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Studies on Bi-Layer Osmotic Pump Tablets of Water-Insoluble Allopurinol with Large Dose: In Vitro and In Vivo

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Controlled release bi-layer osmotic pump tablets (BOPT) of water—insoluble allopurinol with large dose (150 mg/BOPT) were successfully prepared merely with sodium chloride as osmotic promoting agent and polyethylene oxide (PEO) as suspending agent. Formulations of the two kinds of agents were investigated in order to discuss their effects on the release behavior of BOPT, and then the optimal formulation was evaluated. The pharmacokinetics studies of allopurinol and its active metabolite oxypurinol in two-preparation and two-period crossover design relative to the equivalent dose of commercially common allopurinol tablets were evaluated in six Beagle dogs. And the pharmacokinetics results showed that allopurinol BOPT were able to provide a slow release of allopurinol, and oxypurinol were bioequivalent between allopurinol BOPT and common allopurinol tablets. A good in vitro–in vivo correlation of allopurinol was also proved. In conclusion, water-insoluble drugs with large dose can be designed to BOPT for efficacy and safety use.

Keywords bi-layer osmotic pump tablets; pharmacokinetics; in vitro-in vivo correlation; allopurinol; oxypurinol

INTRODUCTION

The osmotic pump tablets (OPT) have been the major interest in the field of pharmacy due to its obvious advantages of easier administration and better patient compliance in the treatment of chronic conditions (Keith, 2006; Verma et al., 2000a,b). However, the elementary osmotic pump tablets (EOPT) are only suitable for the delivery of moderate-solubility drugs. As for water-insoluble drugs, there are mainly two ways to prepare OPT.

1. Adding proper agent in the formulation to improve the solubility of water-insoluble drugs in EOPT. The specific methods are utilizing β-cyclodextrin or its derivation as the solubilizer (Okimoto et al., 1998; 1999a–c), salification the drugs (Gupta et al., 1998; Modi et al., 2000), adding surfactants (Hou & Zhu, 1982) and so on.
2. Increasing the contrast osmotic pressure in and out of the membrane to maintain the power of continual drug release from BOPT or multiple-layer OPT (Goldenberg, 1999; Liu et al., 2000). The most conventional way is adding high polymer as suspending agent (Chen et al., 1998), utilizing the osmotic pressure and swelling pressure after hydrating to push out the suspension.

Both ways would apparently enlarge the tablet weight to an unreasonable range if the dose of water-insoluble drug is large. So it is known that the water-insoluble drugs which are prepared into the OPT are mostly with small dose (Swanson et al., 1987; Kuczynski et al., 1991). Reports about water-insoluble drugs OPT with large dose in proper tablet weight range have seldom been found.

Allopurinol is an oxypurine base, analogue of hypoxanthine. It is effective for the treatment of both primary hyperuricemia of gout and secondary hyperuricemia related to haematological disorders or antineoplastic therapy. Allopurinol is converted by xanthinoxidase to its main metabolite, oxypurinol. They both act as inhibitors of the xanthine oxidase-mediated conversion of hypoxanthine to xanthine and of xanthine to uric acid.

Because it may take several months or even longer before the benefit of allopurinol can be felt, it is necessary to prepare allopurinol sustained-release preparations. The allopurinol sustained –release capsules with the dose of 300 mg once daily have been on the market outside China, while only common tablets with the dose of 100 mg three times daily are commercially sold in China. For low solubility in water (0.48 mg/mL at 25°C, Merck Index) and large dose, the solubility in EOPT can hardly be improved even though proper agents are added. Herein, allopurinol BOPT with the dose of 150 mg was studied. The tablet was designed once daily (2 tablets/time). It is very valuable for the study on allopurinol BOPT as a

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supplement of the water-insoluble drugs which are suitable to prepare OPT.

MATERIALS AND METHODS

Materials

Allopurinol (Zhejiang Haizheng Pharmaceutical Company, China), oxypurinol (J&K Chemical Ltd., Beijing, China), PEO N10(Mw 1×10^5, Dow Chem Co.), PEO WSR303 (Mw 7×10^6, Dow Chem Co.), sodium chloride (NaCl, Shenyang Chem., Shenyang, China), cellulose acetate (CA, 54.5–56.0 wt.% acetyl content, Shanghai Chem., Shanghai, China), Polyethylene glycol 2000 (PEG2000, Pudong Gaonan Chem., Shanghai, China). Triethylamine (Use for high-performance liquid chromatography (HPLC), Shandong Yuwang Industrial Co. LTD., Shandong, China). The other chemicals used were of analytical grade.

TABLE 1
Basic Tablet Core Formulation and Varying Range of Some Ingredients

Ingredients	Basic Amount (mg)	Varying Range (mg)
The drug layer		
Allopurinol	150	/
PEO N10	250	200–300
NaCl	50	30–70
Magnesium stearate	2	/
The push layer		
PEO WSR-303	40	110–170
NaCl	30	15–45
Magnesium stearate	1	/
Total tablet weight	623	

The Preparation of BOPT

Certain amount of allopurinol, NaCl, PEO N10 and magnesium stearate according to the formulation were mixed manually after each component passed through 80-mesh screen respectively. The resultant powder mixture was prepared as the drug layer. The polymeric osmotic ingredients for the push layer were obtained by the same way with appropriate content of PEO WSR-303, NaCl and magnesium stearate powder being described in the formula. Tiny colorant (Fe_2O_3) was added to the push layer as the mark for drilling. The drug layer and the push layer were compressed into bi-layer tablets using a single station-punching machine by double compression method, with 12-mm concave punches. And the pressure was 5 $kg.cm^{-2}$ – 7 $kg.cm^{-2}$. Based on our preliminary study on allopurinol BOPT, the basic tablet core formulation and the varying range of some ingredients were listed in Table 1.

The tablets were coated using a coating pan. CA (3% w/v) in acetone: PEG2000 (10% w/v) in distilled water (97:3) was used as coating formulation. The diameter of the coating pan was 230 mm, 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 hr at 40°C, to remove the residual solvent. Then the side of the drug layer was drilled by a microdrill of known diameter.

Dissolution Testing

The tests of allopurinol from osmotic pump system of various formulations were carried out according to the United States Pharmacopoeia Apparatus II (paddles) method, at 75 rpm, 37 ± 0.5°C, and 900 mL of simulated gastric fluid (pH 1.0 HCl) as the medium. 5 mL samples were collected at 2, 4, 6, 8, 10, 12, and 14 hr, then filtered through 0.8 μm filter membrane. 5 mL of fresh dissolution medium was added after each sampling. The filtrate was diluted to a certain concentration with dissolution medium and determined at 250 nm using UV spectroscope. The results were used to calculate the cumulative release amount of allopurinol from the osmotic delivery system versus time and figure out the release profiles for further evaluation. Throughout the study, similarity factors (f_2) were used to compare the dissolution profiles and 65 was taken as the critical value (FDA, 1995).

In Vivo Studies

With commercially common allopurinol tablets as the reference, pharmacokinetics studies of self-prepared allopurinol BOPT were performed in six Beagle dogs. Six Beagle dogs were open-label and fasting 12 hr. Five miililiter samples of blood were collected at the following times post-dose: 0, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 24, 36, and 48 hr. Samples were immediately centrifuged at 4000 rpm for 10 min. The plasma was separated and frozen at −20°C until drugs were analyzed. Plasma concentrations of allopurinol and oxypurinol were determined in a blind fashion by means of HPLC.

Pharmacokinetics Data Analysis

Concentrations in plasma versus time data of allopurinol and oxypurinol were determined by using 3P97 Professional (Chinese pharmacological association software), which indicated that the absorption of allopurinol fits for first-order absorption and elimination kinetics. So the Wagner-Nelson method was used to calculate the percent of allopurinol dose absorbed, F_a. F_a (%) was calculated as $(C_t + k_e\ AUC_{0-t})/(k_e AUC_{0-\infty}) \times 100$. Bioequivalence was assessed by means of analysis of the variance (ANOVA), two one-sided tests, and calculating the standard 90% Confidential Interval (CI) of the ratio test/reference.

RESULTS AND DISCUSSION

Formulations and In Vitro Release Studies

Formulation Design

As the tablet core of BOPT needed enough adjuvant to successfully deliver water-insoluble drug at approximate zero-order rate and release completely, the water-insoluble drugs prepared to BOPT were mostly in small dose to ensure that the tablet weight was in a sensible range. How to design allopurinol BOPT with the dose of 150 mg was a great challenge here. The main ideas were increasing the osmotic promoting agent and decreasing the high polymer relatively in drug layer, increasing the weight of push layer and increasing the permeability of the semi-permeable membrane.

Influence of Tablet Formulation Variables on Allopurinol Release

To study the influence of the chemicals amount on allopurinol release, tablet core with various formulations was prepared, subsequently being coated with the same coating formulation, and a 0.8 mm orifice was drilled on the side of the drug layer. f_2 data of analog analysis were showed in Table 2.

Influence of PEO Amount on Allopurinol Release. PEO N10 was used as the suspending agent to improve allopurinol in the form of fine suspension after the fluid was imbibed into the drug layer. PEO WSR303 was used as a kind of swelling agent (Thombre et al., 2004) in the push layer. Different molecular weight of PEO was used in different layer and was compared separately. Figure 1 showed that the allopurinol release decreased as the PEO N10 amount ranged from 200 mg to 300 mg, but no significant influence was found between 250 mg and 300 mg. It might be explained like this: the increase of PEO level of drug layer increased the viscosity of drug suspension, which increased the stability, and inhibited the aggregation and precipitation of alllopurinol in suspension. 250 mg and 300 mg of PEO N10 in drug layer might have the similar viscosity. Figure 2 showed that the influence on different amount of PEO WSR-303 in push layer could be neglected.

Influence of NaCl Amount on Allopurinol Release. NaCl was used as the osmotic promoting agent in both layers. Different amount of NaCl in drug layer and push layer was compared separately. Figure 3 showed that the release increased as the NaCl amount ranged from 30 mg to 50 mg, but the change

TABLE 2
Analog Analysis of Self-made BOPT on Release Profile

Group	Comparison	f_2	Results
Different PEO amount in drug layer	250 mg/200 mg	70.68	+
	250 mg/300 mg	50.36	–
	200 mg/300 mg	52.84	–
Different PEO amount in push layer	140 mg/110 mg	83.55	+
	140 mg/170 mg	72.37	+
	110 mg/170 mg	68.68	+
Different NaCl amount in drug layer	50 mg/70 mg	69.37	+
	50 mg /30 mg	57.37	–
	30 mg/70 mg	57.28	–
Different NaCl amount in push layer	30 mg/15 mg	78.43	+
	30 mg/45 mg	68.32	+
	15 mg/45 mg	66.34	+
Different stirring speed	75 rpm/50 rpm	81.92	+
	75 rpm/100 rpm	85.44	+
	50 rpm/100 rpm	76.42	+
Different pH of media	pH 1.0/pH 6.8	90.41	+
	pH 1.0/pH 7.4	88.36	+
	pH 6.8/pH 7.4	93.35	+

("+" means similar; "–" means dissimilar).

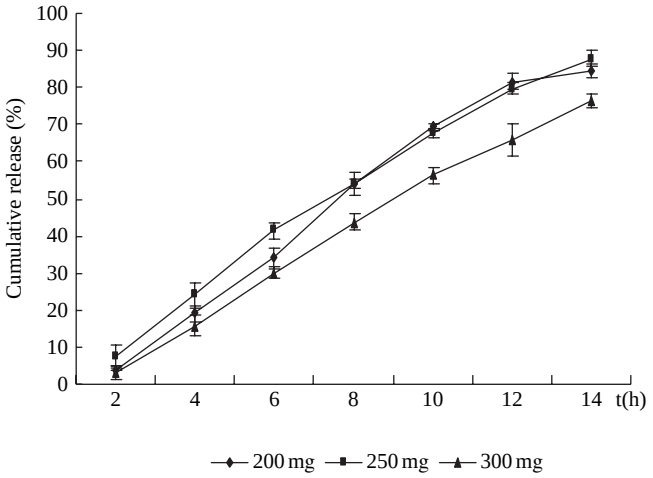

FIGURE 1. Effect of amount of PEO (N10) of drug layer on allopurinol release (n = 3).

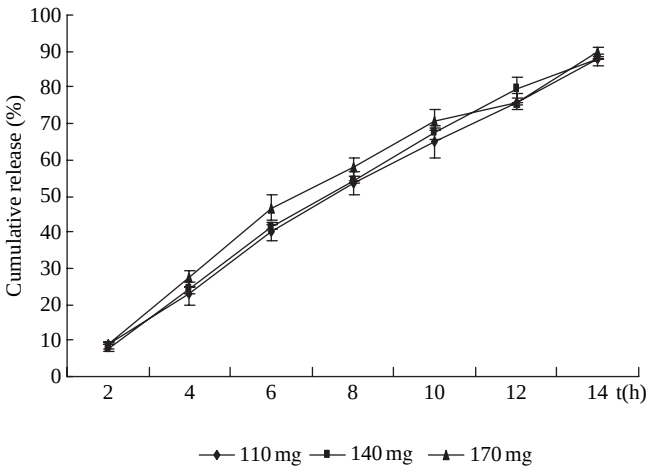

FIGURE 2. Effect of amount of PEO (WSR-303) of push layer on allopurinol release (n = 3).

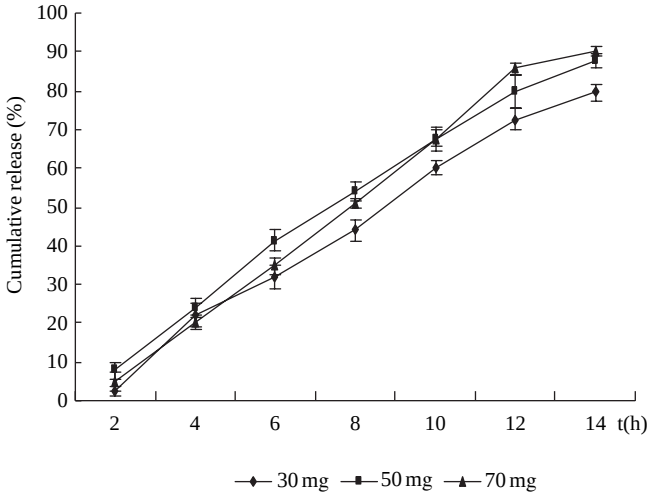

FIGURE 3. Effect of amount of NaCl of drug layer on allopurinol release (n = 3).

which was observed between 50 mg and 70 mg NaCl was not notable. Figure 4 manifested no remarkable influence on different amount of NaCl in push layer.

The optimal formulation was chosen when the coefficient correlation r of the cumulative release-time profile best got close to 1, and the final cumulative release amount was nearly 100%. Based on the results mentioned above, the optimal formulation of tablet core was PEO WSR-303 110 mg in push layer, and the others were just the same as the basic tablet core formulation in Table 1, with the coefficient correlation r of the cumulative release-time profile equaling to 0.9947.

Evaluation of Optimal Formulation

To study the effect of stirring rate on drug release, dissolution tests were carried out at stirring rates of 50, 75 and 100 rpm. Figure 5 showed that the increase rate of stirring did not remarkably affect the drug release. Thus, the mobility of the gastrointestinal tract might scarcely affect allopurinol release from the BOPT.

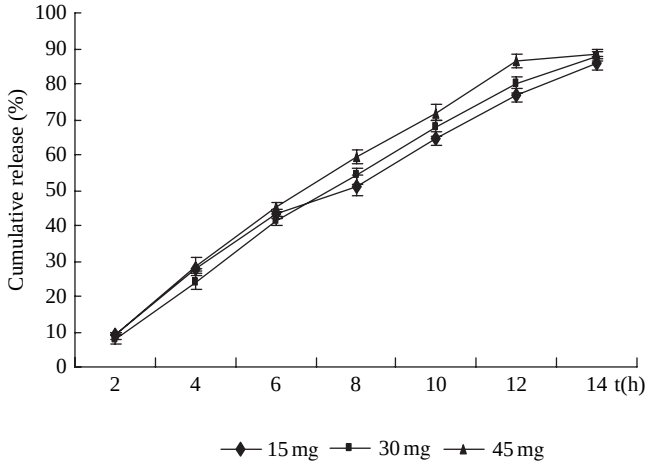

FIGURE 4. Effect of amount of NaCl of push layer on allopurinol release (n = 3).

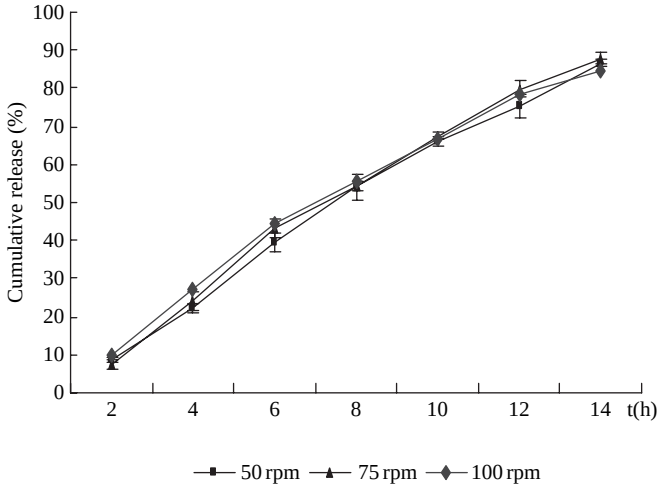

FIGURE 5. Effect of stirring speed on allopurinol release (n = 3).

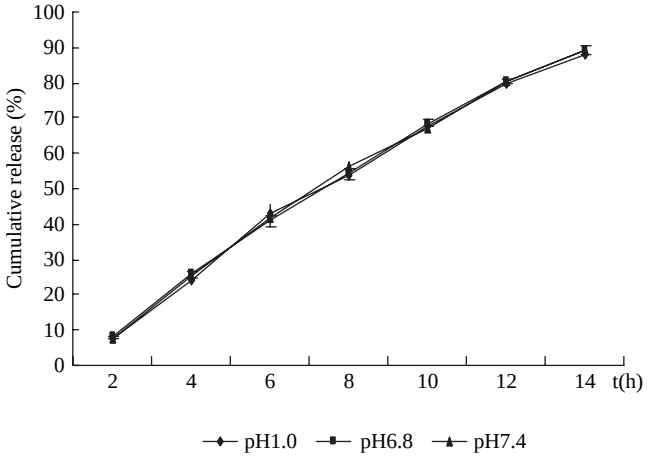

FIGURE 6. Effect of different pH of media on allopurinol release (n = 3).

To study the effect of release media on drug release, dissolution tests were carried out at pH 1.0 HCl solution, pH6.8 phosphate buffered solution and pH 7.4 phosphate buffered solution. Figure 6 showed that the pH value of release media did not affect allopurinol release.

Evaluation In Vivo

Concentration of allopurinol and oxypurinol in blood after oral administration 300 mg of commercially common allopurinol tablets and self-prepared allopurinol BOPT were summarized in Figure 7 and 8. Relative bioavailability of allopurinol and oxypurinol was 87.51% and 103.96%, respectively.

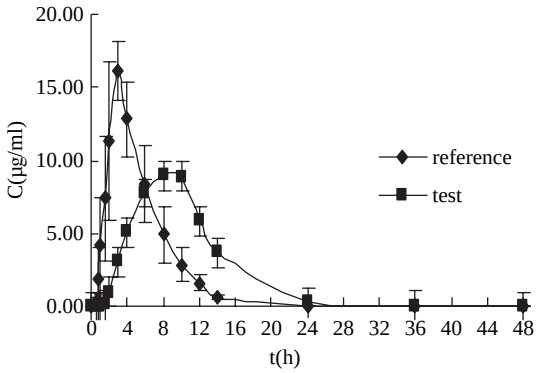

FIGURE 7. Mean plasma concentration-time profile of allopurinol after single dose (n = 6).

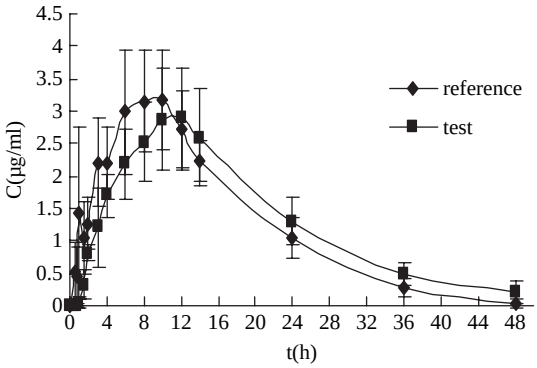

FIGURE 8. Mean plasma concentration-time profile of oxypurinol after single dose (n = 6).

Results of bioequivalent assay indicated that allopurinol was not bio- equivalent, oxypurinol was bioequivalent between allopurinol BOPT and common allopurinol tablets. The obviously lower C_{max} of allopurinol was due to the constant release pattern of the osmotic tablets in vivo, which indicated that allopurinol BOPT zero-order release was obtained in vivo environment. Allopurinol could be rapidly transformed into its active metabolite, oxypurinol (Barthel et al., 1999). In common allopurinol tablets, plasma level of metabolite was assumed as oxypurinol formation rate-limited (Chen & André, 1991). But in allopurinol BOPT, plasma level of metabolite was assumed as allopurinol release rate-limited. For allopurinol, oxypurinol formed by xanthine oxidase is responsible for maintaining a stable and prolonged level of xanthine oxidase inhibition. Considering allopurinol merely as a prodrug, oxypurinol is therefore responsible for the hypouricemic effect of allopurinol formulations (Walter-Sack et al., 1995; Walter-Sack et al., 1996). So it is more reasonable to assess the bioequivalence of allopurinol BOPT on oxypurinol than on allopurinol. And the results indicated that allopurinol BOPT and common allopurinol tablets were bioequivalent.

TABLE 3
Drug Release of Allopurinol BOPT In Vitro and In Vivo

T	2	4	6	8	10	12	14
$\mathbf{F_r}$	7.70	24.04	41.32	54.04	67.53	79.81	87.75
$\mathbf{F_a}$ **(%)**	4.31	26.11	50.80	71.77	85.97	89.85	92.02

A in vitro–in vivo correlation was investigated using the percent of dissolved F_r versus the percent of absorbed F_a (Table 3). The in vitro-in vivo relationship was $F_a = 1.1475 \times F_r + 0.0075$ and the correlation coefficient r was equal to 0.9802, indicating that a close correlation could be established in vitro–in vivo.

CONCLUSION

Based on the results of the studies on the formulation variables above, optimal formulation was obtained. The allopurinol BOPT was found to be able to release drug approximately in a zero-order fashion and the cumulative release amount of allopurinol at 14 hr can over 85% of initial loading amount. This study also showed that it was possible to formulate a water-insoluble drug with large dose into BOPT to overcome the poor release behavior.

In addition, studies of this report on pharmacokinetics indicated that it is more reasonable to assess the bioequivalence of allopurinol controlled release preparations on oxypurinol than on allopurinol. And there is a good in vitro–in vivo correlation for allopurinol BOPT.

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