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Floating matrix dosage form for phenoporlamine hydrochloride based on gas forming agent: In vitro and in vivo evaluation in healthy volunteers

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Abstract

Phenoporlamine hydrochloride is a novel compound that is used for the treatment of hypertension. The purpose of this study was to develop a sustained release tablet for phenoporlamine hydrochloride because of its short biological half-life. Three floating matrix formulations of phenoporlamine hydrochloride based on gas forming agent were prepared. Hydroxypropyl methylcellulose K4M and Carbopol 971P NF were used in formulating the hydrogel drug delivery system. Incorporation sodium bicarbonate into matrix resulted in the tablet floating over simulated gastric fluid for more than 6 h. The dissolution profiles of all tablets showed non-Fickian diffusion in simulated gastric fluid. Moreover, release of the drug from these tablets was pH-dependent. In vivo evaluations of these formulations of phenoporlamine hydrochloride were conducted in six healthy male human volunteers to compare the sustained release tablets with immediate release tablets. Data obtained in these studies demonstrated that the floating matrix tablet containing more Carbopol was capable of sustained delivery of the drug for longer periods with increased bioavailability and the relative bioavailability of formulation (containing 25% Carbopol 971P NF, 8.3% HPMC K4M) showed the best bioequivalency to the reference tablet (the relative bioavailability was 1.11 ± 0.19).

Keywords: Phenoporlamine hydrochloride; Floating matrix; Sustained release; Bioavailability; In vitro–in vivo correlation

1. Introduction

Phenoporlamine hydrochloride (DDPH) is a novel compound that works against a variety of types of hypertension and has also been used in the treatment of arrhythmia and the therapy of benign prostatic hyperplasia (Zheng et al., 2001). Chemically, phenoporlamine hydrochloride is designated as 1-(2,6-dimethylphenoxy)-2-(3,4-dimethoxyphenylethylamino) propane hydrochloride (Fig. 1) (Ni et al., 1996). It exists as crystalline aggregates and approximately appears as white powder with melting point of 168 °C. DDPH has a relatively high aqueous solubility at neutral pH (10 mg/ml at pH 7.0). It is dissolved rapidly in intestinal fluid and reaches its maximum blood concentration within 30 min. However, this compound has a relatively short elimination half-life time (about 2.2 h) in humans, requiring a four times 60 mg per time daily dosing regimen. In view of this characteristic, many attempts have been made to develop sustained-release preparations with extended clinical effects and reduced dosing frequency.

In order to develop desired sustained release dosage form for DDPH, it is necessary to optimize both the residence time of the system in the gastrointestinal (GI) tract and the release rate of the drug from the system. Various approaches used to increase the GI residence time include mucoadhesive system (Wang et al., 2001; Tamburic and Craig, 1996), flotation system (Lee et al., 1999; Li et al., 2003) or swellable system (Fix et al., 1993). For soluble drugs, Carbopol gel could extend the release time remarkably but the release profiles had considerable fluctuations (Samani et al., 2003). In previous work, it was obvious that the release of DDPH in early hours was very slow from the hydrophilic matrix containing Carbopol alone. Therefore, in this study, blends of HPMC and Carbopol were used as a matrix former to improve the release rate of DDPH from matrices.

Gastric floating devices may be highly useful for the drug delivery system (Joseph et al., 2002; Thanoo et al., 1993). For many drugs that absorbed mainly from the proximal small intestine, controlled release in the stomach would result in improved bioavailability (Sato et al., 2004). In previous work, DDPH was

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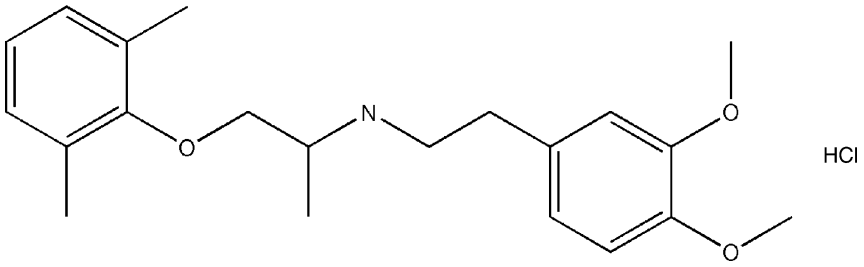

Fig. 1. Chemical structure of phenoporlamine hydrochloride.

found to be well absorbed from wide regions of the gastrointestinal (GI) tract including colon. In this paper, the floating drug delivery employed sodium bicarbonate as a gas forming agent dispersed in a hydrogel matrix. The matrix was a mixture using the combination of HPMC K4M and Carbopol 971P NF. During formation of the floating tablets, the evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix.

The objective of this experiment was to prepare a gastric floating hydrogel delivery system combined hydrogel polymers with gas forming agent for the novel antihypertensive drug. The effects of different polymer concentration on the drug release rate and the buoyancy properties of the drug delivery system were investigated. In addition, the in vivo absorption and bioavailability of these formulations were evaluated in healthy volunteers, in vitro dissolution and in vivo absorption correlations were attempted.

2. Materials and methods

2.1. Materials

The following materials were used in the study: DDPH (Department of Medical Chemistry, China Pharmaceutical University, China), sodium bicarbonate (Shanghai Shiyi Chemicals Reagent Co., Ltd., China), hydroxypropyl methylcellulose (HPMC) (Methocel K4MP CR, Colorcon, England), carbomer (CP) (Carbopol® 971P NF, BF Goodrich, Brecksville, OH), Magnesium stearate (Ph.Eur. grade) as a lubricant in tableting, and immediate release tablet, 60 mg, as a reference product (Changzhou Third Pharmaceutical Factory, Changzhou, China). All other chemicals used were of reagent grade.

2.2. Formulations

The tablet formulations evaluated consisted of DDPH, sodium bicarbonate, polymer(s), fillers and magnesium stearate. Three different DDPH tablets were formulated to produce different drug release profiles. These formulations contained 15% Carbopol 971P, 7.3% HPMC K4M (formulation A), 25% Carbopol 971P, 5.3% HPMC K4M (formulation B) and 25% Carbopol 971P, 8.3% HPMC K4M (formulation C). Each formulation contained 60 mg of DDPH, 75 mg sodium bicarbonate and 1.5% (w/w) of magnesium stearate. The total weight of the entire tablet was maintained around 300 mg. Matrix tablets were produced by wet granulation (ethanol was used as wetting agent).

2.3. Buoyancy lag time determination

The buoyancy of the tablets was studied at $37 \pm 0.5\,^{\circ}C$, in 100 ml of simulated gastric fluid at pH 1.2 (without pepsine) (US Pharmacopoeia). The time of duration of tablet floatation was observed visually.

2.4. In vitro dissolution test

The in vitro release rates of DDPH from the matrix tablets were determined using the USP XXVI (basket apparatus). The basket rotation speed was kept at 150 rpm, and a temperature of $37 \pm 0.5\,^{\circ}C$ was maintained. Release testing was carried out in 900 ml of different dissolution media: pH 1.2 artificial gastric fluid, pH 6.8 phosphate buffer and distilled water. Five-milliliter samples were withdrawn at 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12 and 24 h. The samples were replaced by its equivalent volume of dissolution medium and were filtered through a 0.8 μm filter and assayed at 278 nm by UV spectrophotometry (UV9200, Ruili Assay Apparatus Co., Beijing, China) (the value of $E^{1\%}_{1\,cm}$ was 80). Six tablets of each formulation were used in the dissolution test. A linear correlation between the absorbency and DDPH concentrations ($r^2 > 0.999$) was obtained over the range of 10–100 μg/ml. High accuracy and precision were also confirmed (average recovery = 100.0 ± 0.28%; CV within run = 0.44–0.50%; CV between day = 0.57–0.77%).

2.5. Mechanism of the in vitro release

The release data were evaluated by the model-dependent (curve fitting) method. In present study, the Korsmeyer–Peppas model describing drug release from polymeric systems was used. The Korsmeyer–Peppas model takes into account that the drug release mechanism often deviates from Fick's law and follows an anomalous behavior described by the following equation (Korsmeyer et al., 1983):

$$\frac{M_t}{M_\infty} = k \cdot t^n \quad (1)$$

where M_t is the drug released at time t, M_∞ the quantity of drug released at infinite time, k the kinetic constant and n is the release exponent. The value of n is related to the geometrical shape of

the delivery systems and determines the release mechanism. For the evaluation of the release data by the described models, the portion of the release curve where $M_t/M_\infty < 0.7$ was used only as described in literature (Higuchi, 1963).

2.6. In vivo study

Male healthy volunteers in a group of six participated the study. The mean age of the volunteers was 22 years (range 20–26 years), mean weight 65 kg (range 62–70 kg), and mean height 168.2 cm (range 164–175 cm). Three open, single dose, randomized crossover trials with at least four weeks intervals were conducted to evaluate concentrations in plasma after administration of three formulations and the reference product. Each subject received a 60 mg dose as one tablet.

Each treatment period in every trial was followed by a one-week wash out period to eliminate the effects of the tested dose before the next treatment. The above studies in humans were designed and carried out according to ethical and regulatory requirements for the pharmacokinetics trial. The study was approved by the Ethics Committee on Clinical Studies at the China Pharmaceutical University, China.

Blood samples were collected over 24 h after each drug administration. Plasma samples were assayed for DDPH concentration using the high performance liquid chromatograph (HPLC) procedure.

2.7. Assay of DDPH concentration in plasma samples

The samples were centrifuged at 3500 rpm and the plasma separated into plain containers and then kept frozen at −20 °C until analysis. The drug was extracted from the plasma using a suitable extraction method.

To 1 ml of plasma, 0.2 ml of 8% sodium hydroxide solution was added in a stoppered test tube. The drug was extracted by 5 ml of ether. The solution was centrifuged at 3000 rpm for 5 min. The organic phase was collected separately and evaporated until dry under nitrogen gas at 40 °C. Then 100 μl mobile phase was added and clonidine hydrochloride was mixed as internal standard. This was vortexed for 1 min and then centrifuged at 18,000 rpm for 10 min, and 20 μl was injected onto HPLC for analysis.

The HPLC analysis was done as follows: a SiO_2 column (200 mm × 4.6 mm, 5 μm, Hypersil, Dalian, China), an injection loop of 20 μl, mobile phase (1% $C_2H_3O_2NH_4$–ethanol, 1:100, v/v), flow rate of 1.0 ml/min, UV detector wavelength of 278 nm, column temperature of 25 ± 1.0 °C. All reagents were of analytical grade. No interfering peaks were detected at the retention time of DDPH (6.4 min).

A linear correlation ($r^2 > 0.9996$) between the ratio of peak area and the DDPH concentration was obtained between the range of 20–2000 ng/ml. The limit of quantification was 10 ng/ml. Precision of the method was evaluated at concentration of 2000, 200 and 20 ng/ml. The coefficient of variation of intra- and inter-day precision was 1.7–2.5% and 2.2–3.2% at all concentrations, respectively.

2.8. Pharmacokinetic analysis

The maximum plasma level (C_{max}) was obtained from the individual plasma concentration–time data. The area of the first moment of the concentration–time curve from time zero to time t (AUC_{0-t}) was determined by the trapezoidal rule. The area from time t to infinity ($AUC_{0-\infty}$) was estimated according to the equation:

$$AUC_{0-\infty} = AUC_{0-t} + \frac{C_t}{k_{el}} \quad (2)$$

where C_t is the plasma concentration observed at time t and k_{el} is the apparent elimination rate constant of DDPH obtained from the slope of the linear portion of the curve by least square regression analysis (Gibaldi and Perrier, 1982). The mean residence time of the drug (MRT) and the relative bioavailability (BV) of the formulations were calculated using the following equations:

$$MRT = \frac{AUMC}{AUC} \quad (3)$$

$$\text{Relative BV (\%)} = \left(\frac{AUC_{(0-t)\text{of test}}}{AUC_{(0-t)\text{of reference}}}\right) \times 100\% \quad (4)$$

where AUMC is the area of the first moment of the concentration–time curves. $AUC_{(0-t)\text{ of test}}$ and $AUC_{(0-t)\text{ of reference}}$ are the areas under the curve after test and reference administration, respectively.

2.9. Statistical evaluation

All results are expressed as mean ± S.D. Differences between two related parameters were considered statistically significant for p-values of or less than 0.05. Analysis of variance (ANOVA) was carried out on the pharmacokinetic parameters. Bioequivalence between the test and reference formulations was assessed by a two one-sided test procedure via 90% confidence intervals from analysis of relative BV values.

3. Results and discussion

3.1. Evaluation buoyancy of the tablets

In this investigation the gastric floating system employed sodium bicarbonate as a gas forming agent dispersed in hydrogel matrix. After reacting with hydrochloride acid sodium bicarbonate creates carbon dioxide whose bubbles were on the surface of the tablets, caused tablets floating in the fluids more than 6 h in vitro (Fig. 2). In general, the gastric emptying time was about 4 h. The extended residence time of drug in stomach could cause increased absorption due to the fact that the duodenum was the main absorption site for DDPH. Moreover, during formation of the floating tablets, the evolving gas permeated through the matrix leaving gas bubbles or pores, which also increased the release rate of the active ingredient from the matrix. In previous work, it was found that the absorption of basic DDPH was

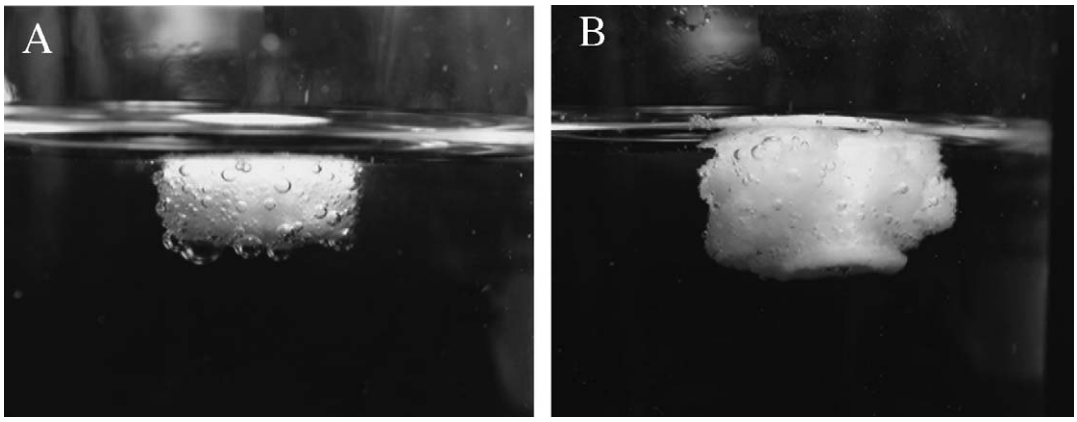

Fig. 2. Photographs of DDPH floating matrix tablet floating in the artificial gastric fluid (A: 0 h and B: after 6 h).

much better than that of its hydrochloric salt (the value of pK_a is 7.47). Therefore, sodium bicarbonate also acted as a pH regulator in the formulation, increased the pH value around the DDPH.

3.2. Mechanism of the in vitro release

The in vitro drug release from the matrices containing hydrophilic polymers at various concentrations was shown in Fig. 3. The coefficients of variation within formulations for dissolution profiles were below 3.4% in each case. The faster release rate was observed from the matrix containing 15% Carbopol 971P NF than the matrix containing 25% Carbopol 971P NF. The Korsmeyer–Peppas model fits all profiles up to 70% ($r^2 > 0.98$). The value of n is 0.45 for a Fickian release, and for an anomalous or non-Fickian release the release is mainly by diffusion with n values >0.45 and <1.0 (Schliecker et al., 2004). The DDPH release from various formulations showed a linear relationship between logarithmic values of the amount of drug release and time. The parameters are listed in Table 1. The mechanism of DDPH release from the hydrophilic matrix system involves polymer swelling/erosion and Fickian diffusion of the drug.

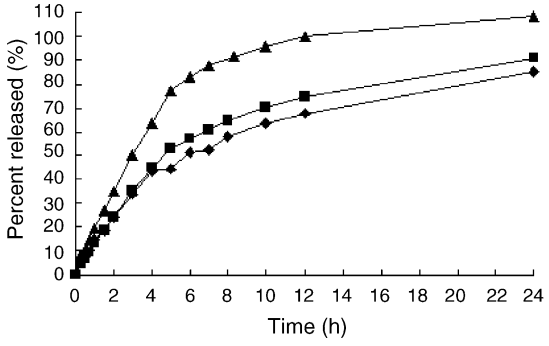

Fig. 3. In vitro mean dissolution profiles of DDPH (60 mg) from controlled release formulations ((▲) formulation A 15% Carbopol 971P, 7.3% HPMC K4M; (■) formulation B 25% Carbopol 971P, 5.3% HPMC K4M; (♦)formulation C 25% Carbopol 971P, 8.3% HPMC K4M; USP I, 150 rpm, pH 1.2 artificial gastric fluid, $n = 6$).

3.3. Effect of pH on drug release

When formulation A was tested at different dissolution media (pH 1.2 artificial gastric fluid, pH 6.8 phosphate buffer and distilled water), it was found that release of DDPH was significantly ($p < 0.01$) faster under acidic condition than neutral pH (Fig. 4). Similar results were obtained in further studies using formulation B and C under different dissolution media as shown in Figs. 5 and 6. Since HPMC is a pH-independent polymer, this phenomenon is attributed to the pH-dependent nature of Carbopol. The carboxyl groups of Carbopol dissociate highly in an neutral or alkaline environment, the electrostatic repulsions between the negatively charged carboxyl groups cause uncoiling and expansion of the molecule, resulting in the complete swelling of the polymer and gel formation (Singla et al., 2000).

Table 1
In vitro release parameters of Korsmeyer–Peppas model and the time of DDPH dissolved 20%, 50%, 80% in artificial gastric fluid for three sustained release formulations

	Release exponent (n)	Mechanism	r^2
A	0.752	Non-Fickian	0.980
B	0.837	Non-Fickian	0.994
C	0.702	Non-Fickian	0.980

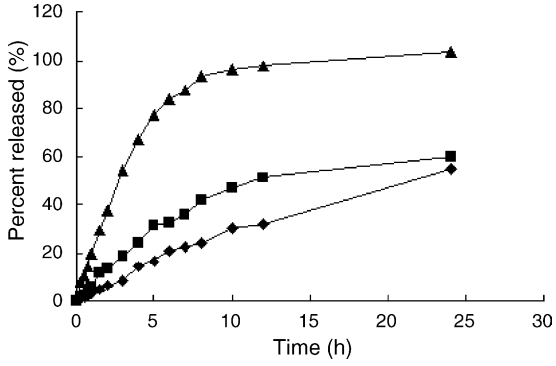

Fig. 4. Effect of pH on in vitro dissolution profiles of formulation A with 15% Carbopol 971P and 7.3% HPMC K4M ((▲) pH 1.2; (■) pH 6.8; (♦) water, USP I, 150 rpm, $n = 6$).

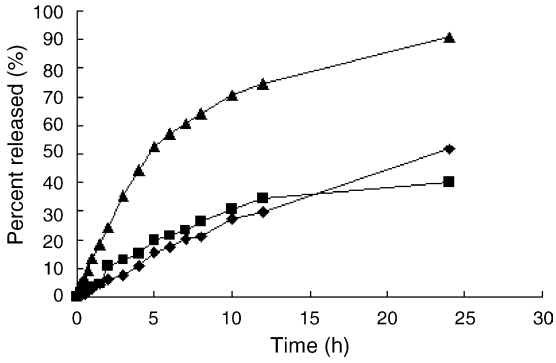

Fig. 5. Effect of pH on in vitro dissolution profiles of formulation B with 25% Carbopol 971P and 5.3% HPMC K4M ((▲) pH 1.2; (■) pH 6.8; (♦) water, USP I, 150 rpm, $n = 6$).

As the release rates for this system were influenced by pH, the Carbopol content would be important. As seen in recent literature, Carbopol has been used as the principal excipient to achieve adhesion to the oral mucous membrane and to control the drug release from the tablet (Owens et al., 2005). In previous work, it was found that DDPH was well absorbed from wide regions of the GI tract including colon. In view of this absorption characteristic, formulation containing more Carbopol may have an increased bioavailability, which was later confirmed by the in vivo study.

3.4. In vivo study

3.4.1. Bioavailability

The plasma DDPH levels after a 60 mg single dose of formulation A–C were shown in Figs. 7–9. In this study in human subjects, prolonged drug absorption was achieved with all formulations (Table 2). The average peak concentration of sustained release formulation was significantly lower than that of reference (0.544 ± 0.240 μg/ml, 0.294 ± 0.148 μg/ml and 0.716 ± 0.472 μg/ml for test formulations versus 0.970 ± 0.335 μg/ml, 0.759 ± 0.242 μg/ml and 1.062 ± 0.233 μg/ml for references, respectively), and the MRT values were significantly longer in test formulations (4.85 ± 1.62 h, 6.08 ± 1.44 h and 8.12 ± 1.19 h versus 3.91 ± 1.66 h, 2.74 ± 1.35 h and 4.01 ± 1.24 h, respectively).

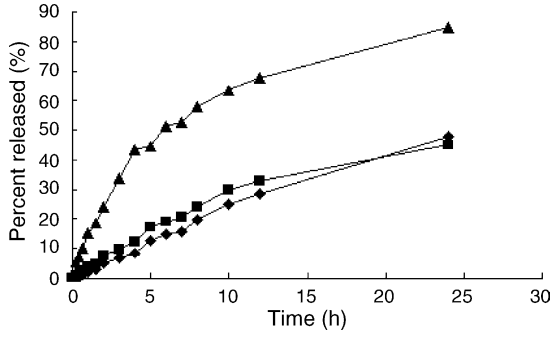

Fig. 6. Effect of pH on in vitro dissolution profiles of formulation C with 25% Carbopol 971P and 8.3% HPMC K4M ((▲) pH 1.2; (■) pH 6.8; (♦) water, USP I, 150 rpm, $n = 6$).

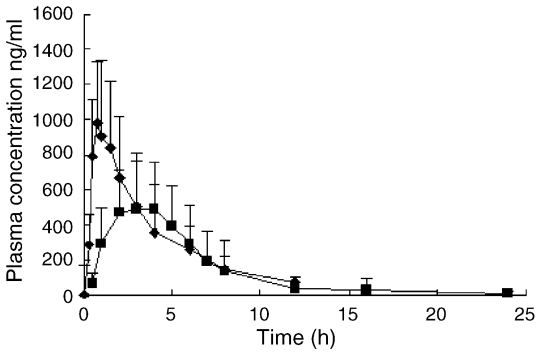

Fig. 7. DDPH plasma concentrations after per oral administration of sustained release formulation (60 mg) ((■) formulation A; (♦) reference, $n = 6$).

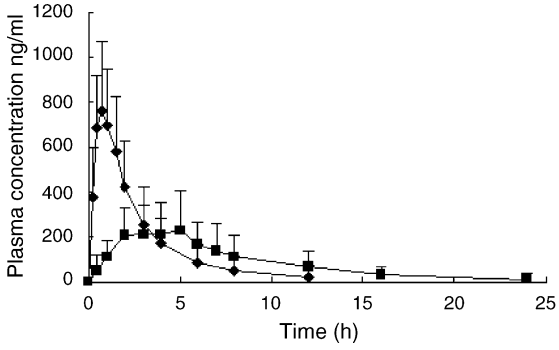

Fig. 8. DDPH plasma concentrations after per oral administration of sustained release formulation (60 mg) ((■) formulation B; (♦) reference, $n = 6$).

The reverse rank order exists between in vitro and in vivo parameters, and T_{max} and MRT increased as in vitro dissolution drug release rate decreased, which confirms that the polymer content is able to modify drug release from tablets in humans.

In our group's previous works, after oral administration DDPH 8, 16, 32 mg/kg in dogs, the C_{max} was 1.37, 2.54, 3.38 μg/ml, respectively and the absolute bioavailability was 0.49. In order to estimate the amount of drug absorbed from the tested formulations, the relative bioavailability was calculated from the AUC of reference and tested formulation. Based on *t*-based 90% confidence interval, the relative bioavailability of formulation C was bioequivalent to the reference formulation with an acceptable range of 98.1–123%. The results indicated

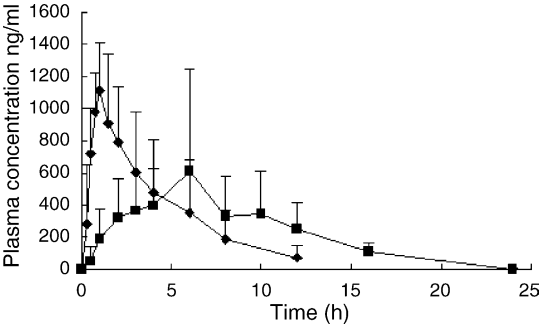

Fig. 9. DDPH plasma concentrations after per oral administration of sustained release formulation (60 mg) ((■) formulation C; (♦) reference, $n = 6$).

Table 2
Pharmacokinetic parameters ($n = 6$) each value represents the mean ± S.D.

Trial no.	C_{max} (μg/ml)	T_{max} (h)	MRT(h)	$AUC_{0\text{-inf}}$ (μg h/ml)	Relative BV
1					
Reference	0.970 ± 0.335	0.66 ± 0.28	3.91 ± 1.66	4.24 ± 2.89	0.81 ± 0.19
Formulation A	0.544 ± 0.240**	3.33 ± 1.21**	4.85 ± 1.62	3.27 ± 2.39	
2					
Reference	0.759 ± 0.242	0.60 ± 0.18	2.74 ± 1.35	2.30 ± 1.36	1.08 ± 0.62
Formulation B	0.294 ± 0.148**	4.09 ± 1.11**	6.08 ± 1.44**	2.07 ± 1.17	
3					
Reference	1.062 ± 0.233	0.88 ± 0.44	4.01 ± 1.24	5.00 ± 2.84	1.11 ± 0.19
Formulation C	0.716 ± 0.472*	6.00 ± 2.19**	8.12 ± 1.19**	5.46 ± 2.99	

* $p < 0.05$, compared with the reference.
** $p < 0.01$, compared with the reference.

that all formulations could increase the bioavailability of DDPH in humans effectively (Table 2). In addition, it was found that DDPH was absorbed in vivo completely from formulations B and C, but the statistical bioequivalency was not achieved for formulation B due to the large inter-subject variability.

The increased bioavailability was attributed to the polymer Carbopol. Carbopol was observed to increase the pharmacological availability of drug by protecting from being attacked by the luminal enzymes (Lueßen et al., 1997). The inhibition of mucolysis in the pig colon (Hutton et al., 1990) and inhibition of enzymes activity from the pig stomach by Carbopol have been reported (Foster et al., 1994). In previous work, DDPH is well absorbed from wide regions of the gastrointestinal tract, especially, the drug is well absorbed in the lower part of the small intestine including colon due to the pK_a value of drug. Therefore, the bioavailability of drug from oral controlled release system is influenced by the GI residence time of the system. Enhancing the content of polymer in sustained release systems might result in more improved drug bioavailability. In addition, the vitro release profiles showed that less drug in formulation A was reserved to enter the lower tract than formulation B and C due to the faster release rate of drug. This could explain, in part, the higher bioavailability for formulation B and C compared to that for formulation A.

3.4.2. *In vivo–in vitro correlation*

Exploring a relationship between in vivo absorption and in vitro drug release from a controlled release dosage form is an important part of the dosage form development process. The in vivo absorption profiles of the drug for the sustained release formulations were calculated according to the method of Wagner and Nelson using the systemic elimination rate determined from plasma concentration profiled of the reference tablet (Wagner and Nelson, 1964). The calculated in vivo absorption sustained for more than 8 h, which consist with the actual gastrointestinal transit time including colon (Davis et al., 1986).

The absorption profiles versus percent released in vitro at the same time point were shown in Figs. 10 and 11. A non-linear correlation could be achieved for formulation A indicating the dissolution test is not biorelevant for formulation A. A polynomial regression seems to be able to explain the relationship between dissolution and absorption for formulation A:

$$Y = -0.0208X^2 + 3.124X - 6.7356 \ (r^2 = 0.9786)$$

where Y is fraction absorbed in vivo and X represents fraction released in vitro.

A good correlation between in vivo and in vitro drug release was obtained in the formulation B and C (Fig. 8; Table 3). Slopes greater than 1 suggested in vivo drug release was much faster than that from in vitro dissolution tests due to the peristalsis of the GI tract (Shameem et al., 1995). Negative intercept value for formulation C may be attributed to lag time in drug absorption

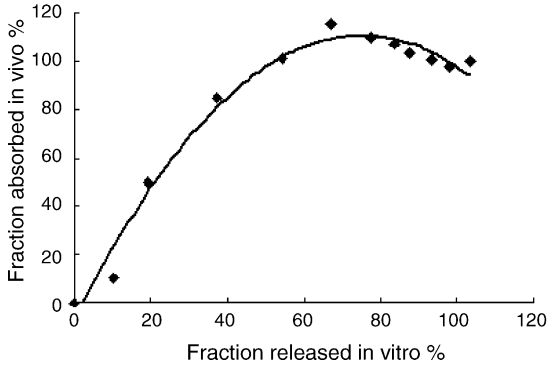

Fig. 10. Relationships between the percent released the percent absorbed for sustained release formulation A in humans.

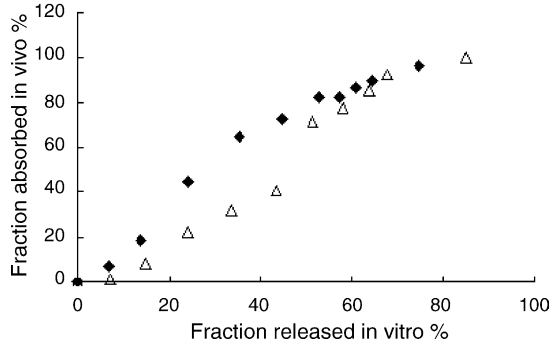

Fig. 11. Relationships between the percent released the percent absorbed for sustained release formulation B and C in humans ((♦) formulation B; (△) formulation C).

Table 3
Results of linear regression between fraction released in vitro vs. fraction absorbed in vivo for formulation B and C

Formulation	Slope	Intercept	r^2
B	1.372	4.549	0.9621
C	1.379	−7.975	0.9632

due to the slowest drug release from the matrix. Although the slopes obtained were similar, the relationships were clearly formulation dependent, therefore, in vitro release test conditions would need to be altered to develop a single in vitro–in vivo correlation.

4. Conclusion

This was the first time when DDPH, a novel antihypertensive, was prepared as an oral sustained release dosage form based on gastric floating matrix tablets. The release of DDPH from three different formulations was determined in different media. A non-Fickian diffusion was confirmed as the drug release mechanism from these tablets. This meant that water diffusion and the polymer rearrangement have essential roles in the drug release. In order to prolong the gastric residence time, a gas forming agent was used to keep the tablets floating over simulated gastric fluid for more than 6 h. The in vivo experiments showed that keeping the amount of Carbopol 971P NF at a higher concentration (formulation B and C) effectively increased the relative bioavailaility of drug. In addition, a good correlation between in vivo and in vitro drug release was obtained in the formulation B and C. The statistical bioequivalency was achieved for the relative bioavailability of formulation C with an acceptable range of 98–123%. In conclusion, the gastric floating matrix tablets prepared from mixtures of Carbopol 971P and HPMC K4M proved to be useful devices for DDPH oral delivery systems.

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References

Davis, S.S., Hardry, J.G., Fera, J.W., 1986. Alimentary tract and pancreas: transit of pharmaceutical dosage forms through the small intestine. Gut 27, 886–892.

Fix, J.A., Cargill, R., Engle, K., 1993. Controlled gastric emptying: Part 3. Gastric residence time of a nondisintegrating geometric shape in human volunteers. Pharm. Res. 10, 1087–1089.

Foster, S.N.E., Pearson, J.P., Hutton, D.A., Allen, A., Dettmar, W., 1994. Interaction of polyacrylate with porcine pepsin and the gastric mucous barrier: a mechanism for mucosal protection. Clin. Sci. 87, 719–726.

Gibaldi, M., Perrier, D., 1982. Noncompartmental analysis based on statistical moment theory. In: Dekker, M. (Ed.), Pharmacokinetics. Marcel Dekker Inc., New York, pp. 409–417.

Higuchi, T., 1963. Mechanism of sustained-action medication. The oretical analysis of rate of release of solid drugs dispersed in solid matrices. J. Pharm. Sci. 52, 1145–1149.

Hutton, D.A., Pearson, J.P., Allen, A., Foster, S.N.E., 1990. Mucolytic activity of the colonic mucus barrier by fecal proteinases: inhibition by interacting poly(acrylate). Clin. Sci. 78, 265–271.

Joseph, N.J., Lakshmi, S., Jayakrishnan, A., 2002. A floating-type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. J. Control. Release 79, 71–79.

Korsmeyer, R.W., Gurny, R., Doelker, E.M., Buri, P., Peppas, N.A., 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25–35.

Lee, J.H., Park, T.G., Choi, H.K., 1999. Development of oral drug delivery system using floating microspheres. J. Microencapsul. 16, 715–729.

Li, S., Lin, S., Daggy, B.P., Mirchandani, H.L., Chien, Y.W., 2003. Effect of HPMC and Carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int. J. Pharm. 253, 13–22.

Lueßen, H.L., Bohner, V., Pérard, D., Langguth, P., Verhoef, J., de Boer, A.G., Merkle, H.P., 1997. Protection of peptide drugs from intestinal brush border membrane vesicle degradation by poly(acrylates). J. Control. Release 46, 187.

Ni, P., Sun, H., Pen, J., 1996. Resolution of (±)DDPH and α_1-adrenoceptor antagonizing activities of both (±) and (−) DDPH. J. China Pharm. Univ. 27, 462–465.

Owens, T.S., Dansereau, R.J., Sakr, Adel, 2005. Development and evaluation of extended release bioadhesive sodium fluoride tablets. Int. J. Pharm. 288, 109–122.

Samani, S.M., Montaseri, H., Kazemi, A., 2003. The effect of polymer blends on release profiles of diclofenac sodium from matrices. Eur. J. Pharm. Bio. 55, 351–355.

Sato, Y., Kawashima, Y., Takeuchi, H., Yamamoto, H., 2004. In vitro and in vivo evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. Int. J. Pharm. 275, 97–107.

Schliecker, G., Schmidt, C., Fuchs, S., 2004. In vitro in vivo correlation of buserelin release from biodegradable implants using statistical moment analysis. J. Control. Release 94, 25–37.

Shameem, M., Katri, N., Aoyagi, N., Kojima, S., 1995. Performance of oral solid controlled release dosage forms in human: role of GI-mechanical destructive forces and colonic release in fasted and fed drug absorption. Pharm. Res. 12, 1049–1054.

Singla, A.K., Chawla, M., Singh, A., 2000. Potential applications of carbomer in oral mucoadhesive controlled drug delivery system: a review. Drug Dev. Ind. Pharm. 26, 913–924.

Tamburic, S., Craig, D.Q.M., 1996. The effects of aging on the rheological, dielectric and mucoadhesive properties of poly(acrylic acid) gel systems. Pharm. Res. 13, 279–283.

Thanoo, B.C., Sunny, M.C., Jayakrishnan, A., 1993. Oral sustained-release drug delivery systems using polycarbonate microspheres capable of floating on the gastric fluid. J. Pharm. Pharmacol. 45, 21–24.

Wagner, J.G., Nelson, E., 1964. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single dose of drug. J. Pharm. Sci. 53, 1392–1403.

Wang, J., Tabata, Y., Bi, D., Morimoto, K., 2001. Evaluation of gastric mucoadhesive properties of aminated gelatin microspheres. J. Control. Release 73, 223–231.

Zheng, H., Qian, J.-Q., Shao, C.-L., Xia, L., Ni, P.-Z., 2001. Effect of 1-(2,6-dimethylphenoxy)-2-(3,4s-dimethoxyphenylethylamino) propanehydrochloride on cystometry and benign prostatic hyperplasia in rats. Chin. J. Pharmacol. Toxicol. 15, 150–154.