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In Vitro and In Vivo Evaluation of a Novel Push–Pull Osmotic Pump with Orifices on Both Side Surfaces

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A novel push–pull osmotic pump (PPOP) was developed for delivery of water-insoluble drug gliclazide. Compared to conventional PPOP, which only had orifice(s) on the side of the drug layer, the novel PPOP had orifices of the same diameter on both side surfaces. The in vitro drug-release behavior of both novel PPOP and conventional PPOP were studied and compared; it was found that the drug-release rate of both kinds of PPOP could be influenced by coating level and core hardness whereas orifice size did not have much influence on it, and the study also showed that none of the former factors could influence the similarity of the drug-release profiles of the two kinds of PPOP. Mechanism of drug release from novel PPOP was illustrated using Poiseuille's law of lamina flow, and it was found that under regular formulation, the dissolution profiles of the two kinds of PPOP were similar. In vivo study also showed that the concentration–time profiles of gliclazide in plasma of the two PPOP were comparable and both of them had good in vitro–in vivo correlation. By simply drilled on both side surfaces, the novel PPOP did not need side identification when drilled, so it was more suitable for industrial manufacture than the conventional ones.

Keywords push–pull osmotic pump (PPOP); gliclazide; orifice; polyethylene oxide

INTRODUCTION

Osmotic pump is a drug-delivery system that utilizes osmosis to drive drugs out. The simplest osmotic pump is elementary osmotic pump (EOP) (Theeuwes, 1975; Theeuwes & Higuchi, 1972). As known to all, drugs with moderate water solubility could be easily made into EOP. Another kind of osmotic pump that was suitable for the delivery of water-soluble drugs was porosity osmotic pump (Verma, Mishra, & Garg, 2000); such osmotic pumps contain leachable water-soluble components in their membrane; thus, delivery orifice was formed in situ when the water-soluble components dissolved; pore-forming agent that can be used are sodium chloride, urea, potassium chloride, and so forth. For those poor water-soluble drugs and water-insoluble drugs, because they could hardly be dissolved in water, they could not produce osmotic pressure by themselves, and if the viscosity inside the system was not proper, sedimentation of drugs might probably happen, which result in incomplete drug release. Thus, although researchers had put some effort to develop monolithic osmotic pumps for water-insoluble drugs (Chen & Chou, 1998; Chen, Lee, & Xie, 1998; Liu, Khang, Rhee, & Lee, 2000a; Lu, Jiang, Zhang, & Jiang, 2003), the push–pull osmotic pump (PPOP), which was presented by Theeuwes in 1970s (Theeuwes, 1978), was still the most practical way to prepare the water-insoluble drugs into osmotic pump system,and most of the osmotic pump products of water-insoluble drugs we could purchase from market were of this kind, for example, nifedipine PPOP (Procardia XL®, Pfizer and Adalat®, Bayer) and glipizide PPOP (Glucotrol®, Pfizer).

The PPOP gave scientists a reliable method to make water-insoluble drugs into osmotic pump system, but a disadvantage of such conventional PPOP existed until now, which was the complex manufacture technique. Such conventional PPOP consists of a semipermeable membrane that comprises a drug layer and a push layer, and a delivery orifice in the membrane on the side of the drug layer; thus, during the process of manufacture, the two layers of the core tablet must have different colors, and a color-identifying device must be employed so that an orifice could be drilled on the side of the drug layer. However, most drugs and vehicles were white or colorless, as a result, some inorganic pigment such as ferric oxide must be used to endow the two layers with different colors, which made the manufacture process even complex.

To avoid such disadvantage, perforated coated tablet was developed (Benkorah & Mcmullen, 1994; Hansson, Giardino, Cardinal, & Curatolo, 1988); such tablet had a preformed delivery orifice during the tableting process by using modified tooling. In other studies, sandwiched osmotic tablet system

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(SOTS) was disclosed in patent literature by Cortese (Cortese, Barclay, & Theeuwes, 1984), and the mechanism was studied by Liu et al. (2000b); the SOTS consists of a middle push layer and two attached drug layers; the two drug layers of SOTS were identical; thus during the drilling process, delivery orifices were simply drilled on both side surfaces. By using SOTS, side identification was avoided, but the preparation of core tablets was even complex than that of conventional PPOP because a tri-layer tableting machine must be used.

In this article, a novel PPOP was disclosed by the author. Such PPOP had two orifices on both side surfaces of the system. During the manufacture process, orifices were simply drilled on both side surfaces; so the inorganic pigment and the color-identifying device could be cast aside, thus simplifying the manufacture procedure and lowering the cost. Water-insoluble drug gliclazide which was used in the treatment of diabetes, was selected as model drug. It had been found that extended release matrix tablet of 30 mg gliclazide (Diamicron®) could achieve satisfying therapeutic effect. Many factors that might influence the drug-release behavior of osmotic pump have been reported in literatures (Liu et al., 2000b, Lu et al., 2003, Verma, Krishna, & Garg, 2002); in this article, the influence of coating level, orifice size, core tablet hardness, and different categories of polyethylene oxide (PEO) used in the system on the drug-release behavior of the conventional PPOP and the novel PPOP were studied and the similarity between the profiles of the two kinds of PPOP was evaluated. Mechanism of drug released from novel PPOP was illustrated using Poiseuille's law of lamina flow. In vivo properties of the novel PPOP was also evaluated compared with that of the conventional PPOP.

MATERIALS AND METHODS

Materials

The materials used were as follows: gliclazide was purchased from Shandong medicine industry graduate school system pharmaceutical factory, Shandong, China; PEO was a gift from Dow Chemical, NJ, USA; cellulose acetate and polyethylene glycol 2000 (PEG 2000) were purchased from Shenyang Chemical Reagent Company, Shenyang, China; sodium chloride and potassium dihydrogen phosphate were purchased from Tianjin Bo-di Chemical Industry, Tianjin, China. All other chemicals were of analytical reagent; deionized double-distilled water was used throughout the study.

Formulations and Preparation of PPOP

Basic core formulation was chosen according to the experience of our research group as summarized in Table 1.

Preparation of core tablets: gliclazide and all vehicles were screened through an 80-mesh screen before being mixed; Granules of both the drug layer and the push layer were prepared by wet granulation method using 97.5% alcohol as granulation fluid, and the wet granules were passed through a 20-mesh screen and dried at 40°C for 24 h. Magnesium stearate was added to the dry granules as lubricant. The tablet cores were prepared by pressing the two compositions together using a single station-punching machine with concave punches (diameter 9 mm). First, the granules of the drug layer were fed into the cavity of the die and compressed into a solid layer, and then, the granules of the push layer were fed into the cavity overlaying the compressed layer and compressed into a solid layer to form a two-layered tablet core.

TABLE 1
Basic Formulation of Tablet Core of Two Kinds of PPOP

Ingredients	Amount (mg/tablet)
Drug layer	
Gliclazide	30
PEO N-10 (mol. wt. 100,000)	150
Magnesium stearate	trace
Push layer	
PEO WSR-303 (mol. wt. 7,000,000)	70
NaCl	20
Magnesium stearate	trace

Coating and Drilling

Twenty six grams of cellulose acetate was dissolved in 970 mL acetone and 2 g PEG2000 was dissolved in 30 mL water, then the two solutions was mixed together as coating solution. The tablets were coated using a traditional coating pan. The diameter of the coating pan was 230 mm and the tilt angle was 45°. Pan-rotating rate was 40 rpm, spray rate of coating solution was 7 mL/min, drying temperature was 50–55°C, and the tablets were dried for 12 h at 40°C to remove the residual solvent. The coated tablets of each batch were divided into two groups at random, for each tablet in the first group, one orifice was drilled only on the drug layer side (conventional PPOP) while for tablets in the second group, one orifice was drilled on each side surface (novel PPOP), the orifice size was controlled by using microdrills of known diameter.

In Vitro Drug-Release Studies

In vitro drug-release studies were performed according to USP paddle method at 37 ± 0.5°C, the agitation rate was 100 rpm, and 900 mL of pH 8.6 phosphate buffer was employed as dissolution medium. During the release studies, 5 mL of samples were withdrawn at 2, 4, 6, 8, 10, 12 and 14 h, and replaced by fresh medium of identical volume and temperature. The concentration of gliclazide released from PPOP was determined by UV method at 228 nm. The similarity of two drug-release

profiles was evaluated by similarity factor ($f2$), which was suggested by FDA. The $f2$ factor can be calculated as follows (Shah, Tsong, Sathe, & Liu, 1998):

$$f2 = 50 \times \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (1)$$

where R_t and T_t stand for the dissolution value at time t of the reference batch (traditional PPOP) and the test batch (novel PPOP), respectively; n is the number of time points.

Restrictions associated with the use of $f2$ test estimate include:

(a) The dissolution measurements of the test and reference batches must be made under exactly the same condition.
(b) There should only be one measurement considered after either product has achieved 85% dissolution.
(c) The percent coefficient of variation at the earliest point should not exceed 20% and the CV (%) should not exceed 10 at all other time points.

If the similar factor ($f2$) was not less than 50, the two drug-release profiles were considered to be similar.

In Vivo Evaluation

In vivo evaluation of novel PPOP was performed relative to the equivalent dose of conventional PPOP by a crossover design in six beagle dogs. The beagle dogs were fasted for 12 h before experiment. During experiment, 5 mL of blood sample was collected predose and at the following time point postdose: 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, and 36 h. All samples were centrifuged immediately at 2,750 × g for 10 min. The plasma was separated and frozen at –20°C for use. Mean concentration versus time data was evaluated using 3P97 professional (Chinese pharmacological association software), the Wagner–Nelson equation was used to obtain in vivo input profile of gliclazide from two kinds of PPOP.

Determination of gliclazide in plasma: 0.5 mL plasma was first added with 100 μL glipizide (20.4 μg/mL) as internal standard and then acidified with 200 μL 0.25 M HCl; the plasma was then vortex-mixed for 1 min. The acidified plasma was then vortex-mixed with 5 mL methylbenzene for 4 min and centrifuged at 2,750 × g for 10 min. The organic layer was separated and dried at 50°C under a stream of nitrogen, and thereafter, the residue was dissolved by 200 μL methanol. Separation was performed on a Diamonsil C18 column (5 μm, 25 × 4.6 mm, Dikma, Japan) at 30°C; the mobile phase was methanol-pH 5.8 phosphate buffer solution (47:53, vol/vol). Mobile phase was passed through column by a flow rate of 1 mL/min and sample was determined at 228 nm. Injection volume was 20 μL.

RESULTS AND DISCUSSIONS

In Vitro Evaluation of Two Kinds of PPOP

Influence of Coating Level on the Drug-Release Profiles of the Two Kinds of PPOP

To study the influence of coating level on the drug-release profiles of the two kinds of PPOP, novel PPOP and traditional PPOP with the same core formulation were coated to 5, 10, and 15% weight gain up, and the orifice diameter was fixed to 0.8 mm.

From Figure 1 when the coating level went up, a gradual decrease in the drug-release rate of both kinds of PPOP was observed. According to Liu et al.'s study (2000b), the increase of coating level would result in the decrease of water imbibing through the membrane; thus, both the rate of hydration of the drug layer and the expansion of the push layer were decreased, which resulted in decrease of release rate of model drug.

Figure 1 also showed that at each coating level, the drug-release profiles of the two kinds of PPOP match fairly well, which meant that the similarity of the drug-release profiles of the two kinds of PPOP would not be influenced by coating level (the $f2$ value between the drug-release profiles of the two kinds of PPOP under three coating levels was 80.9, 94.5, and 92.6, respectively). From Figure 1 we could also see that when the coating level was 10%, the linearity of the drug-release profiles of both kinds of PPOP was good and both of them could deliver drug up to 12 h; the cumulative release of model drug was over 90%; thus, the 10% of coating gain up was selected in the following studies.

Influence of Orifice Size on the Drug-Release Profiles of the Two Kinds of PPOP

To study the influence of orifice size on the drug-release profiles of two kinds of PPOP, orifices of different size were

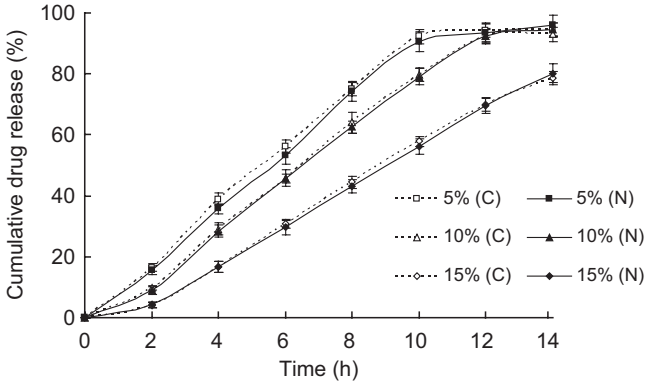

FIGURE 1. Influence of coating level on the drug-release profiles of two kinds of PPOP where C and N stands for conventional PPOP (one orifice on the drug layer side) and novel PPOP (one orifice on each side) (USP apparatus || (with sinker), 37 ± 0.5°C, 100 rpm, 900 mL pH 8.6 phosphate buffer, n = 6).

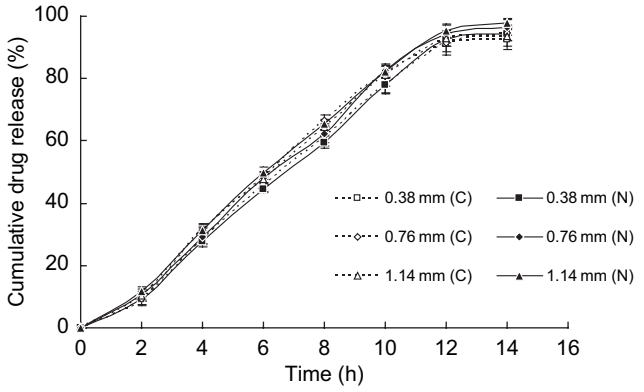

FIGURE 2. Influence of orifice size on the drug-release profiles of two kinds of PPOP (USP apparatus || [with sinker], 37 ± 0.5°C, 100 rpm, 900 mL pH 8.6 phosphate buffer, $n = 6$).

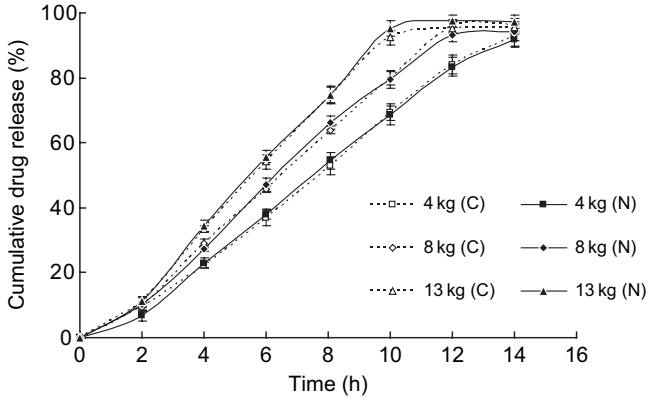

FIGURE 3. Influence of core tablet hardness on the drug-release profiles of two kinds of PPOP (USP apparatus || [with sinker], 37 ± 0.5°C, 100 rpm, 900 mL pH 8.6 phosphate buffer, $n = 6$).

prepared using microdrills with diameter of 0.38, 0.76, and 1.14 mm, respectively. On the basis of the results of former studies, coating level was focused on 10%.

From Figure 2 we could see that the orifice size did not have much influence on the drug-release rate of both kinds of PPOP and at each orifice size level. The drug-release profiles of the two kinds of PPOP match fairly well, which meant that the orifice size had little influence on the similarity of the drug-release profiles of the two kinds of PPOP (the $f2$ value between the drug-release profiles of the two kinds of PPOP under three orifice size levels was 91.2, 80.2, and 86.2, respectively); in Liu et al.,'s study, it was also found that the orifice size did not influence the drug-release profiles in the range of 0.5 to 1.41 mm (Liu et al., 2000a). Considering that when the orifice size was 0.38 mm, the orifice might be jammed by the drug or excipients (Lu et al., 2003) and when the orifice size was 1.14 mm, the orifice would not be so easy to be drilled by laser beam, so the 0.76-mm orifice was chosen.

Influence of Core Hardness on the Drug-Release Profiles of the Two Kinds of PPOP

To study the influence of tablet core hardness on the drug-release profiles of the two kinds of PPOP, tablet cores were prepared to different hardness which was 4, 8, and 13 kg, respectively. According to the former studies, the coating level was maintained at 10% and the diameter of delivery orifice was 0.76 mm.

From Figure 3 we could see that tablet core hardness had dramatic influence on the drug-release profiles of both kinds of PPOP. As the hardness of the tablet core went up, the drug-release rate of both kinds of PPOP went up. This might because when the hardness of tablet core went up, the thickness of the tablet core went down; thus, after coating, there was less room inside the semipermeable membrane. Because the push force of the push layer would not change, the drug was pushed out from the tablet more quickly. The dimension of the tablets at different hardness was listed in Table 2.

TABLE 2
Dimension of the Tablets at Different Hardness

Core hardness (kg)	4	8	13
Diameter (mm)	9.00	9.00	9.00
Thickness (mm)	5.24	4.72	4.42

Figure 3 also showed that at each tablet core hardness level, the drug-release profiles of the two kinds of PPOP match fairly well (the $f2$ value between the drug-release profiles of the two kinds of PPOP under three tablet core hardness levels was 88.5, 85.1, and 85.5, respectively).

Because when tablet core hardness was 4 kg, chipping or breaking of the tablet core might probably happen during the coating process, whereas when the tablet core hardness was 13 kg, the cumulative release amount of model drug was only about 80% at 12 h; thus, 8 kg was chosen for the hardness of the tablet core.

Mechanism of Drug Release from Novel PPOP

In Lu et al.'s paper (2003), Poiseuille's law of lamina flow was employed to explain the drug-release mechanism of monolithic osmotic tablet system (MOTS); such law can also be employed here to explain the drug-release mechanism of the novel PPOP, which was shown schematically in Figure 4.

The equation of Poiseuille's law can be displayed as follows:

$$\frac{dV}{dt} = \frac{\pi R^4 (P_1 - P_2)}{8\eta L} \tag{2}$$

where dV/dt is the flow rate in tube, R is the radius of tube, η is the viscosity of flow, $(P_1 - P_2)$ is the pressure difference between two end of tube, and L the length of the tube. When the equation is applied to PPOP, as it was shown in Figure 4,

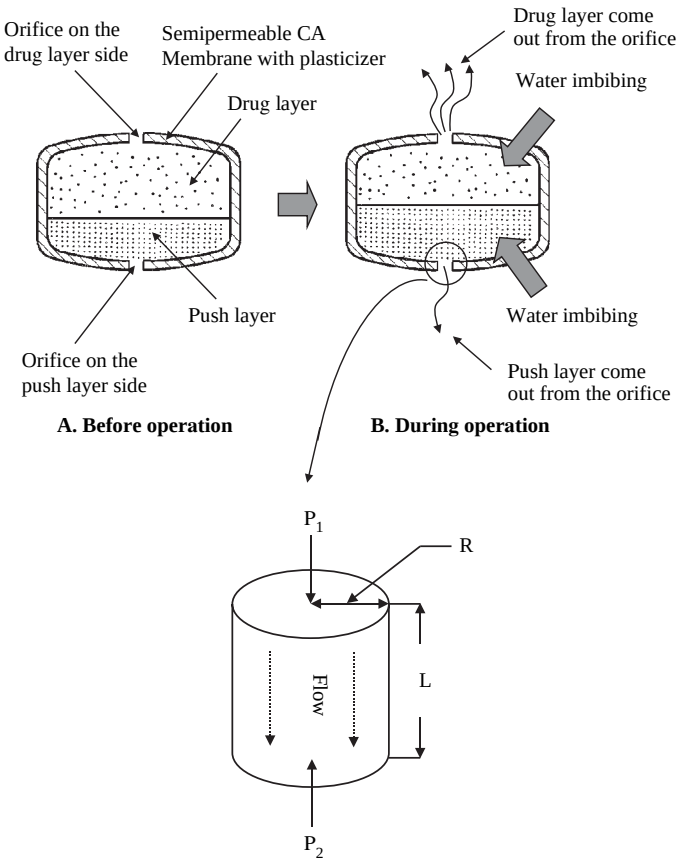

FIGURE 4. Schematic diagram of drug-release mechanism from novel PPOP (modified from Lu et al., 2003 and Liu et al., 2000b).

the tube is replaced by the orifice; thus, L is the thickness of the membrane, R is the radius of the orifice and $P_1 - P_2$ stands for the pressure difference between inside and outside of the tablet.

From Equation 1, the flow rate is proportional to R^4 and $(P_1 - P_2)$, inversely proportional to η and L. As to the two orifices on the drug layer side and the push layer side, the radius of the orifice (R) and membrane thickness (L) are the same, because the drug layer and the push layer were enclosed by the rigid membrane; the pressure difference between inside and outside the membrane $(P_1 - P_2)$ is also supposed to be the same at the two orifices and only the solution (suspension) viscosity (η) is different.

PEO is a polymer whose water solution viscosity goes up as the molecule weight goes up when the concentration was kept constant. The PEO used in the drug layer of a PPOP usually had a molecule weight from 100,000 to 600,000 g/mol whereas the PEO used in the push layer usually had a molecule weight from 400,000 to 800,000 g/mol (Liu et al., 2000b; Thombre et al., 2004). In this study, three formulations were prepared to study the mechanism of drug release from the novel PPOP which were listed in Table 3; two of them (F1 and F2) were regular formulations, which meant that the PEO molecule

TABLE 3
PEO of Different Molecule Weight Used in the Core Formulations

Number	PEO MW (g/mol, drug layer)	PEO MW (g/mol, push layer)
F1 (C)	100,000	7,000,000
F1 (N)	100,000	7,000,000
F2 (C)	600,000	4,000,000
F2 (N)	600,000	4,000,000
F3 (C)	100,000	200,000
F3 (N)	100,000	200,000

weights used in the core were regular for PPOP, and another one was extreme formulation (F3) whose push layer contained PEO, which had a molecule weight of 200,000 g/mol.

From Figure 5 we could see that for the two regular formulations, the similarity between the dissolution profiles of the conventional PPOP and the novel PPOP was very high, whereas for the extreme formulation, the similarity factor was low ($f2$ value of three formulations was 86.3, 85.4, and 43.5, respectively). The reason for this result might be that for the two regular formulations, the molecule weight of PEO in the push layer was much higher than that in the drug layer; thus, the viscosity of the solution formed by the push layer was much higher than the viscosity of suspension formed by the drug layer; the dV/dt of the push layer was then much lower than that of the push layer, which meant that only a very small amount of the push layer was squeezed out of the tablet during operation that could be ignored, thus making the drug-release profiles of the two kinds of PPOP very similar. On the contrary, for the extreme formulation, when the molecule weight of PEO in the push layer was 200,000 g/mol whereas the molecule weight of PEO in the drug layer was 100,000 g/mol, the

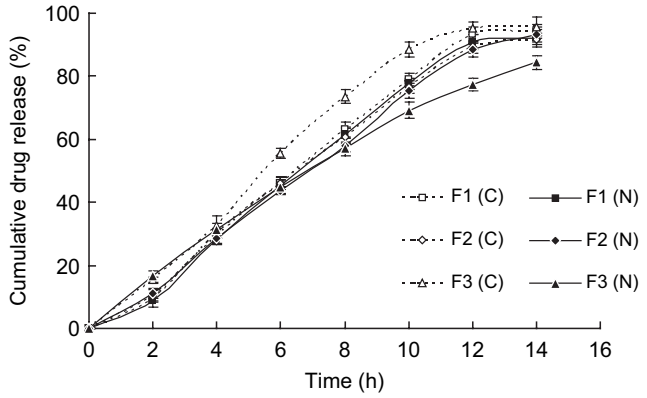

FIGURE 5. Drug-release profiles of gliclazide from PPOP with regular core formulation and extreme formulation (USP apparatus || [with sinker], 37 ± 0.5°C, 100 rpm, 900 mL pH 8.6 phosphate buffer, n = 6).

viscosity of the solution formed by the push layer was similar to that of suspension formed by the drug layer; thus, the d*V*/d*t* of the drug layer side and the push layer side was similar, which meant that the pressure inside the tablet could be released from both the drug layer side and the push layer side; so, a part of the push layer was also squeezed out of the tablet, thus resulting in the loss of push force in the push layer, which made the drug-release rate of the novel PPOP much lower than that of the conventional PPOP.

In Vivo Evaluation

Concentration–time profiles of gliclazide in plasma after oral administration of two kinds of PPOP were shown in Figure 6, which showed that both the novel PPOP and the conventional PPOP were characterized by peak blood levels at 10 h after dose; mean relative oral bioavailability of novel PPOP was 97.95% compared with that of conventional PPOP. When the percentage of in vivo input was plotted as a function of percentage of drug release in vitro (Figure 7), linear in vivo–in vitro correlation were obtained for both kinds of PPOP (r = 0.9703 and 0.9649, respectively).

CONCLUSIONS

A novel PPOP with orifices on both side surfaces was studied; the in vitro and in vivo characterization of novel PPOP was studied compared with that of conventional PPOP; it was found that both the in vitro drug release and the in vivo input of novel PPOP were comparable to that of conventional PPOP; both kinds of PPOP showed good in vivo–in vitro correlation. Because the novel PPOP did not need side identification when drilled and could release drug at the same behavior as the conventional PPOP, it could be a better drug-delivery system than the conventional one.

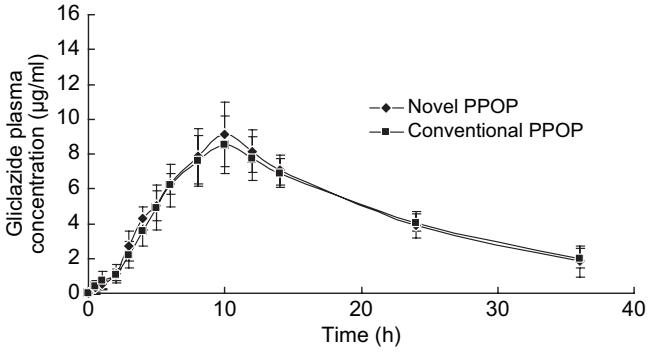

FIGURE 6. In vivo pharmacokinetics profiles of gliclazide in beagle dogs from two kinds of PPOP (USP apparatus || [with sinker], 37 ± 0.5°C, 100 rpm, 900 mL pH 8.6 phosphate buffer, n = 6).

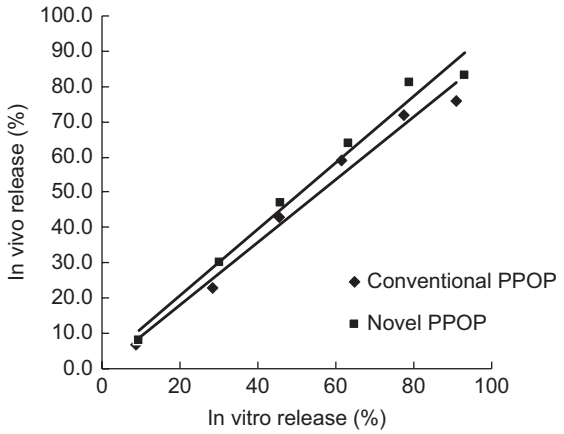

FIGURE 7. IVIVC model linear regression plots of percentage absorbed in vivo versus percentage released in vitro from two kinds of PPOP.

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