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Optimization of innovative floating gastro retentive dosage form and evaluation of their residence time

Sarojini Sarangapani[1*], Sowmya Priyadarsini[2], Manavalan Rajappan[3], Jayanthi Bangaru [3]
1. PRIST College of Pharmacy, PRIST University, Abishekapakkam, Puducherry-605007, India,
2. SRM College of Pharmacy, SRM University, Chennai, India,
3. Institute of Pharmaceutical technology, Annamalai University Chidambaram,Tamilnadu, India

ABSTRACT

The present work investigates the formulation and optimization of floating tablets of Domperidone. Formulations were optimized for gas generating agent content, different viscosity grades of HPMC and its concentration. Study revealed that percentage of $NaHCO_3$ and different grades of HPMC had a major influence on release of drug from hydrophilic matrix tablets and floating properties. Eleven trial batches were undertaken in order to optimize and find out the most suitable formulation and evaluated for various parameters like weight variation, hardness, thickness, friability, floating lag time, total floating time, swelling index, dissolution profile and stability study. The formulation F_{11} containing 20 mg/ tab. HPMC ($K_{100}M$) was optimized as the best formulation. Optimized formulations were studied for effect of hardness on floating properties and as well as accelerated short term stability study. Hardness of tablets had greater impact on floating lag time which might be due to decreased porosity. Dissolution profiles were subjected to various kinetic drug release equations and found that drug release from hydrophilic matrixes occurred via anomalous transport mechanism (i.e.) follows both diffusion and erosion mechanism. Hence it is evident from this investigation that gas powered matrix tablet could be promising delivery system for Domperidone with sustained release action and improved drug availability.

Keywords: Domperidone. Sustained release. Hydroxyl propyl methyl cellulose. Direct compression. Floating lag time.

*Corresponding Author Email: tsr_m.pharm@yahoo.co.in
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INTRODUCTION:

Gastric residence time (GRT) is one of the important factors affecting the drug bioavailability of pharmaceutical dosage form. Variable and short gastric emptying time can result in incomplete drug release from drug delivery system above the absorption time (stomach or upper part of small intestine) leading to a diminished efficacy of the administered dose.[14]

Prolonged GRT and controlled release of drugs within the gastro intestinal tract helps to reduce dosing frequency and total dose improves patient compliance and convenience, maintains a less fluctuating plasma level as well as reduce gastric intestinal side effects.[3,19] Prolonging the GRT of therapeutic agents thought to be beneficial especially under several circumstances such as for drugs acting locally in stomach, primarily absorbed in stomach, poorly soluble in alkaline $P^{H,}$ narrow window of absorption, absorbed rapidly from GIT, degrade in the colon.[9]

Methods for prolonging gastric retention of drug disease have been attempted based on mechanism such as buoyancy, expansion high density agent or adhesion to mucosa. The domperidone floating tablets are formulated by incorporating a gas generating agent like sodium bicarbonate using direct compression technique. This is based on the mechanism that when the dosage forms comes in contact with gastric fluid CO_2 is generated which remains entrapped in hydrocolloid of the polymer thereby providing buoyancy to the dosage form to float.[11]

Domperidone is a synthetic benzimidazole compound that act as a domain D_2 receptor antagonist. Domperidone is also used as prokinetic agent for the treatment of upper gastro intestinal motility disorders. After oral administration domperidone is rapidly absorbed from stomach and upper part of GIT with fewer side effects. It is a weakly base with good solubility in acidic P^H but reduced solubility in alkaline medium such as weak base, formulated as oral controlled release dosage form is exposed to environments of increasing P^H with subsequent precipitation of poorly soluble free base within the formulation that is no longer capable of being released from formulation. Hence the present study lays emphasis on formulating it as gastro retentive dosage form. [1, 17, 21]

MATERIALS AND METHODS

Domperidone is obtained as a gift samples from vasudha pharmchem Ltd., Mumbai. HPMC from Dow Chemicals Ltd., USA, MCC from colorcon Asia pvt. Ltd., Mumbai. Sodium bicarbonate and Magnesium Stearate from S.D.fine chemicals Ltd., Mumbai. All other ingredients were of analytical grades and were used as procured.

Formulation of Domperidone floating tablet

Effervescent floating tablets of domperidone was prepared by using direct compression techniques owing to the fact that both drugs as well as excipients have flow property and compressibility index and dose of drug is also low. The drug sieved through 30 mesh sieve and excipients like Microcrystalline cellulose, Sodium bicarbonate and HPMC are screened through 70 mesh sieve and are dry mixed for 20 minutes. Magnesium stearate is sieved through 60 mesh sieve and mixed with dry mix for 5 minutes. The lubricated blend is compressed into tablet having average weight of 100mg using 6mm sc flat punch on cadmach 8 stations GMI. The composition of formulation is given in Table 1.

TABLE 1 - Formulation of domperidone effervescent floating tablets

Ingredients	Quantity in mg										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Domperidone	10	10	10	10	10	10	10	10	10	10	10
HPMC K_4 M	-	-	-	-	-	10	15	20	-	-	-
HPMC K_{15}M	20	20	20	10	15	-	-	-	-	-	-
HPMC K_{100}M	-	-	-	-	-	-	-	-	10	15	20
Sodium Bicarbonate	5	10	15	10	10	10	10	10	10	10	10
MCC (avicel P^H 102)	64	69	54	69	64	69	59	69	64	59	
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1	1

Evaluation of Tablets

Invitro Buoyancy study

The floating capacity of tablets was determined using USP (type II) dissolution apparatus containing 900ml of 0.1N Hcl. The time taken by the tablet to reach the top from bottom of flask determines floating lag time and time for which the tablet constantly floats on the surface of the medium determines the total floating time.[4]

Swelling index

Swelling of hydrophilic polymer such as PEO greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually also influence the release slowing action and the residence time. For each formulation, one tablet was weighed and placed in a beaker containing 200ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 8 hours. The percentage weight gain by the tablet was calculated by the formula[16]

Swelling index (S.I) = {(Wt-Wo)/WO} x 100

Where,

S.I. =swelling index

Wt=Weight of tablet at time

W_O= Weight of tablet before immersion.

Drug content

Ten tablets were weighed and powdered. Powdered equivalent to average weight of tablets was accurately weighed and transferred to volumetric flask and dissolved in methanol and volume made up mark by 0.1 N Hcl (P^H 1-2). The samples were filtered and analyzed by UV spectrometer at 287 nm after suitable dilution.[6]

Content uniformity

Content uniformity of dosage form is done as the dosage of drug is very low by using the same method as described in drug content.[12]

RESULTS AND DISCUSSION

The results for angle of repose and compressibility index ranged from 34.2 º to 39.2 º and 18.64º t0 22.80º respectively. An angle of repose of less than 30º indicates good flow properties. This was further supported by the lower compressibility index. Granules with Carr's index values around 18% and below are considered to have fair to excellent flow properties.

Domperidone tablets provided good weight uniformity according to ±7.5% variation referring to tablets with 100mg. All the tablets were within USP limits for friability (not greater than 1% weight loss). The tablets were compressed at three hardness levels that are high, low and optimum in order to optimize the best hardness level for the tablet as tablet hardness had an impact on the floating lag time of floating matrix tablet as shown in Table 2. This hardness of tablets was essential to achieve optimum invitro buoyancy.[2]

TABLE 2 - Properties of compressed domperidone tablets

Formulation	Hardness (Newton) ±SD n=3	Thickness (mm) ±SD n=5	Floating lag time in seconds			Floating Time in Hours	Drug Content (%)
			Low Hardness	Optimum Hardness	High Hardness		
F_1	62	2.85	-	-	-	-	98.30
F_2	59	2.86	2	30	40	22	98.46
F_3	58	2.80	2	15	20	-	99.23
F_4	57	2.88	3	32	37	20	98.05
F_5	58	2.82	2	15	52	22	99.16
F_6	65	2.92	2	10	59	16	99.60
F_7	63	2.94	2	33	32	18	99.50
F_8	62	2.88	1	25	41	19	99.00
F_9	59	2.90	1	27	36	23	97.80
F_{10}	60	2.88	2	21	30	24	99.25
F_{11}	59	2.83	1	30	37	24	99.58

To optimize the content of sodium bicarbonate for the trials F_1, F_2 and F_3 were taken by varying the $NaHCO_3$ content (5mg, 10mg and 15mg/tab.) Trial F_3 and F_4 had a floating lag time 30-40 sec. and 14-38 sec. Even through trial F_3 had a lag time less than F_2, it evolved a lot of

effervescence which ultimately resulted in porosity of tablet. The dissolution media could penetrate thorough the pores in the tablet bed leading to faster drug release. Further F_2 (10mg/tab.) was optimized for further trials.

Cellulose polymers showed to be efficient to control the domperidone release from the tablets. Further trials F_4- F_{11} were taken by varying the concentration of polymers amount and viscosity grades in order to optimize and find out the best formulation based on its invitro release pattern, floating lag time and total floating time. As polymers percentage and viscosity increased in tablet formulations the amount of drug delivered decreased in dissolution test as shown in Figure 1.

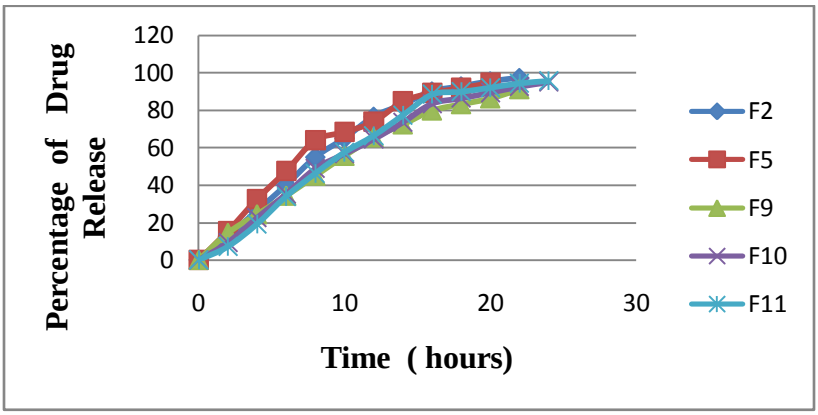

FIGURE 1 - *In-vitro* drug release of Domperidone floating tablets of trials F2, F5, F9, F10 and F11.

From the study of floating properties, (Table II) it was observed that the floating lag time ranges from 15 to 60 seconds and tablets of each trial except trial F_{10} and F_{11} had a total floating time of 24 hours. In later case it was observed that the tablet dissolved in 18 to 20 hours only which might be due to low viscosity of polymers. This finding was in good agreement by studying of Li and co-workers who reported that HPMC of higher viscosity grade generally exhibited greater floating capability.[18]

From the dissolution profile of all batches, it was observed that tablets of trial F_{11} gave comparatively good dissolution profile of 95.5 % at the end of 24 hours, despite of presence of high viscosity grade of HPMC (K100M) which should decrease the drug release compared to tablets of trial F_9 and F_{10} containing 5% and 10%. HPMC of same grade gave 91.2% and 95% at the end of 22 and 24 hours.[5]

Tablets of trial F_{10} and F11 gave somewhat similar dissolution profile. As discussed earlier, the tablets of trial F_{10} and F_{11} had higher floating lag time and also gave 9.3% and 7.20% drug release in 2 hours compared to 12.6% to 24.3% drug release in 2hours of other trials. From the ongoing discussion, it was concluded that tablets of trial F_{11} had good performance among the trials F_9 and F_{10}.

Buoyancy of tablet is governed by both the swelling of hydrocolloid particles on the tablet surface when it contacts the gastric fluids, which in turns in an increase in the bulk volume and the presence of void in the dry centre of the tablet, porosity. On increasing the hardness of tablets trial F_{11} from low, medium and high resulted in significant increase in floating lag time from 1 sec, 30 sec and 37 sec, respectively which might be due to higher compression may results in reduction of porosity of the tablets and moreover the computed surface hydrocolloid particle on the surface of the tablet cannot hydrate rapidly when the tablet contacts the gastric fluids and as a result of this the capability of the tablet to float is significantly reduced.[13]

In the present study, the higher swelling index was found for tablets of F_{11} containing HPMC ($K_{100}M$) having nominal viscosity of 1, 00,000 cps and lowest for formulation F_6 containing HPMC ($K_{100}M$) having nominal viscosity of 4000cps. These values clearly indicate that increase in viscosity the swelling index increases. Hence from the above observation, trials F_{11} containing HPMC ($K_{100}M$) as the optimized and best formulation on the basis of its best tablet integrity, slow drug release profile, higher swelling index and higher floating time in comparison to other formulation.[20]

The results of dissolution data from dissolution profile fitted to various drug release kinetic equation of zero order, First order, higuchi, hixon-crowell and kossemeyer-peppas having r, n and k as shown in Figure 2 and Table 3.[7,8,15]

The final optimized formulation was subjected to stability study to ensure that the products maintains its physical and chemical integrity when exposed to extreme temperature and humidity as shown in Table 4.

Tablets of trials F_{11} was characterized by DSC for any physical and chemical incompatibility and it was observed that there was not any significant change in melting point peak of drug in tablet sample which indicate there was no physical and as well as chemical incompatibility of drug with the formulation excipients.

TABLE 3 -Regression Co-efficient and Release exponent (n) of Domperidone floating Tablet release data of formulation F2, F_5, F9, F_{10} and F11 from different mathematical models

Trials	First Order (R^2)	Zero Order (R^2)	Higuchi (R^2)	Hixon Crowel (R^2)	Korsemeyer peppas	
					(R^2)	n
F2	0.9763	0.9553	0.9714	0.9973	0.9898	0.8718
F5	0.9940	0.9193	0.9785	0.9906	0.9895	0.7613
F9	0.9888	0.9733	0.9778	0.9972	0.9889	0.7840
F10	0.9685	0.9509	0.9629	0.9955	0.9895	0.9604
F11	0.9754	0.9457	0.9574	0.9912	0.9899	0.9804

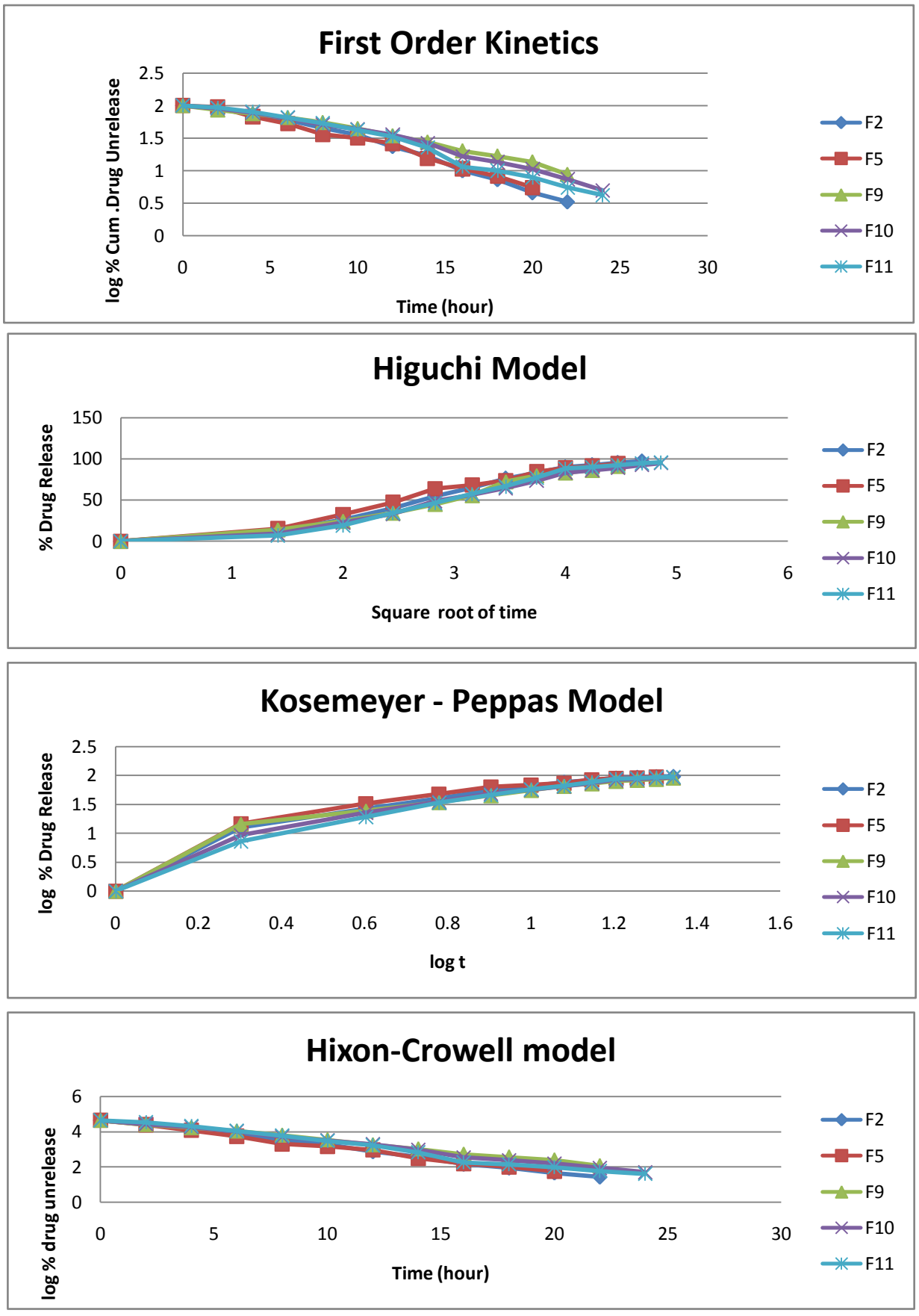

FIGURE 2 - Various type of kinetics model.

TABLE 4 - OPD Study of Domperidone floating Tablets of optimized Formulation – F_{11}.

Parameters	Initial	After 15 days	
		55º C	45º C/25%RH
Average weight	101.38	101.3	101.33
Hardness	59	59	58
Thickness	2.83	2.83	2.84
Floating Lag Time	30	30	30
Total Floating Time	24	24	24
Drug Content	99.58	99.50	99.55

CONCLUSION

This study discusses the preparation of effervescent floating matrix tablet of domperidone in order to reduce the gastric emptying time and prolong the gastric retention time and thereby increase the bioavailability of the drug. The addition of gel forming polymer HPMC and gas generating agent $NaHCO_3$ was essential to achieve in vitro buoyancy. There exist a linear relationship between swelling process and viscosity of polymer.

REFERENCES

1. Baungastner S, Kristl J, Vrecer F, Zorko B. Optimization of floating matrix tablets and evaluation of their gastric residence time. Int J Pharm 2000; 195:125-135.
2. Bravo SA, Lamas MC, Salomon CJ. Invitro studies of diclofenac sodium controlled release biopolymeric hydrophilic matrixes. J Pharm Sci 2002; 5: 213-219.
3. Bosewell-Smith V, Cazzola M, Page CP. Are Phosphodiesterase 4 inhibitors just more theophylline? J Allergy Clin Immunol 2006; 117: 1237-1243.
4. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. Pharm Technol 2003; 27:50-68.
5. Patel DM, Patel NM, Patel VF, Bhatt DA. Floating Granules of Ranitidine Hydrochloride Gelucire 43/01.Formulation optimization using factorial design. AAPs Pharm Sci Tech 2007; 2: E1-E7.
6. Dhawan S, Dhawan K, Varma M , Sinha V.R. Application of polyethylene oxide in drug delivery system. Pharm Technol 2005; 20:72-79.
7. Higuchi T. Mechanism of sustained action medication theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci 1963; 52:1145-1149.
8. Hixon AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. Ind Eng Chem 1931; 23: 923-931.
9. Lauritsen K, Laursen LS, Rask-Madsen J. Clinical pharmacokinetics of drug used in the gastrointestinal diseases. (Ppart-I) Clin Pharmacokinetics 1990; 19 (1):11-31.

10. Lauritsen K, Laursen LS, Rask-Madsen J. Clinical pharmacokinetics of drug used in the gastrointestinal diseases. (Part-II) Clin Pharmacokinetics. 1990; 19 (2):94-125.
11. Lenaerts VM, Gurny R. Gastrointestinal tract-Physiological variables affecting the performance of oral sustained release dosage forms. In: Lenaerts V, Gurny R. Editors Bioadhesive drug delivery system. Boca Raton CRC Press 1990.
12. Levina M, Rajabi-Siahboomi AR. The influence of excipients on drug release from hydroxy propylmethyl cellulose matrices. J Pharm Sci 2004; 93(11): 2746-2754.
13. Nur AO, Zhang JS. Captopril floating and/or bioadhesive tablets: Design and release kinetics. Drug Develop Int Pharm 2000; 26: 965-969.
14. Parvez N, Ahmed T, Monif T, Saha N, Sharma PL. Comparative bioavailability of three oral formulation of sustained release Theophylline in health human subjects. Ind J Pharmacol 1985; 36:29-33. 2004;
15. Peppas NA. Analysis of Fickian and non-Fickian drug release from polymers. Pharm Acta Heln 1985; 60:110-111.
16. Pinto JF, Wunder KF, Okoloekwe A. Evaluation of the potential use of poly (ethylene oxide) as tabled and extrudate forming material. AAPS Pharm Sci 2004; 6(2): 17-26.
17. Pouchel G, Irache JM. Specific and Non-specific Bioadhesive particulate system for delivery to the gastrointestinal tract. Adv Drug Del Rev 1998; 34:191-219.
18. Shoufeng Li, Senshang Lin, Bruce P, Daggy Haresh L, Mirchandani, Yiew.Chien. Effect of HPMC and carbopol on the release and floating properties of gastric floating drug delivery system using factorial design. Int J Pharm 2003; 253: 13-22.
19. Siemann J, Peppas NA. Modeling of drug release delivery system based on hydroxyl propylmethyl cellulose (HPMC). Adv Drug Rev 2001; 48:139-157.
20. Srisagul Sungthongjeen A, Ornlaksana Paeratakul B, Sontaya Limmatvapirat C, Satit Puttipipatkhachorn. Preparation and *in vitro* evaluation of a multiple-unit floating drug delivery system based on gas Formation Technique. Int J Pharm 2006; 324: 136-143.
21. Suigh B, Kuin K. Floating drug delivery systems and approach to oral controlled drug delivery via gastric retention. J Control Release 2000; 63:235-259.
22. Wagner JG. Interpretation of percent dissolved from *in vitro* testing of conventional tablets and capsules. J Pharm Sci 1969; 58:1253-1257.