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Overcome side identification in PPOP by making orifices on both layers

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ABSTRACT

The original purpose of this research was to build a database for an expert system. Unexpectedly, it was found that the color-identifying device in push–pull osmotic pump (PPOP) manufacturing process could be unnecessary. Water-insoluble drug indapamide, gliclazide and dipyridamole were employed as model drugs. Bunches of conventional formulations were designed; and traditional preparation procedures were used. In vitro drug release was studied; and the similarity between the conditions of orifice only on the side of the drug layer and orifices of the same diameter on both sides was evaluated. It was found that the drug release from PPOP could be influenced by formulation and core hardness while it could hardly be influenced by orifice size. No significant difference was observed between the dissolution profiles of orifice only on the side of the drug layer and orifices of the same diameter on both sides. Mechanism of drug release was discussed. The conclusion was that the disadvantage of side identification in PPOP manufacturing process could be overcome by drilling orifices on both sides.

1. Introduction

Osmotic pump is a drug delivery system that utilizes osmosis to drive drugs out from the device. There has been increasing interest in the development of oral osmotic pumps in the past 30 years. Various types of oral osmotic pumps have been developed to deliver drugs possessing different aqueous solubility. In the 1970s, elementary osmotic pump (EOP) (Theeuwes and Higuchi, 1972; Theeuwes, 1975) was developed. As known to all, drugs with moderate water solubility are easy to make into EOP. Another kind of osmotic pumps that is suitable for the delivery of water-soluble drugs is porosity osmotic pump (Verma et al., 2000). Such osmotic pump contains leachable water-soluble components in its membrane, thus delivery orifices form when the water-soluble components dissolved. Pore-forming agents are sodium chloride, polyethylene glycol (PEG), potassium chloride, etc.

For those poor water-soluble drugs and water-insoluble drugs, since they could hardly dissolve in water, they could not produce osmotic pressure by themselves. Many effective ways were employed to increase the solubility in order to improve drug release. For example, convert drugs into ionic substance by reacting with or adding alkali/acid (Lu et al., 2002; Ouyang et al., 2005); using $(SBE)_{7m}$-β-CD as solubilizers (Okimoto et al., 1999, 2004). It is suitable for water-insoluble drug to release in the form of suspension. Polyethylene oxide (PEO) (Liu et al., 2000) was used as the suspending and osmotic agent to prepare nifedipine monolithic osmotic tablet system (MOTS). If the viscosity inside the system was not proper, drug sedimentation might occur which results in incomplete drug release. Thus, although researchers had put some effort to develop monolithic osmotic pumps for water-insoluble drugs, the push–pull osmotic pump (PPOP) (Theeuwes, 1978) is 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 could be purchased from market are of this kind, for example, nifedipine push–pull osmotic pump (Procardia XL®, Pfizer and Adalat®, Bayer) and glipizide push–pull osmotic pump (Glucotrol®, Pfizer).

Conventional PPOP consists of a semi-permeable membrane, a core that comprises drug layer and push layer. A delivery orifice is 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 has to be employed to confirm that an orifice could be drilled only 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 has to be used to endow the two layers with different colors, which made the manufacture process even complex.

The disadvantage of PPOP, side identification (color identification), exists until today, which makes the manufacture technique complex and increases the risk of defective goods. Many inventions have been introduced to avoid the disadvantage. Perforated tablet

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was developed (Hansson et al., 1988; Benkorah and Mcmullen, 1994) which had a delivery orifice pre-formed during the compressing process by modified tooling. In another study, sandwiched osmotic tablet system (SOTS) was disclosed in patent literature (Cortese et al., 1984). The sandwiched osmotic tablet system 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 preparing of core tablets was even more complex than that of conventional PPOP because a tri-layer tableting machine has to be used.

In this paper, the authors disclosed a breakthrough of PPOP. The new idea of orifices on both sides will cast aside the side identification and simplify the manufacturing process of PPOP. Water-insoluble drug indapamide used in the treatment of essential hypertension, gliclazide used in the treatment of diabetes and dipyridamole used in the treatment of throm were selected as model drugs. It had been found that extended release matrix tablet of 1.5 mg indapamide (Brand name: Natrilix®), one tablet per day; extended release matrix tablet of 30 mg gliclazide (Brand name: Diamicron®), one tablet per day could achieve satisfying therapeutic effect. According to AGGRENOX™ and dipyridamole extended release capsule manufactured by Northeast Pharmaceutical group (China), it should be taken twice a day, 200 mg per time. On the consideration of dosage interval, PPOP formulations of 1.5 mg indapamide per tablet, 30 mg gliclazide per tablet and 50 mg, 100 mg and 200 mg dipyridamole per tablet were designed. According to the factors that might influence the drug release from osmotic pump reported (Lu et al., 2003; Verma et al., 2002): coating level, orifice size, core tablet hardness, different doses and categories of PEO used in the system and other factors that may influence the drug release behavior were studied in this paper. The similarity of profiles between only orifice on the side of the drug layer and orifices of the same diameter on both sides was evaluated. Mechanism of drug released from PPOP was discussed.

2. Materials and methods

2.1. Materials

Indapamide was purchased from Beijing Yanjing pharmaceutical plant, Beijing, China; gliclazide was purchased from Shandong Medicine Industry Graduate School System Pharmaceutical Factory, Shandong, China; dipyridamole was a gifted sample from Shenyang No. 1 Pharmaceutical Factory, Liaoning, China; PEO was a gift from Dow Chemical, NJ, USA; hydrochloric acid (HCl) was purchased from Shenyang Chemical Reagent Company, Shenyang, China; Cellulose acetate (CA, 54.5–56.0 wt.% acetyl content) was purchased from Shanghai Chemical, Shanghai, China; PEG was purchased from Pudong Gaonan Chemical, Shanghai, China; sodium chloride and potassium dihydrogen phosphate were purchased from Tianjin Bo-di Chemical Industry, Tianjin, China; polyvinyl pyrrolidone (PVP) was a gift from International Specialty Procucts (ISP) Company, NJ, USA. All other chemicals were of analytical-reagent, deionized double-distilled water was used throughout the study.

2.2. Preparation

Preparation of core tablets: Drug and all vehicles were passed through an 80-mesh screen. Tablet cores were prepared by pressing the two compositions together using a single station-punching machine with concave punches. First, the granules/powder mixture of the drug layer was fed into the cavity of the die and pre-compressed into a solid layer, and then, the granules/powder mixture of the push layer was fed into the cavity overlaying the pre-compressed layer and compressed into a solid layer to form a two-layered tablet core.

Coating and drilling: Cellulose acetate was dissolved in acetone and PEG was dissolved in water, then the two solutions were 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; while for tablets in the second group, one orifice was drilled on each side surface, and the orifice size was controlled by using micro drills of known diameter.

2.3. In vitro dissolution test

In vitro drug release studies were performed using USP paddle method (with sinker) at 37 ± 0.5 °C. 5 ml of samples were withdrawn after predetermined time intervals, replaced by fresh medium of identical volume and temperature.

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 et al., 1998):

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-(1/2)} \times 100 \right\}$$

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 similar.

3. Results and discussions

3.1. Comparison between orifice only on the side of the drug layer and orifices of the same diameter on both sides in the condition of same formulation with different orifice sizes

Orifices of different sizes were prepared using micro-drills with diameter of 0.6 mm, 0.9 mm and 1.2 mm, respectively, using same formulations.

First, it could be seen from Fig. 1 that the orifice size did not have much influence on the drug release of all drugs. Most important thing, which was seen that, for the same formulation, there was no significant difference between tablets with orifice only on the drug layer and tablets with orifices on both sides of the tablet (f2 over 50). 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 0.25–1.41 mm (Liu et al., 2000).

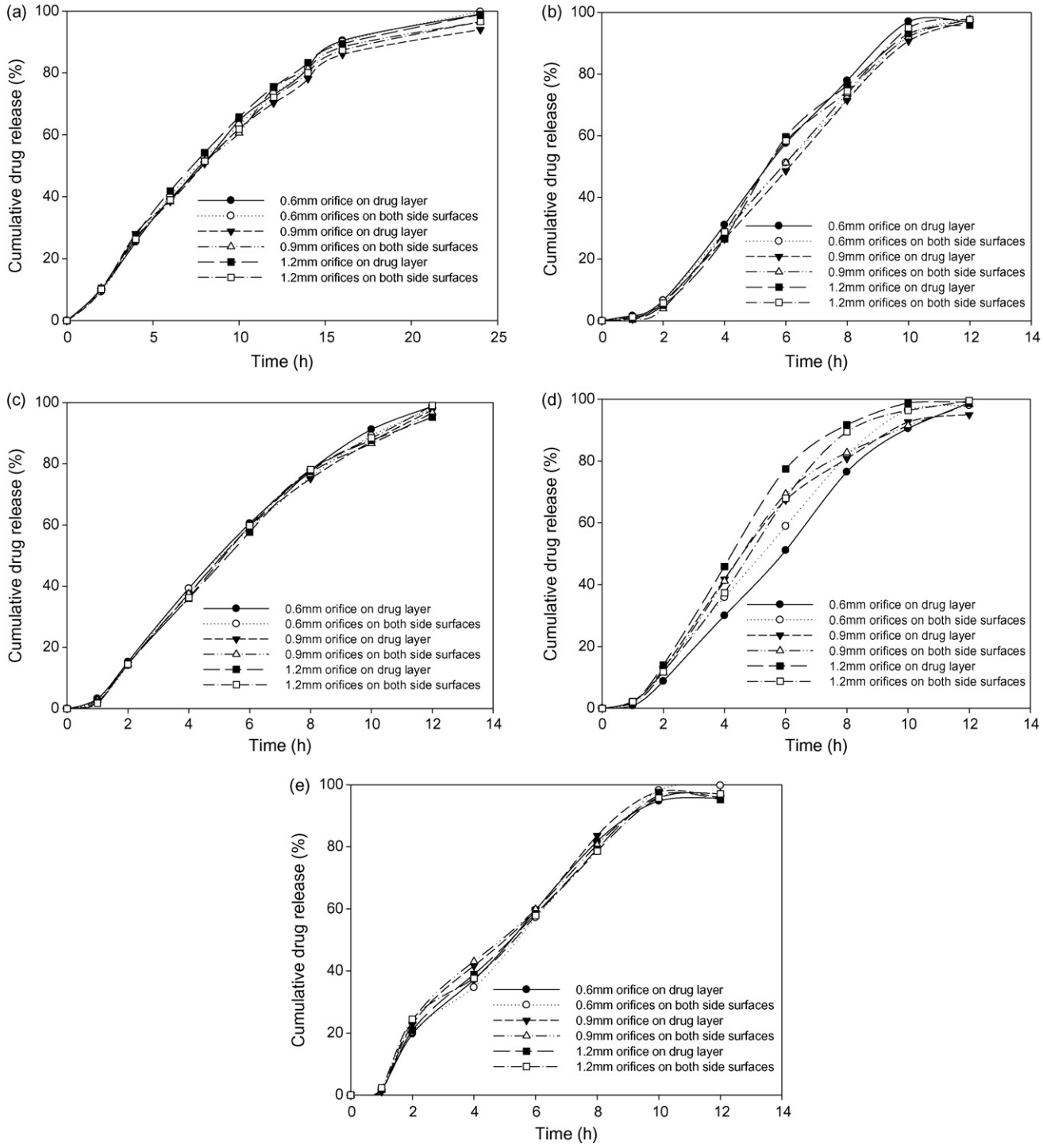

Fig. 1. In vitro drug release profiles of different orifice sizes ($n = 3$). Dissolution profiles of indapamide PPOP are shown in (a) (50 rpm, 200 ml water); dissolution profiles of gliclazide PPOP are shown in (b) (100 rpm, 900 ml pH 8.6 phosphate buffer); dissolution profiles of dipyridamole PPOP are shown in (c) (50 mg per tablet), (d) (100 mg per tablet) and (e) (200 mg per tablet) respectively (500 rpm, 1000 ml 0.1N HCl).

3.2. Comparison between orifice only on the side of the drug layer and orifices of the same diameter on both sides in the condition of different formulations and procedures

In this part, dipyridamole (50 mg per tablet, dosage I), 0.9 mm orifice size, of different formulations and procedures was taken as a representative for the discussion. Additional discussion would be added when anything different was observed in the cases of indapamide, gliclazide, dipyridamole (100 mg per tablet, dosage II) and dipyridamole (200 mg per tablet, dosage III).

3.2.1. Coating weight gain level

From Fig. 2, a gradual decrease in drug release rate was observed when the coating weight gain went up. At each level, the drug release profiles of the two conditions of orifice(s) match fairly well which meant that the similarity of the drug release profiles would

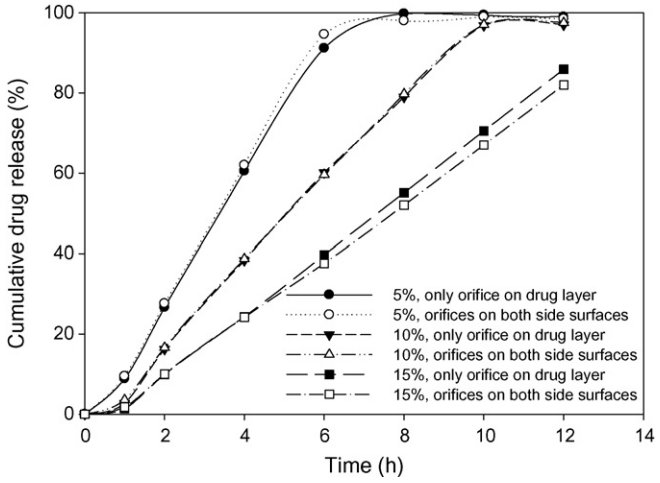

Fig. 2. In vitro drug release profiles of different coating weight gain levels (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

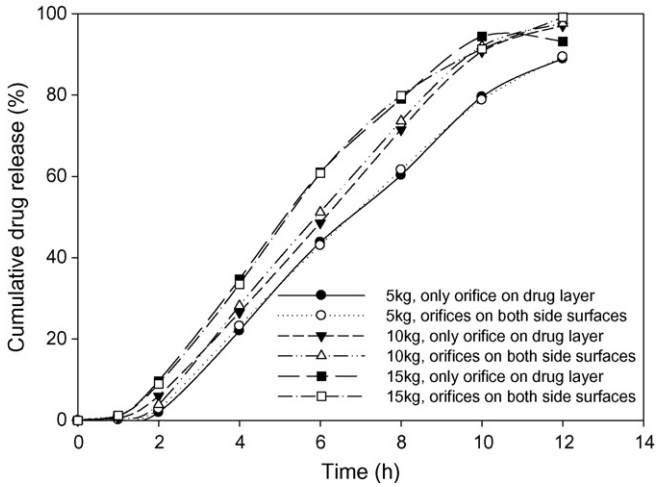

Fig. 4. In vitro drug release profiles of different tablet core hardness (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

not be influenced by coating level (the f2 value between the drug release profiles of the two conditions of orifice(s) under three coating levels was 85.8, 97.2 and 79.0, respectively).

3.2.2. Pore former level in coating

Fig. 3 showed that the rate of PEG contained in coating had much influence on the drug release while the category of PEG did not have much influence on the drug release. It was also observed that the drug release profiles of the two conditions of orifice(s) match well, which meant that the PEG level in coating had little influence on the similarity. f2 value between the two conditions of orifice(s) under different PEG levels was, 74.2, 97.2, 67.0, 70.0 and 78.9, respectively.

3.2.3. Tablet core hardness

It could be seen from Fig. 4 that tablet core hardness had dramatic influence on the drug release profiles, as the hardness of the tablet core went up, the drug release rate went up. Obviously, at each tablet core hardness level, the drug release profiles of only orifice on the side of the drug layer and orifices of the same diameter on both sides match fairly well (the f2 value between the drug release profiles of the two conditions of orifice(s) under three tablet core hardness levels was 93.9, 85.2 and 77.7, respectively). It meant that the similarity of the drug release profiles of the two conditions of orifice(s) was not affected by the tablet core hardness.

3.2.4. PEO level in drug layer

The category of PEO used in drug layer had much influence on the drug release behavior. Fig. 5 showed no significant difference between the profile of N10 (mol. wt. 100,000 g/mol) and N80 (mol. wt. 200,000 g/mol) used in drug layer, while the profile of N750 (mol. wt. 300,000 g/mol) used in drug layer was significantly different from the other two conditions. It was easy to see that the drug release profiles of orifice only on the side of the drug layer and orifices of the same diameter on both sides match well, which meant that the category of PEO in drug layer had little influence on the similarity. f2 value of the drug release profiles between the two orifice(s) conditions under three categories of PEO was 97.2, 68.8 and 70.6, respectively.

In the case of indapamide and glicladize, same phenomena were observed while something different was observed in the case of dipyridamole (dosages II and III). Drug sedimentation happened when PEO WSR-N80 or WSR-N10 was used in dosage II, and when PEO WSR205 (mol. wt. 600,000 g/mol) or WSR-N750 was used in dosage III. It might because the viscosity of those PEO was too low. However, the similarity of the drug release profiles of the two conditions of orifice(s) in those cases was unchanged.

When the amount of PEO used in drug layer increased, the release rate decreased. Fig. 6 also showed that at each level of PEO

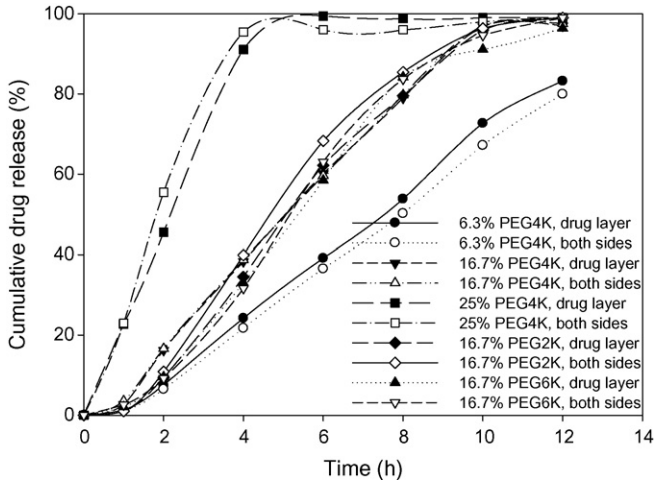

Fig. 3. In vitro drug release profiles of different PEG levels in coating (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

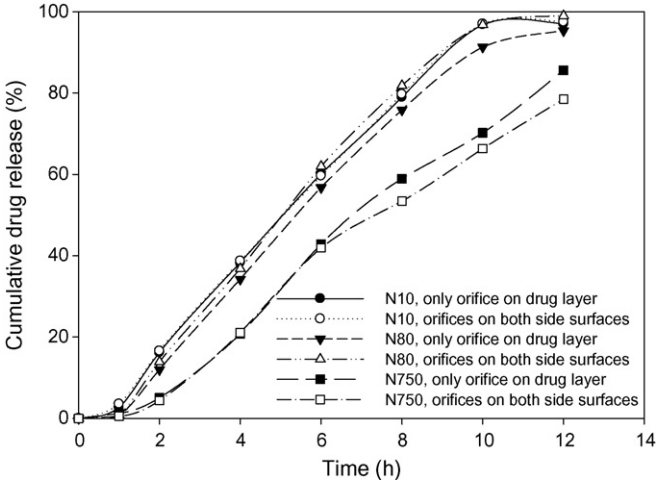

Fig. 5. In vitro drug release profiles of different PEO levels in drug layer (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

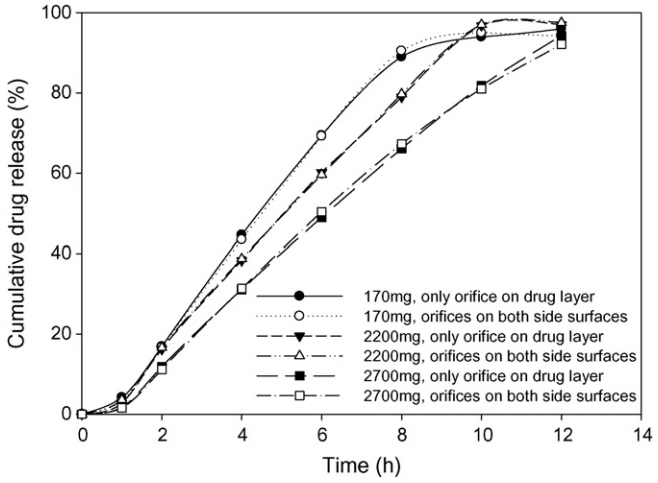

Fig. 6. In vitro drug release profiles of different PEO levels in drug layer (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

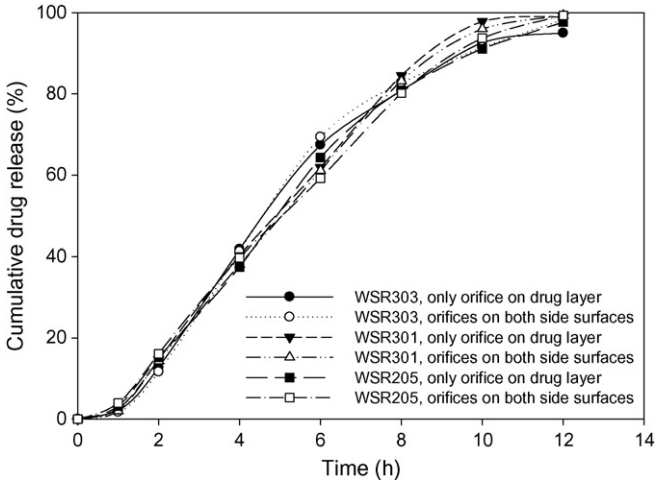

Fig. 8. In vitro drug release profiles of different PEO levels in push layer (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

used in drug layer, the profiles of the two conditions of orifice(s) match well, which meant that the similarity of the drug release of the two conditions would not be influenced by the PEO amount in drug layer. f2 value between the two conditions under three PEO levels in drug layer was 91.3, 97.2 and 90.9, respectively).

Same phenomena were observed in the cases of indapamide, glicladize and dipyridamole (dosages II and III). Of course, drug sedimentation happened when the amount of PEO used in drug layer was not enough in the case of dipyridamole (dosages II and III).

3.2.5. Penetration enhancer level in drug layer

From Fig. 7 we could see that penetration enhancer in drug layer had dramatic influence on the drug release. The drug release behavior was almost the same when NaCl was used; while the release rate slowed down when NaCl was not used. The profile of orifice only on the side of the drug layer and orifices of the same diameter on both sides was similar (f2 value was 71.4, 84.8 and 78.0, respectively). Similar phenomena occurred in the case of dipyridamole (dosage III), while penetration enhancer had little influence on the drug release in the cases of indapamide, glicladize and dipyridamole (dosage I). That might because the large percent of drug in drug layer and the PEO category affected the property of the drug layer.

3.2.6. PEO level in push layer

The decreasing of amount and molecular weight of PEO used in push layer may reduce the viscosity of push layer and revoke difference between dissolution profiles of only orifice on the side of the drug layer and orifices of the same diameter on both sides. However, it could be seen from Fig. 8 that the release behavior was not influenced by the molecular weight of PEO used in push layer. Moreover, drug release profiles of orifice only on drug layer and orifices with same diameter on both sides match well (the f2 value was 84.8, 89.7 and 78.8, respectively). Same phenomena were observed in different amount of PEO in push layer. In the research of PPOP of indapamide and gliclazide, same regular pattern was observed. In the case of dipyridamole (dosages II and III), similar regular pattern was observed when the PEO level was enough.

3.2.7. Penetration enhancer level in push layer

Penetration enhancer in push layer just had a little influence on drug release. Meanwhile, the drug release profiles of only orifice on drug layer and orifices with same diameter on both sides match fairly well (Fig. 9, the f2 value was 80.5, 93.3 and 88.9, respectively) which meant that the similarity of the drug release profiles of the two conditions would not be influenced by the penetration enhancer level in drug layer. Same phenomena were observed in

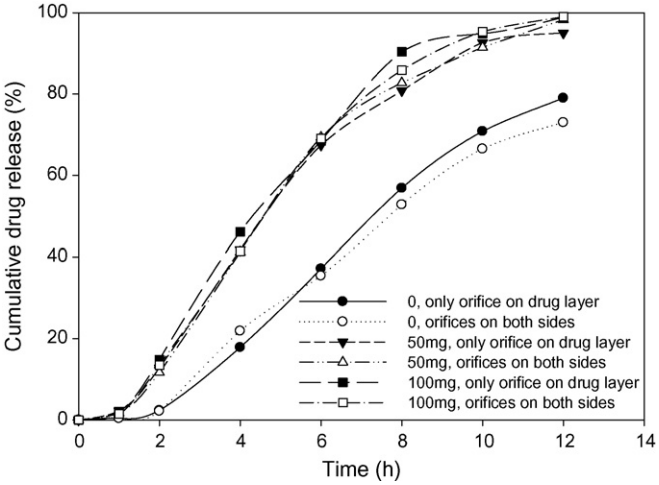

Fig. 7. In vitro drug release profiles of different penetration enhancer levels in drug layer (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

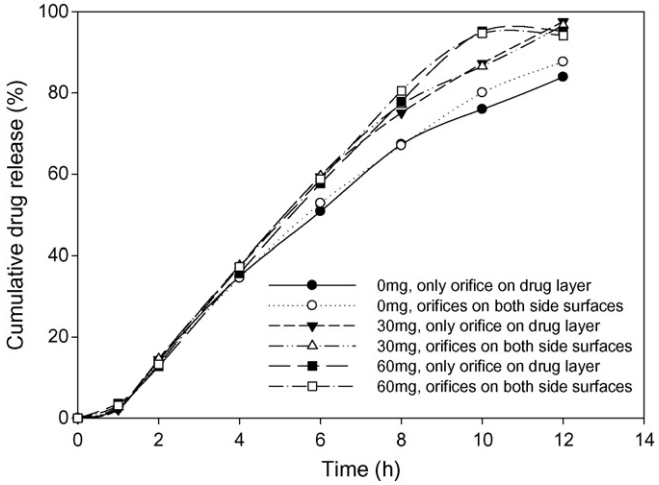

Fig. 9. In vitro drug release profiles of different penetration enhancer levels in push layer (dipyridamole PPOP, 50 mg per tablet, $n = 3$).

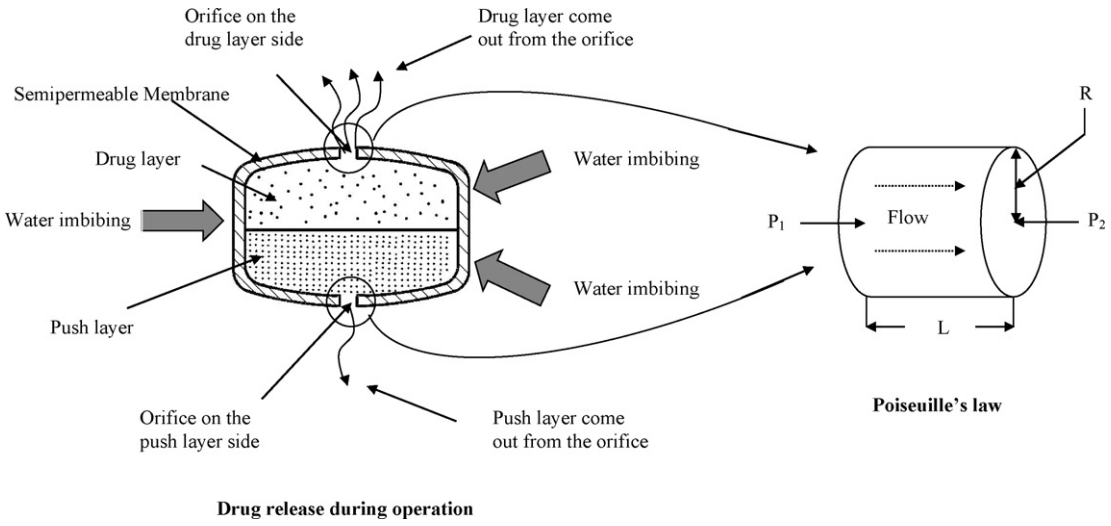

Fig. 10. Schematic of drug release mechanism from novel PPOP.

the cases of indapamide, gliclazide and dipyridamole (dosage II). Finally, in case of dipyridamole (dosage III), the semi-permeable coating membrane was broken due to the usage of penetration enhancer which caused rapid expansion of the push layer.

3.3. Mechanism of drug release

Poiseuille's law of lamina flow (Lu et al., 2003) was employed here to discuss the drug release mechanism of the PPOP with orifice of same diameter on both side surfaces. The equation of Poiseuille's law can be displayed as follows:

$$\frac{dV}{dt} = \frac{\pi}{8}\frac{R^4}{\eta}\frac{\Delta P}{L} \tag{1}$$

where dV/dt is the flow rate in tube, R is the radius of tube, η is the viscosity of flow, ΔP is the pressure difference between two end of tube ($\Delta P = P_1 - P_2$) and L is the length of the tube. When the equation is applied to PPOP, as it was shown in Fig. 10, the orifice replaces the tube; thus, L is the thickness of the membrane, R is the radius of the orifice and ΔP stands for the pressure difference between inside and outside of the tablet.

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. Since the drug layer and the push layer were enclosed by the rigid membrane, the pressure difference between inside and outside the membrane ΔP is also supposed to be the same at the two orifices, remain only the solution (suspension) viscosity (η) is different.

From Eq. (1), the rate of drug layer goes out of the tablet could be express as follows:

$$S(\text{drug}) = \frac{\pi}{8}\frac{R^4}{\eta_{\text{drug}}}\frac{\Delta P}{L} \tag{2}$$

where S(drug) is the flow rate of drug layer, η_{drug} is the viscosity of drug layer during operation.

From Eq. (1), the rate of push layer goes out of the tablet could be express as follows:

$$S(\text{push}) = \frac{\pi}{8}\frac{R^4}{\eta_{\text{push}}}\frac{\Delta P}{L} \tag{3}$$

where S(push) is the flow rate of push layer, η_{push} is the viscosity of push layer during operation.

According to Eqs. (2) and (3), the rate of push layer goes out of the tablet could be express as follows:

$$S(\text{push}) = \frac{\eta_{\text{drug}}}{\eta_{\text{push}}}S(\text{drug}) \tag{4}$$

According to Eq. (4), the viscosity of drug layer and push layer determined whether the release rate of the tablets with orifice only on the drug layer and that of tablets with orifice on both sides was similar or not. It was noted that the viscosity of the drug layer was mainly dependant on the PEO.

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 g/mol to 600,000 g/mol while the PEO used in the push layer usually had a molecule weight from 4,000,000 g/mol to 8,000,000 g/mol (Liu et al., 2000, 2003; Thombre et al., 2004). Since the molecule weight of PEO in the push layer is much higher than that in the drug layer, the viscosity of the solution formed by the push layer is much higher than the viscosity of suspension formed by the drug layer. So S(push) is much lower than S(drug) which meant that only very small amount of the push layer was squeezed out the tablet during operation which could be ignored. Finally, the drug release profiles of the two conditions of orifice(s) turned out to be very similar.

4. Conclusion

PPOP of different dosage (1.5 mg, 30 mg, 50 mg, 100 mg and 200 mg per tablet) were designed in this paper. Factors that may have influence on drug release, and the similarity between orifice only on the side of the drug layer and orifices of the same diameter on both sides were studied. It was found that drug release from the PPOP with orifices of the same diameter on both sides was similar to PPOP with orifice only on the side of the drug layer when the drug release from the conventional PPOP was regular and complete. It could be concluded that side identification in PPOP could be overcome by making orifice on both sides when the dosage is no more than 200 mg per tablet.

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