*Drug Development and Industrial Pharmacy*, 35:131–137, 2009

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040701657388

informa
healthcare

# Monolithic Osmotic Tablet Containing Solid Dispersion of 10-hydroxycamptothecin

**Huanhuan Chen, Guoqiang Jiang, and Fuxin Ding**
*Depatment of Chemical Engineering, Tsinghua University, Beijing, China*

**A novel monolithic osmotic tablet composed of solid dispersion of water-insoluble 10-hydroxycamptothecin (HCPT) was prepared. The tablet core was made of a suspending agent, polyethylene oxide, an osmotic agent, sodium chloride, and a solid dispersion consisting of polyethylene glycol 6000 and HCPT. Optimized formulation was able to deliver HCPT at the constant rate of 1.21 mg/hour for 12 hours with cumulative release above 90% in vitro, independent of environmental media and stirring rate, and the release rate is co-controlled by osmotic pressure, suspending effect, and drug solubility in solid dispersion. The monolithic osmotic tablet containing solid dispersion has great potential in the controlled delivery of water-insoluble drugs.**

**Keywords** monolithic osmotic tablet; solid dispersion; water insoluble; 10-hydroxycamptothecin

## INTRODUCTION

The oral osmotic pump tablet system utilizing osmotic pressure for the delivery of drugs has many advantages, such as reducing the risk of adverse reactions and improving patient compliance. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastrointestinal tract (GIT) to a large extent, and the release characteristics can be adjusted easily by formulation parameters (Verma, Mishra, & Garg, 2000; Verma, Krishna, & Garg, 2002). The elementary osmotic pump (EOP) introduced by Theeuwes (1975) could maintain a zero-order release rate; however, it is only suitable for water-soluble drugs. Thus, two-compartment (Theeuwes, 1981), two-layer push-pull (Cortese & Theeuwes, 1982), and three-layer (Liu et al., 2000) osmotic tablet systems were developed for water-insoluble drugs. However, these osmotic tablet systems require sophisticated preparation technique, and the orifice should be drilled only on the drug compartment. In order to avoid additional procedures and simplify the preparation process, much research has been conducted in the field of monolithic osmotic tablet (MOT).

Address correspondence to Fuxin Ding, Depatment of Chemical Engineering, Tsinghua University, Beijing 100084, China. E-mail: dingfx@tsinghua.edu.cn

The bioavailability of sparingly water-soluble drugs is well known to be limited and profoundly affected by the rate of absorption in the GIT. As the low solubility of drugs is one of the most important factors affecting the drug release process, many methods have been proposed to enhance the drug solubility. Inclusion complex was applied to promote drug solubility and stability in MOT for water-insoluble drugs (Yong, Pan, Wei, & Zhang, 2002; Okimoto et al., 2004). However, not all drugs could form an inclusion complex and it may be more suitable to the delivery of drugs in suspension. Polyethylene oxide (PEO) was used as a suspending and osmotic agent to prepare nifedipine MOT (Liu, Khang, Rhee, & Lee, 2000), but this suspending effect required high amounts of excipients.

Solid dispersion, which could achieve a super saturation of drugs in carriers, is a method that is widely used to increase the solubility, dissolution rate, and bioavailability of water-insoluble drugs (Urbanetz & Lippold, 2005). However, solid dispersion is generally immediate release, as this maximizes the amount of drug absorbed. Sustained release may be obtained by combining solid dispersion technique with MOT so as to increase the therapy efficacy and patient compliance.

It is new concept to combine the solid dispersion technique and osmotic pump technique for water-insoluble drugs in order to obtain much higher solubility and controlled release of water-insoluble drugs at the same time. The present study aimed to develop a solid-dispersion MOT containing 10-hydroxycamptothecin (HCPT), an antitumor drug (Ling & Xu, 1993), which is sparingly water soluble (Zhang, Li, Cai, Liu, & Sun, 1998). HCPT is a kind of cell cycle specific agent and its release time significantly affects treatment efficacy. Since the $t_{1/2\alpha}$ value of HCPT in tablet form is about 1.73 hours (Su et al., 2004) and its solubility is quite low, enhanced dissolution characteristics and sustained release are required to improve its therapeutic effects. The characteristic of HCPT solid dispersion was studied by dissolution and X-ray diffraction. The influences of formulation variables were investigated, and the optimized MOT with HCPT solid dispersion was evaluated. Finally, the delivery mechanism of MOT with solid dispersion is discussed.

## MATERIALS AND METHODS

### Materials

HCPT was purchased from Huangshi Medical Company (Huangshi, Hubei Province, China). Polyethylene glycol 6000 (PEG 6000; Xi'an Huike Medical Company, Xi'an, Shaanxi Province, China) was used as a solid dispersion carrier; sodium chloride (NaCl; Tianjin Damao Chemical Company, Tianjin, China) was used as an osmotic agent; and polyethylene oxides (PEO; $M_w$, $3.5\times10^5$ g/mol; Shanghai Liansheng Chemical Company, Shanghai, China) was used as suspending agent. Cellulose acetate (CA) with 39.7 wt % acetyl content ($M_w$, 50,000 g/mol, Aldrich) was employed as semipermeable membrane material, and polyethylene glycol 1500 (PEG 1500, Pudong Gaonan Chemical Company, Shanghai, China) as a plasticizer for controlling membrane permeability. Methanol (Aldrich) was of HPLC grade, while other chemicals were of analytical grade.

### Preparation and X-ray Diffraction of Solid Dispersion

Solid dispersions containing various amount of drug (Table 1) were prepared by the solvent melt method. The melt PEG dissolving HCPT was stirred at 70°C to maintain better dispersion of the drug and to evaporate the small amount of methanol that was used as the solvent. The melt solution was solidified by shock frozen over silica gel for 30 minutes at -20°C and then kept in a desiccator over silica gel for 24 hours. The prepared solid dispersion was pulverized and then sieved through an 80 mesh screen.

The HCPT crystal in solid dispersions was examined by an X-ray diffraction meter (D8 ADVANCE, Siemens). The samples were irradiated with monochromatized Cu Kα radiation at a voltage of 40 kV and a current of 40 mA, respectively. The scanning rate was adjusted to 12° at 2θ/min and the scanned range was 5° to 50°.

### Preparation of MOT

HCPT solid dispersion powder was mixed with other excipients (all 80-mesh sieved) to prepare the wet granulation. The resulting wet granulation passed through a 20 mesh sieve and was dried overnight at 50°C, after which it was blended with magnesium stearate and sieved through an 80 mesh screen.

TABLE 1
Formulation of HCPT Solid Dispersion

| No. | Carrier | Carrier/Drug (w/w) |
|---|---|---|
| S1 | PEG 6000 | 11:1 |
| S2 | | 9:1 |
| S3 | | 5:1 |

TABLE 2
Formulation of the Core Tablet

| No. | Solid Dispersion no. | Amount of Ingredients (mg) | | |
|---|---|---|---|---|
| | | Solid Dispersion | PEO 350 | NaCl |
| F1 | S1 | 180 | 60 | 60 |
| F2 | S3 | 90 | 100 | 110 |
| F3 | S2 | 150 | 70 | 80 |
| F4 | S2 | 150 | 100 | 50 |
| F5 | S2 | 150 | 50 | 100 |

TABLE 3
Coating Compositions

| No. | Amount of PEG 1500 (CA, w/w %) | Weight gain (w/w %) |
|---|---|---|
| C1 | 6.25 | 3.0 |
| C2 | 4.58 | 3.0 |
| C3 | 2.34 | 3.0 |
| C4 | 4.58 | 4.0 |
| C5 | 4.58 | 5.0 |

The sieved powder was compressed into tablets having an average weight of 300 mg using a single stroke tablet-punching machine (DP30A, Guoyao Company, Beijing, China) fitted with 9-mm round standard concave punches. The core formulations are listed in Table 2.

The core tablets were coated using a coating pan (BY300A, Huanghai Drug Inspection Instrument, Shanghai, China) with a diameter of 200 mm. Acetone containing cellulose acetate (CA; 30 g/L, w/v) and a certain amount of plasticizer (PEG 1500) was used as the coating solution (Table 3). Core tablets were placed in the coating pan along with 30 to 40 filler tablets (tablets made using 9-mm round deep concave punches, containing starch, lactose, and magnesium stearate) with a pan-rotating rate of 30 rpm. The outlet air temperature was maintained between 20 °C to 25 °C. The coating solution was sprayed at the rate of 5 to 8 ml/minute until expected weight gain was obtained on the active tablets. All the active tablets were dried for 24 hours at 50 °C and then an orifice was drilled by a laser driller on both sides of the tablets.

### HPLC Analysis

The HPLC analysis was carried out on an HPLC system (Shimadzu, Japan) equipped with an LC-10 AT VP pump, SIL-10 AD VP auto-injector, and an SPD-10 AVP UV-VIS detector. Chromatographic separation was performed on an ODS C18 column (5 μm, 150 mm × 4.6 mm, Shimadzu, Japan) at room temperature. The mobile phase was a mixture of

methanol and water (58:42, v/v), with an adjusted pH of 4.0 using phosphoric acid. The eluting rate was 0.8 ml/min and it was detected at 254 nm.

### Dissolution Studies and In Vitro Release Test

A paddle apparatus (RCZ-8A, Tianjin Instrument Company, Tianjin, China) according to Ph. Chinese 2005 was used for dissolution studies. The dissolution and in vitro release were carried out at a temperature of 37 ± 0.5°C, at a stirring rate of 100 rpm and in 900 ml of a phosphate buffer solution (pH 6.8) containing 0.5% sodium dodecyl sulfate (SDS) to guarantee the sinking condition. Samples were withdrawn after predetermined time intervals, replaced with fresh medium, and the concentration of HCPT was determined by HPLC.

In order to estimate the effects of pH value of in vitro release mediums and paddle rotation rates on drug release behavior, release tests were conducted with simulated gastric fluid (SGF; pH 1.2), simulated intestinal fluid (SIF; pH 6.8), and simulated colonic fluid (SCF; pH 7.4), at 100 rpm, and at a stirring rate of 75, 100, 125 rpm with SIF, respectively.

All experiments were carried out in triplicate. For each sample a linear regression was carried out for the linear part of the release profile.

## RESULTS AND DISCUSSION

### Characteristic of Solid Dispersions

To increase the oral absorption of poorly water-soluble drugs, it is very important to improve the drug solubility and dissolution rate in the GIT. Figure 1 shows the dissolution profile of HCPT in a physical mixture and solid dispersion in comparison with pure HCPT powder. The maximum supersaturated concentrations of HCPT was about two-fold higher (about 18 μg/ml) than the solubility of HCPT in a phosphate buffer solution (pH 6.8) containing 0.5% SDS. Also, the dissolution rate of HCPT was greatly enhanced by solid dispersion. The dissolution characteristic of HCPT physical mixture with PEG 6000 was similar to pure HCPT, as HCPT was still in the crystal form, but far away from the dispersed form in solid dispersion. It was reported that PEG 6000 was able to dissolve more drug in molecularly dispersed form while hindering precipitation of the drug following dissolution of the carrier (Leuner & Dressman, 2000). The solubility of HCPT in different solid dispersion formulations (Table 1) was tested, and the drug solubility ranged from 15 μg/ml to 18μg/ml. With the increase of carrier-to-drug ratio, the drug supersaturation level and molecular mobility decreased, thereby better dispersion and a favorable solubility, as well as higher stability, (Urbanetz & Lippold, 2005) could be achieved. Slight distinctness of solubility observed with different carrier-to-drug ratios may be due to PEG 6000 high dispersion ability for HCPT.

In order to confirm the differences in crystal form between physical mixture and solid dispersion of HCPT, crystal form of the physical mixture and of the solid dispersion were investigated by X-ray diffraction (Figure 2). The peak at 2θ 11° and 26° denoted the presence of crystal HCPT (marked circle) in the physical mixture and pure HCPT, while solid dispersion with 10% HCPT lacked those two specific peaks. The X-ray diffraction indicated that HCPT might be maintained as molecular or amorphous dispersion, which resulted in the enhancement of dissolution. But the drug in the physical mixture did not show much difference in the dissolution profile as it was

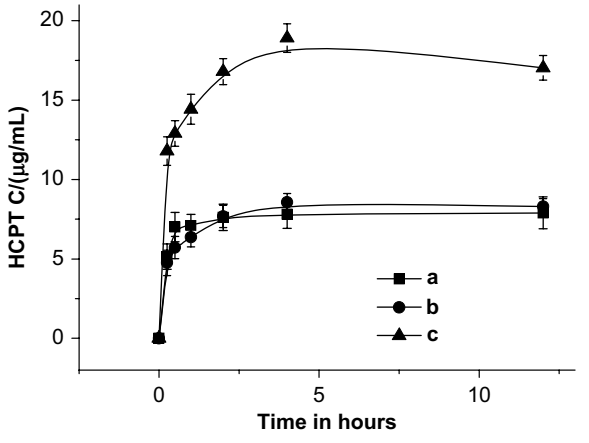


FIGURE 1. Dissolution of (a) pure HCPT, (b) physical mixture (PEG 6000/HCPT=9:1, w/w), and (c) solid dispersion (PEG 6000/HCPT=9:1, w/w) were tested in a phosphate buffer solution (pH 6.8) containing 0.5% SDS at 37 ± 0.5°C. Physical mixture with PEG 6000 rarely changed the dissolution pattern of HCPT, while solid dispersion form greatly enhanced HCPT dissolution.

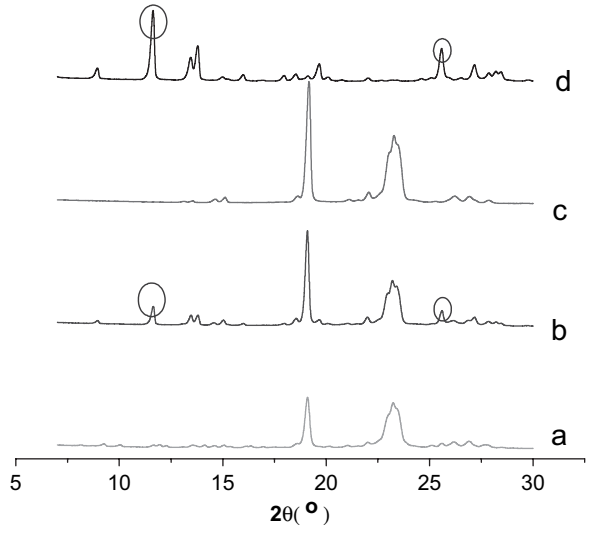


FIGURE 2. X-ray diffraction of (a) solid dispersion (PEG 6000/HCPT=9:1, w/w), (b) physical mixture (PEG 6000/HCPT=9:1, w/w), (c) pure PEG 6000, and (d) pure HCPT. Two characteristic peaks of HCPT at 2θ 11° and 25° were detected in pure HCPT and physical mixture while no characteristic peak was found in solid dispersion.

still in the crystal form (Craig, 2002). This implied that it was the formation of solid dispersion that enhanced the drug dissolution, not only the solubilization and wetting effects of the physical mixture with PEG 6000.

## Development of Monolithic Osmotic Tablet

*Effects of Solid Dispersion*

Tablets with solid dispersion of different formations were prepared and released in vitro. The data in Figure 3 demonstrated that the release profile varied with the change of carrier-to-drug ratio. Lower release rate was attributed to carrier-to-drug ratio at 5:1 because the solubility of HCPT was lower, which was crucial in the release of water-insoluble drug from the osmotic tablet. The drug may be delivered by the extrusion, either in the form of a suspension of solids in water or, primarily, as a solution, depending on the dissolution dynamic of the core (Appel, Curatolo, Herbig, Nightingale, & Thombre, 2000). However, higher carrier-drug ratio at 11:1 may limit the amount of NaCl and PEO with the same total weight, and slow release in the first four hours occurred consequently. Taken these factors into consideration, carrier-drug ratio at 9:1 is appropriate for constant release within 12 hours.

*Effects of Fatio of Osmotic Agent to Suspending Agent*

Figure 4 showed that the ratio of osmotic agent to suspending agent had some influence on the release profile. The more NaCl incorporated into the tablet, the more components in the core would be dissolved so that the viscosity of the core decreased and thus more drug was released. However, lower amount of PEO 350, which played the role of suspending agent, would affect cumulative release. Lower amounts of PEO 350 led to lower viscosity of the suspension and hardly prevented precipitation of HCPT. This was consistent with reported results that osmotic and suspending agents in MOT had coordinative important effect on the release profile (Liu, Khang, et al, 2000). As a consequence, a moderate NaCl/PEO 350 rate approximate to 1 was selected.

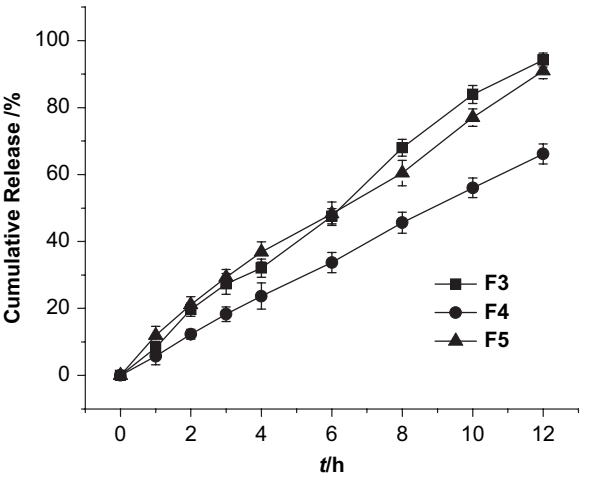


FIGURE 4. Release profile of formulations in Table 2 with a different osmotic agent to suspending agent ratio. Each tablet contains 15 mg HCPT with coating composition C2 in Table 3.

*Effects of Amount of Plasticizer*

Besides the formulation of the tablet, the membrane is also a key factor affecting the release profile of the monolithic osmotic tablet. As PEG is a hydrophilic plasticizer, it would be leached easily and left behind a wholly porous structure, which increases membrane permeability and drug release rate (Lu, Jiang, Zhang, & Jiang, 2003). Figure 5 shows that the increase of PEG content led to an increase of drug release rate. The

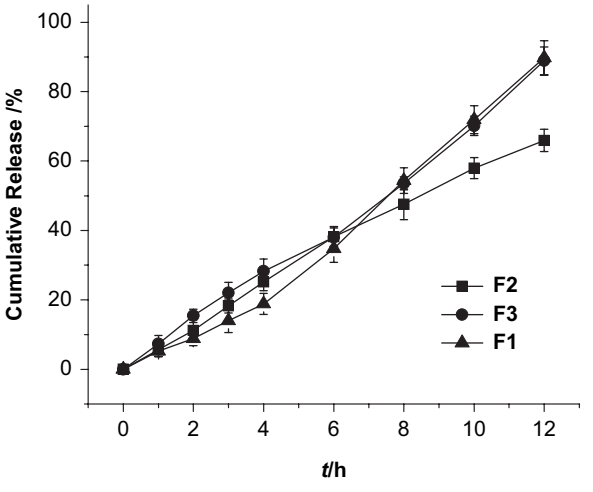


FIGURE 3. Release profile of HCPT in different formulations in Table 2. Each tablet contains 15 mg HCPT with coating composition C2 in Table 3.

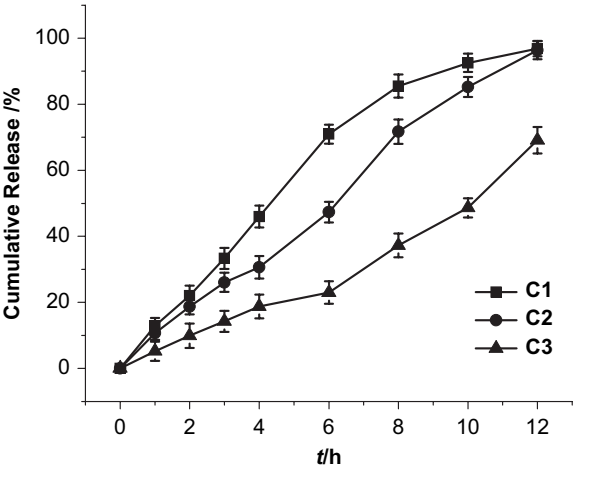


FIGURE 5. Release profile of formulations in Table 3 with different plasticizer PEG 1500 content. Each tablet contains 15mg HCPT with formulation F3 in Table 2.

more PEG incorporated into the membrane, the more void space formed and permeability of the membrane increased; thus, a higher release rate occurred.

*Effects of Membrane Weight Gain*

To study the effects of membrane thickness on the drug release, tablets were coated with different weight gain. Figure 6 illustrateS that drug release decreased with the growth of the weight gain of the membrane. As the weight gain increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased. As a consequence, the drug release rate was reciprocal to the weight gain. It was found that coating formulation C2 together with optimal tablet formulation F3 could attain approximate zero-order release pattern.

## Effects of Orifice Size

It was reported that orifice sizes should be kept in an appropriate range so as to maintain zero-order release. Orifice sizes must be smaller than the maximum limit, to avoid diffusion delivery through the orifice, and larger than the minimum limit, to minimize hydrostatic pressure inside the system (Theeuwes & Higuchi, 1975). The tablet core F3 was coated with formulation C2 and was subsequently drilled with a circular orifice of the same diameter on each side of the surface. Figure 7 showed the effects of orifice size on release profile. Orifice sizes between 300 μm to 400 μm could maintain steady release and high cumulative release percentage, while an orifice size of 200 μm resulted in lower release rate as drug suspension may occlude such a small orifice, therefore leading to a low release rate. An orifice diameter of 300 μm to 400 μm contributed to a similar release profile as it was within the optimal range.

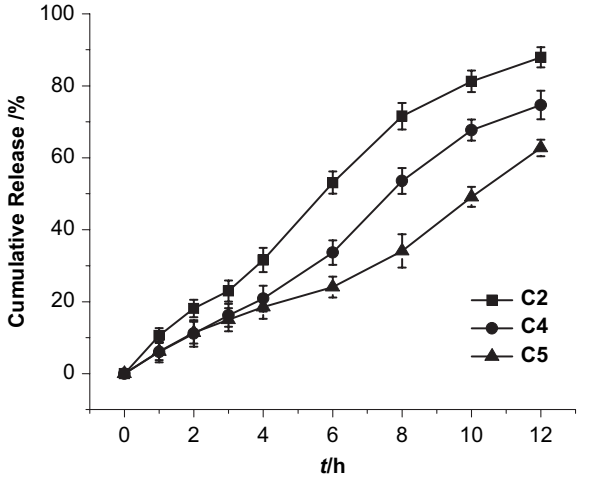


FIGURE 6. Release profile of formulations in Table 3 with different membrane weight gain. Each tablet contains 15 mg HCPT with formulation F3 in Table 2.

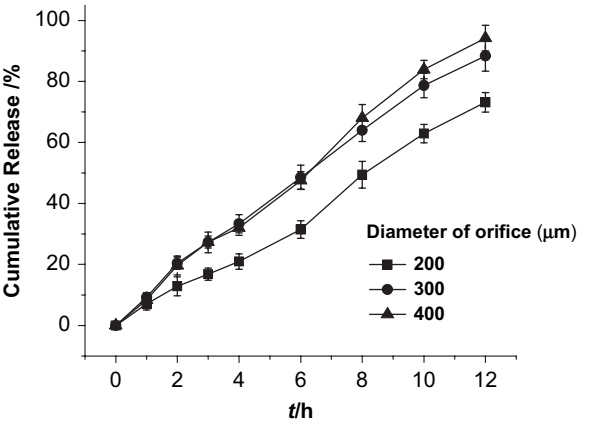


FIGURE 7. Release profile of different orifice size. Each tablet contains 15 mg HCPT with core formulation F3 and coating composition C2.

## Evaluation of the Optimized Formulation

To investigate the influence of release media on drug release, in vitro releases were tested in SGF, SIF, and SCF at 100 rpm. Optimized formulation exhibits a linear release pattern in 12 hours, and no significant difference in release profile could be found in different release media ($p > .05$). Therefore, it may be expected that the drug release from MOT in the gastrointestinal fluid exhibited a media-independent characteristic. The influences of stirring rate on drug release profile (at 75, 100, and 125 rpm) were also examined, respectively. Increasing agitation rate did not influence the release profile significantly ($p > .05$). Thus the mobility of the GIT may scarcely affect the drug release of the MOT. Drug release was independent on release media and agitation rate, and the monolithic osmotic tablet was reported to exhibit a comparable in vitro/in vivo release profile (Theeuwes & Higuchi, 1975). The average drug release rate was 1.21 ± 0.05 mg/hour, while cumulative release at 12 hours was 93.65 ± 1.61% (n=6).

The MOT system containing solid dispersion HCPT was compared with a push-pull osmotic system, which does not contain solid dispersion. The release profile (Figure 8) indicated that there was a time lag (about 3 hours) in the push-pull osmotic system, while the MOT osmotic system containing solid dispersion exhibited zero-order release up to 12 hours. The time lag in the push-pull osmotic system, which may be due to the low solubility of drug in the drug layer and the swelling time needed for the push layer, is the general phenomenon influencing the therapeutic effects. As the solubility of HCPT is extremely low, it is hard to form a suspension solution in the drug layer. Consequently, the release rate and accumulated release percentage at 12 hours is low. Furthermore, the dissolving character of HCPT may restrict its release. So developing a solid dispersion form is beneficial for water-insoluble drugs like HCPT to better dissolve. On the other hand, a push-pull osmotic system depends on the swelling

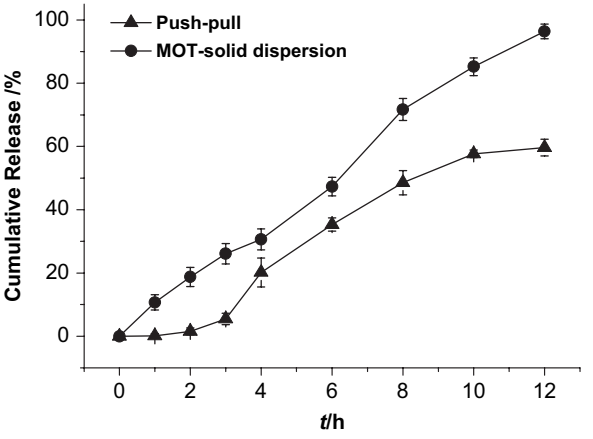


FIGURE 8. Release profile of optimized push-pull osmotic tablet and MOT-solid dispersion osmotic tablet. In push-pull osmotic tablets, PEO 550 was applied as swelling agent in the push layer, while PEO 50 was used as suspending agent in the drug layer.

effect of the push layer high-molecular weight polymers. It takes time for high-molecular weight polymers to hydrate and expand in order to push the up drug layer, which is the general mechanism in a push-pull osmotic system. The MOT system containing solid dispersion overcomes such problems. The simplicity of the MOT system exceeds other complicated osmotic system for water-insoluble drugs, and by integrating the solid dispersion technique water-insoluble drugs could be released at a controlled rate and a higher ultimate accumulated release percentage.

### Discussion of the Drug Release Mechanism

Water-insoluble drug release from MOT containing solid dispersion is somewhat different from that of EOP or a push-pull osmotic tablet. As for the water-insoluble drug, the solubility would be too low to form a homogeneous drug suspension and affect drug dissolution. Thus, solid dispersion formation was applied so as to enhance the solubility and the dissolution rate. NaCl as the osmotic agent played an indispensable role because osmotic mechanism was the main energy source to imbibe water and the basis of all osmotic delivery systems. In addition, carrier PEG 6000 also has the osmotic effect to some extent (Ke & Sun, 2004). Meanwhile, suspending agent PEO was applied to increase the viscosity, stabilize the suspension, and swelling. In operation, water was imbibed owing to the osmotic pressure difference between the inside of the tablet membrane and the outside environment, which was contributed by NaCl. Then HCPT in solid dispersion form dissolved, and a viscous HCPT suspension was created as PEO imbibed water and swelled. The solid dispersion facilitated rapid dissolution and higher drug concentration within the tablet, and the drug suspension was pumped out through the orifices. The drug release was cocontrolled by osmotic and suspension mechanisms, while the solid dispersion form was utilized to increase drug solubility, dissolution rate, and dispersion degree.

It was reported that Poiseuille's law of laminar flow could be applied to describe drug release in MOT (Lu, Jiang, & Zhang, 2003) as in Equation 1:

$$\frac{dM}{dt} = \frac{\pi C}{8}\frac{r^4}{\eta}\frac{P_1 - P_2}{h} \quad (1)$$

Where $dM/dt$ is the drug release rate, $C$ is the concentration of drug in tablet suspension, $r$ is the radius of orifice, η is the viscosity of tablet suspension, $(P_1–P_2)$ is the pressure difference between the inside and outside of the membrane, and is the thickness of membrane.

In this MOT containing HCPT in solid dispersion form, $C$ is largely dependent on the solubility of HCPT in solid dispersion and dispersed degree in tablet core. Solid dispersion helped to improve drug dissolution rate and maintain a high and constant drug concentration in the core. This is because the drug in solid dispersion is in supersaturation form. $(P_1–P_2)$ represents both osmotic pressure and swelling effect, and it was that force driving the drug release. The drug release rate is inversely proportional to ηand. If η is too high, the release rate will be decreased, as a swelling effect could not maintain well-proportioned suspension; if η is too low, the drug solid dispersion may precipitate and be unable to maintain $C$ high enough for constant release. In summary, drug release from MOT containing solid dispersion can be contributed to the osmotic, suspending, and solubility enhancement.

## CONCLUSION

MOT containing solid dispersion of HCPT were prepared. Solid dispersion consisted of PEG 6000, and HCPT could enhance the solubility, dissolution rate of water-insoluble drug HCPT. Drug release was investigated in vitro. The optimal MOT was able to deliver HCPT at a constant rate of 1.21 mg/hour for up to 12 hours in SIF (pH 6.8), and cumulative release at 12 hours is above 90%, independent of environment media and stirring rate. The release is co-controlled by osmotic and suspending effect while integrating solid dispersion for solubility enhancement. Compared with push-pull osmotic tablets, MOT was simple to prepare and there is no need to differentiate the orifice drill surface. The MOT containing solid dispersion has great potential in the controlled delivery of water-insoluble drugs.

## REFERENCES

Appel, L. E., Curatolo, W. J., Herbig, S. M., Nightingale, J. A. S., & Thombre, A. G. (2000). *Osmotic system for delivery of solid amorphous dispersions of drugs*. European Patent EP1027888.

Cortese, R, & Theeuwes, F. (1982). Osmotic *device with hydrogel driving member*. U.S. Patent 4327725.

Craig, D. Q. M. (2002). The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm. 231*, 131–144.

Ke, D., & Sun, G.. (2004). The effect of reactive oxygen species on ethylene production induced by osmotic stress in etiolated mungbean seedling. *Plant Growth Regul. 44*, 149–155.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. 50*, 47–60.

Ling, Y., & Xu, B. (1993). Inhibition of phosphorylation of histone H1 and H3 induced by the 10-hydroxycamptothecin, DNA topoisomerase I inhibitor, in murine ascites hepatoma cells. *Zhongguo Yao Li Xue Bao 14*, 546–550.

Liu, L., Ku, J., Khang, G., Lee, B., Rhee, J. M., & Lee, H. B. (2000). Nifedipine controlled delivery by sandwiched osmotic tablet system. *J. Control. Release 68*, 145–156.

Liu, L., Khang, G., Rhee, J. M., & Lee, H. B. (2000). Monolithic osmotic tablet system for nifedipine delivery. *J. Control. Release 67*, 309–322.

Lu, E.-X., Jiang, Z. Q., Zhang, Q. Z., & Jiang, X. G. (2003). A water-insoluble drug monolithic osmotic tablet system utilizing gum Arabic as an osmotic, suspending and expanding agent. *J. Control. Release 92*, 375–382.

Okimoto, K., Tokunaga, Y., Ibuki, R., Irie, T., Uekama, K., & Rajewski, R. A., et al. (2004). Applicability of (SBE)7m-β-CD in controlled-porosity osmotic pump tablets (OPTs). *Int. J. Pharm. 286*, 81–88.

Royce, A., Li, S., Weaver, M., & Shah, U. (2004). In vivo and in vitro evaluation of three controlled release principles of 6-N-cyclohexyl-2'-O-methyladenosine. *J. Control. Release 97*, 79–90.

Su Li, Li Z., Zhong zhen G., Zhan J., Yu yan L., Wen qi J. (2005). Absolute bioavailability of hydroxycamptothecin tablets in cancer patient.*J. Clin. Pharmacol. 21*, 46–49.

Theeuwes, F. (1975). Elementary osmotic pump. *J. Pharm. Sci*. *64*, 1987–1991.

Theeuwes, F., & Higuchi, T. (1975). *Osmotic dispensing device with maximum and minimum sizes for the passageway*. U.S. Patent 3916899.

Theeuwes, F. (1981). Novel drug delivery systems. In L. F. Prescott & W. S. Nimmo (Eds.), *Drug Absorption* (pp. 157–176). Balgowlah, Australia: ADIS Press.

Urbanetz, N. A., & Lippold, B. C. (2005). Solid dispersions of nimodipine and polyethylene glycol 2000: Dissolution properties and physico-chemical characterization. *Eur. J. Pharm. 59*, 107–118.

Verma, R. K., Mishra, B., & Garg, S. (2000). Osmotically controlled oral drug delivery. *Drug Dev. Ind. Pharm*. *26*, 695–708.

Verma, R. K., Krishna, D. M., & Garg, S. (2002). Formulation aspects in the development of osmotically controlled oral drug delivery systems. *J. Control. Release 79*, 7–27.

Gan, Y., Pan, W., Wei, M., & Zhang, R. (2002). Cyclodextrin complex osmotic tablet for glipizide delivery, *Drug Dev. Ind. Pharm*. *28*, 1015–1021.

Zhang, R. W., Li, Y. F., Cai, Q. Y., Liu, T. P., & Sun, H. (1998). Preclinical pharmacology of the natural product anticancer agent 10-hydroxycamptothecin, an inhibitor of topoisomerase I. *Cancer Chemother. Pharmacol*. *41*, 257–267.