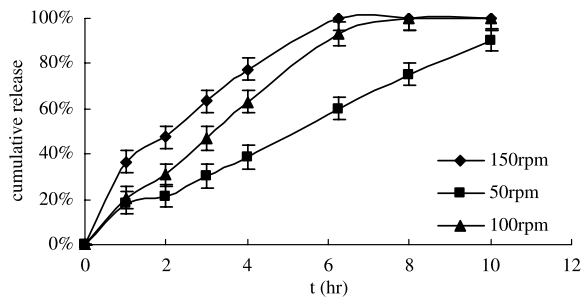

FIGURE 13 **Influence of the Stirring Rate on Glipizide Release Profiles from BT (n=6).**

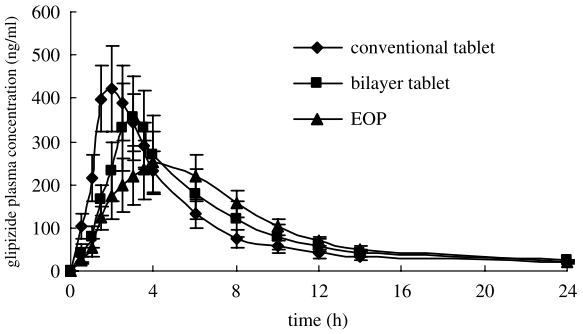

FIGURE 15 **In Vivo Pharmacokinetic Profiles of Glipizide in Beagle Dogs of Two Controlled Release Formulations (n=6).**

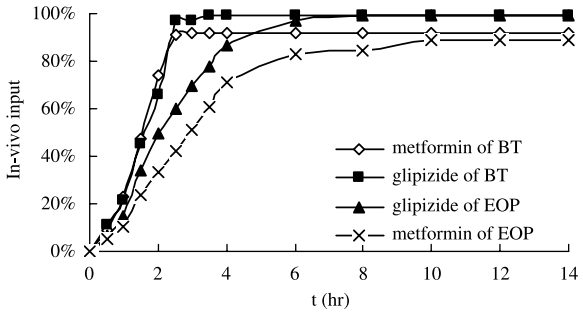

FIGURE 16 **Mean Percent In Vivo Input Profiles for Metformin and Glipizide Using the Deconvolution Method.**

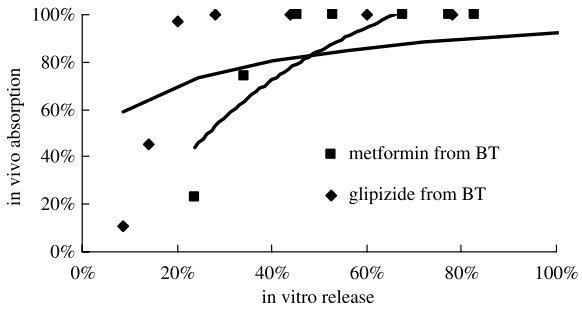

FIGURE 18 **IVIVC Model Linear Regression Plots of % Absorbed vs. % Dissolved for BT.**

indication that true zero-order release was obtained for the osmotic system under the in vivo environment. Comparing with the conventional tablets, mean relatively oral bioavailability of metformin and glipizide of EOP was 89.1% and 102.8%, respectively. The sustained blood levels were not evident after dosing BT. Concentration-time profiles were characterized by peak blood levels at 3 h post dose, which declined rapidly thereafter. The HPMC formulations yielded the highest average peak concentration between two extended formulations tested. The short T_{max} of the HPMC matrix tablets could be attributed to initial burst effect. The high C_{max} values observed following the HPMC formulations were evidence of "dose dumping," i.e., an initial burst effect. In another words, the matrix tablets behaved more like an immediate release formulation due to hydrodynamic conditions.

The results of the deconvolution analysis for metformin and glipizide are shown in Fig. 16. Percent in vivo input was plotted as a function of time and compared with percent dissolved in vitro to seek an in vivo-in vitro correlation. The absorption was close to zero order with a slight decrease after 10 h. When % in vivo input was plotted vs. % dissolved (Fig. 17), the linear correlations were obtained (r=0.9655 and 0.9526), indicating a close correlation could be established between the in vitro release rate of osmotic system with its in vivo absorption. Although there was only one formulation for the osmotic system, an IVIVC was still meaningful since the release from the osmotic system was independent of in vitro test conditions (agitation, pH, etc.).

For BT, a correlation could not be established by comparison of the in vivo input (% dose) profile to the in vitro release profile (Fig. 18). The curvature of fraction absorbed in vivo vs. fraction dissolved in vitro for hydrophilic matrix tablets indicated that there was a time-scale difference between in vivo and in vitro testing. So it could be seen that in vitro-in vivo correlation was very important to extended release oral dosage forms.

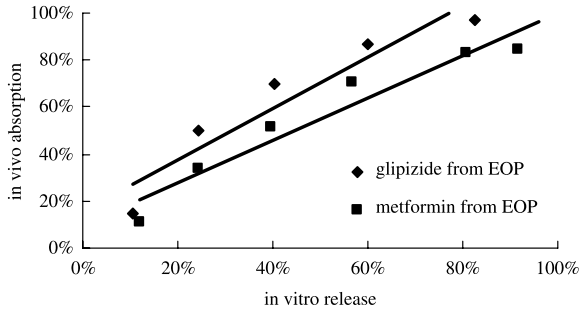

FIGURE 17 **IVIVC Model Linear Regression Plots of % Absorbed vs. % Dissolved for EOP.**

CONCLUSIONS

A combination of metformin and glipizide was formulated into extended release formulations exhibiting comparable in vitro release profiles using two formulation principles, i.e., elementary osmotic pump tablets and bilayer hydrophilic matrix tablet. Drug release from the osmotic system was independent of in vitro and in vivo conditions, where best sustained release effect was achieved, whereas the in vitro dissolution test employed for hydrophilic matrix tablets needed to be optimized to be biorelevant.

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