Thai Journal of Pharmaceutical Sciences (TJPS)

5th International Conference on Pharmaceuticals,
Nutraceuticals and Cosmetic Science (IPNaCS 2017)

Development and Evaluation of floating *In situ* gel for oral delivery of propranolol HCl

Worrawee Siripruekpong[1], Nattha Kerdsakundee[1,2], Thanapon Parinyakub[1], Ruedeekorn Wiwattanapatapee [1,2*]

[1] *Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand*
[2] *Phytomedicine and Pharmaceutical Biotechnology Excellence Research Center, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla 90112, Thailand*

* Corresponding author: Tel. +66 74 288915; fax: +66 74 428148; E-mail address: ruedeekorn.w@psu.ac.th

Keywords: *In situ* gel, propranolol HCl, alginate, pectin, gellan gum

Introduction

Propranolol HCl, a non-selective β - adrenergic receptor blocking agent, has been widely used for treatment of hypertension, angina pectoris, arrhythmia, and migraine prevention. It shows good stability and well dissolves in acidic environment of stomach. Even though propranolol is completely absorbed in gastrointestinal tract, the oral bioavailability is very low because of its short half-life and high first pass metabolism. Thus, the gastro-retentive dosage form is selected to improve oral bioavailability of propranolol.[1]

The floating *in situ* gel forming systems are one of the most interesting systems in oral drug delivery. They have been designed to prolong the gastric residence time and control the rate of drug release which can improve oral bioavailability and reduce frequency of dosing. When the system contacts with the gastric fluid, a gel is formed and floats on the surface of the stomach content. The drug then has a sustained release from the gel in the stomach.[2] The floating *in situ* gels have been shown to improve the efficacy and oral bioavailability of many compounds for example, they have superior efficacy in the treatment of chronic gastric ulcer by curcumin[3] and increase oral bioavailability of mebeverine HCl.[4] The main components of such systems are the gelling agents that form a gel in the acidic environment and an agent to generate gas that makes the system float. The incorporated drugs in this *in situ* gel forming system should be acid stable.[2] Herein, the *in situ* gel forming systems incorporating propranolol HCl were developed using different type of polymer base (alginate, pectin and gellan gum). The obtained formulations were evaluated for their viscosity, gelation capacity, floating abilities and *in vitro* drug release.

Methods

Preparation of the floating in situ gel incorporating propranolol HCl

The compositions of the floating *in situ* gel using sodium alginate, pectin and gellan gum as the main gelling polymer are shown in Table 1. Either sodium alginate, pectin or gellan gum was dissolved in 40 mL of purified water containing 0.5% (w/v) sodium citrate at temperature 40-50ºC. The Carbopol 934, PEG 4000 or HPMC K4M (the additional polymer) was dissolved in 40 mL of purified water separately and then added into the main gelling polymer solution. Then calcium carbonate was added and continued stirring until thoroughly dispersed. Finally, propranolol HCl dissolved in 20 mL of purified water was added in the *in situ* gel systems. The volume was adjusted to a final volume of 100 mL with purified water. The obtained formulations were stored in ample bottles, protected from light until used.

Physical appearances and pH measurements

The physical appearance of the obtained formulation were observed and pH of each formulation was measured using pH meter (Ultra BASIC®, Becthai Bangkok Equipment & Chemical Co., Ltd., Bangkok, Thailand).

.

Table 1 Composition of floating *in situ* gel incorporating propranolol HCl

Ingredient	%w/v												
	A1	A2	A3	A4	A5	A6	A7	A8	A9	P1	P2	P3	P4
Sodium alginate	0.5	1	1.5	2	2	2	2	2	2	-	-	-	-
Pectin	-	-	-	-	-	-	-	-	-	0.5	1	1.5	2
Gellan gum	-	-	-	-	-	-	-	-	-	-	-	-	-
Carbopol 934	-	-	-	-	1	-	-	-	-	-	-	-	-
PEG 4000	-	-	-	-	-	1	-	-	-	-	-	-	-
HPMC K4M	-	-	-	-	-	-	1	2	3	-	-	-	-
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium carbonate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Propranolol HCl	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Water q.s. to	100	100	100	100	100	100	100	100	100	100	100	100	100
Floating lag time (min)	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Duration of Floating (h)	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24
pH	8.08	8.13	8.18	8.0	5.58	8.01	8.25	8.34	8.36	7.97	7.99	8.00	8.15

Ingredient	%w/v													
	P5	P6	P7	P8	P9	G1	G2	G3	G4	G5	G6	G7	G8	G9
Sodium alginate	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pectin	2	2	2	2	2	-	-	-	-	-	-	-	-	-
Gellan gum	-	-	-	-	-	0.0625	0.125	0.25	0.5	0.25	0.25	0.25	0.25	0.25
Carbopol 934	1	-	-	-	-	-	-	-	-	1	-	-	-	-
PEG 4000	-	1	-	-	-	-	-	-	-	-	1	-	-	-
HPMC K4M	-	-	1	2	3	-	-	-	-	-	-	1	2	3
Sodium citrate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Calcium carbonate	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Propranolol HCl	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Water q.s. to	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Floating lag time (min)	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1
Duration of Floating	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24	>24
pH	5.67	8.01	8.18	8.20	8.24	8.0	8.04	8.06	8.20	6.52	7.95	8.13	8.25	8.39

Viscosity measurements

Viscosity of *in situ* gel formulations was measured using a Brookfield Viscometer with spindle 64 at temperature of 25±1 °C. The viscosity measurement of each formulation was taking approximately 30 s and was done in triplicate.

In vitro floating studies

Two hundred mL of the medium (0.1 N hydrochloric acid; pH 1.2) was introduced into 250 mL beaker and the temperature was maintained at 37ºC. 10 mL of liquid preparation was added into a medium. The time that the formulation took to emerge on the medium (floating lag time) and the time that the formulation consistently floated on the medium surface (floating duration) were then measured.[5] The optimized floating lag time and duration of floating should be less than 1 min and more than 4 h, respectively.

In vitro drug release studies

The drug release studies were employed using USP 30 rotating paddle apparatus at 37± 0.5 ºC and a rotating speed of 50 rpm. 900 mL of 0.1N hydrochloric acid (pH 1.2) was the dissolution medium. 10 mL of the floating *in situ* gel was added into the dissolution medium. Samples (10 mL) were withdrawn and replaced with fresh medium after 30, 60, 120, 180, 240, 300, 360, 420 and 480 min. The amount of propranolol in the withdrawn samples was measured by a UV spectrophotometer at a wavelength of 289 nm. Each formulation was tested in triplicate. The data was reported as a mean value ± S.D. A plot of the cumulative % release of the propranolol against time was constructed to illustrate the drug release profiles.

Results

Physical appearances and pH measurements

The obtained floating *in situ* gelling formulations were yellowish white viscous liquid which become a gel after contacting the acidic gastric fluid. Moreover, the floating gel maintained on the surface of the acidic medium for a prolonged period and provided a sustained drug release into the stomach content. The pH of most formulations were more than 7 as shown in Table 1.

Viscosity measurements

The viscosity of raft forming systems was important for oral administration of the formulations. The formulations should not be too viscous to pour from the package. The viscosity of developed *in situ* gel incorporating propranolol HCl is shown in figure 1. The viscosity of the formulations obviously increased with the increments in the concentrations of the main gelling polymer and additional polymer.

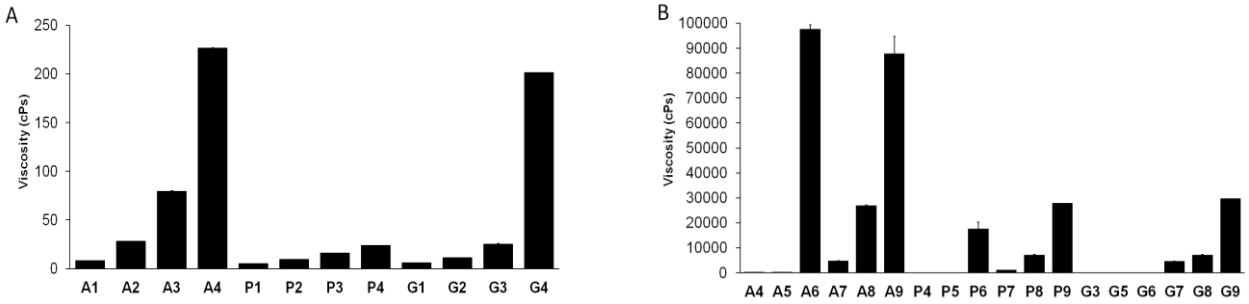

Figure 1. The viscosity of floating *in situ* gel formulation at 20 rpm A) Effect of main gelling polymer concentration B) Effect of additional polymer

In vitro floating studies

The floating lag times and the duration of floating are demonstrated in table 1. All the formulations floated on the medium within 1 minute and maintained floating for up to 24 h.

In vitro drug release studies

The drug release profiles of the floating *in situ* gelling systems are shown in Figure 2. The total drug release was between 60-90 % in an 8 h period. The results show that an increase of the main gelling polymer obviously reduced the release rate of propranolol. The additional polymer also showed a significant effect on the release profile when compared to the formulations with main gelling polymer alone. HPMC K4M provides more sustained release pattern and higher drug release compared to the others.

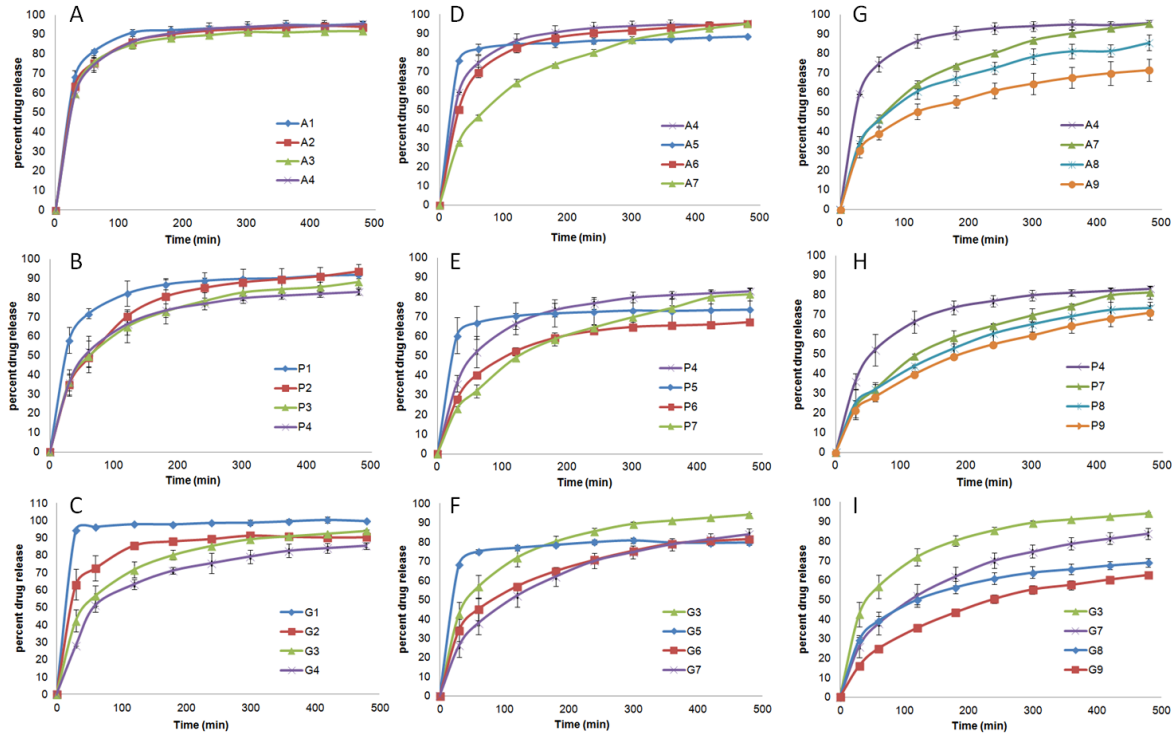

Figure 2. . Effect of main gelling polymer concentration (A-C), effect of additional polymer (D-F) and effect of HPMC K4M concentration (G-I) to *in vitro* drug release from floating in situ gel incorporating propranolol HCl in 0.1N HCl (pH 1.2). Bars represent mean±S.D. (n = 3)

Discussion

The developed floating *in situ* gel formulation was composed mainly of the main gelling polymer (sodium alginate, pectin or gellan gum) and calcium carbonate for generating calcium ions and the carbon dioxide bubble. The additional polymer was added to obtain the sustained drug release pattern of the developed formulations. After contacting acidic medium, calcium carbonate dissolved and generated calcium ion; interacting with main gelling polymer to form gel; and carbon dioxide; entrapped in gel and kept the low density of the systems. All formulations immediately transformed to gel and floated on the surface of acidic medium within 1 min and maintain floating more than 8 h. The higher concentration of main gelling polymer produced a more dense matrix and the drug took a longer time to diffuse into the medium resulting in a slower drug release rate which was similar to results obtained in a previous study.[6] The additional polymer affected the drug release by retarding the drug released from floating gel because of its swelling and an increase in the gel thickness that acted as a barrier for drug release. From the drug release study, HPMC K4M was the best additional polymer because it provided the sustained release pattern with higher amount of drug released compared to Carbopol 934 and PEG 4000. The increase of concentration of HPMC K4M decreased the drug release because it increase gel thickness which the drug slowly diffuse from the gel similar to previous study.[7]

The formulations composed of 2% alginate with 1% HPMC K4M (A7), 2% pectin with 1% HPMC K4M (P7) and 0.25% gellan gum without additional polymer (G3) were selected as the suitable formulations because they showed a sustained release pattern of propranolol with a highest percent drug release (80-90%) over an 8 h period. Moreover, they could be easily pour out of the container.

Conclusion

Three different types of main gelling polymer can be used to prepare floating *in situ* gels to deliver drug via oral route. The HPMC K4M was used as the additional polymer to provide a sustained drug release pattern of formulations. The selected formulations (A7, P7 and G3) rapidly formed gels and floated in the acidic medium with a sustained release pattern of propranolol over an 8 h period. The floating *in situ* gel systems may provide a useful dosage form for improvement of oral bioavailability of propranolol HCl.

Acknowledgements

This study was supported by Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand. The authors would like to thank Miss Kanokkarn Chaikarn, Prince of Songkla University for her assistance with statistic analysis.

References

1. Meka VS, Dharmanlingam SR, Kolapalli VRM. Formulation of gastroretentive floating drug delivery system using hydrophilic polymers and its in vitro characterization. Brazilian Journal of Pharmaceutical Sciences. 2014;50:431-439
2. Prajapati VD, Jani GK, Khutliwala TA, Zala BS. An upcoming approach of gastroretentive drug delivery system. Journal of Controlled Release. 2013;168(2):151-165.
3. Kerdsakundee N, Mahattanadul S, Wiwattanapatapee R. Development and evaluation of gastroretentive raft forming systems incorporating curcumin-Eudragit® EPO solid dispersions for gastric ulcer treatment. European Journal of Pharmaceutics and Biopharmaceutics. 2015;94:513-520
4. El Nabarawi MA, Teaima MA, Abd El-Monem RA, El Nabarawy NA, Gaber GA. Formulation, release characteristics, and bioavailability study of gastroretentive floating matrix tablet and floating raft system of Mebeverine HCl. Drug Design, Development and Therapy. 2017;11:1081-1093.
5. Hampson FC, Farndale A, Strugala V, Sykes J, Jolliffe IG, Dettmar PW. Alginate rafts and their characterisation. International Journal of Pharmaceutics. 2005;294:137-147.
6. Rajinikanth PS, Balasubramaniam J, Mishra B. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. International Journal of Pharmaceutics. 2007;335:114-122.
7. Kerdsakundee N, Wiwattanapatapee R, Mahattanadul S. Floating gellan gum-based in situ gels containing curcumin for specific delivery to the stomach. Thai Journal of Pharmaceutical Sciences. 2016;40(special issue):33-36.