WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 6, Issue 1, 587-597. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF GASTRORETANTIVE FLOATING TABLET USING EUDRAGIT RSPO WITH NATURAL POLYMERS

Kamlesh J. Wadher*, Shrikant W. Bute and Milind J. Umekar

Department of Pharmaceutical Technology, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, India-441002.

Article Received on
26 Oct. 2016,

Revised on 16 Nov. 2016,
Accepted on 06 Dec. 2016

DOI: 10.20959/wjpr20171-7561

***Corresponding Author**
Dr. Kamlesh J. Wadher
Department of Pharmaceutical Technology, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee, Nagpur, India-441002

ABSTRACT

The present study involved the design of gastro retentive floating matrix tablets of weakly basic drug Domperidone by using combination of Eudragit RSPO with natural polymers Guar and Xanthan Gum. The tablets were prepared by wet granulation process. The prepared tablets were investigated for the pre-compression and post-compression parameters. FTIR and DSC studies proved that no chemical interaction in Domperidone and polymers. All the batches evaluated for swelling and floating properties also, the batches containing combination of Eudragit RSPO with natural polymers Guar and Xanthan Gum shows good swelling properties since natural gums swells rapidly and efficiently in water. The *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer concentration and the polymer used. The sustained drug release with better floating was achieved with natural polymers. The developed floating tablet of Domperidone used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient compliance. The best fitting model for all formulation was calculated. The plain polymer batches F1- F3, the best fitted models was found to be Higuchi release. The batch F4-F9 batches followed Korsmeyer peppas model.

KEYWORDS: Domperidone, Floating tablets, Eudragit RSPO, Natural polymers, Release kinetics.

INTRODUCTION

Oral dosage forms for gastric retention have drawn more and more attention recently because of their advantage of control the release of drug over the specific period of time.[1] Floating systems or Hydro dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.[2-3] The Gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability.[4]

Domperidone (DMP) is a synthetic benzimidazole compound that acts as a dopamine D2 receptor antagonist, used for the treatment and prevention of acute nausea and vomiting. According to biopharmaceutical classification system (BCS), it is classified under class-II drugs and is chosen as a model weakly basic drug.[5] It has poor aqueous solubility and the oral bioavailability of Domperidone has been reported at the range of 13- 17%. The poor aqueous solubility may be one possible reason for its low bioavailability. In order to increase the bioavailability of Domperidone, a controlled release dosage form has been prepared to increase the solubility of Domperidone.[6]

Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression.[7] Xanthan gum is a linear, high molecular weight extracellular heteropolysaccharide, produced commercially by viscous fermentation of gram negative bacterium *Xanthomonas campesteris*. It has been also used as effective excipients for sustained release formulation; it not only retards drug release, but also provides time independent release kinetics.[8] Guar gum is used primarily for preparation of hydrophilic matrix tablets because of its unique properties such as swelling, gel formation, non toxicity and biodegradability.[9-10]

Eudragit RSPO copolymer as a fully polymerized copolymer of methacrylic acid and an acrylic or methacrylic ester, The permeability of drug through Eudragit RSPO is independent of the pH of the digestive tract. The degree of permeability depends on the relative proportion of quaternary ammonium groups in Eudragit. Eudragit RSPO is widely used as tablet coatings and as retardants of drug release in sustained released formulations.[11]

The aim of the current study was to develop gastric floating matrix tablet of domperidone using combination of Eudragit RSPO with xathan gum and guar gum to improve bioavailability, therapeutic efficacy and patient compliance. Another objective of this work was to evaluate drug release data using various kinetic models in order to determine the mechanism of drug release.

MATERIALS AND METHOD

Materials

Domperidone was obtained as gift sample from Dr Reddy's Laboratories Ltd, Hyderabad, India. EudragitRSPO obtained as a gift sample from Degussa, Mumbai, India. Natural polymer Xanthan gum and guar gum were purchased from Himedia, Mumbai, India. All other ingredients used were of Analytical grades.

Methods

Drug polymer compatibility studies

FT-IR studies

The FTIR spectra of pure domperidone and its physical mixtures (1:1) with Eudragit RSPO, xanthan gum and guar gum were carried out using FT-IR (Shimadzu 8400 S, CE).

DSC studies

Thermal analysis of drug and polymer was carried out using Differential Scanning Calorimetry (Mettlor Toledo DSC 822).

Formulation of floating tablets of Domperidone

Floating matrix tablet of Domperidone were prepared by wet granulation method according to the formula given in Table 1. Ingredients except Glidant and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done using isopropyl alcohol as granulating agent. The wet mass was passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc. Tablet compression was carried out in rotary compression machine using 5 mm concave punches. Compression force was kept constant throughout the study. Tablet weight was adjusted to 100 mg.

Table 1: Composition of Floating Matrix tablets of Domperidone

Ingredients(mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone	30	30	30	30	30	30	30	30	30

Eudragit RSPO	30	-	-	20	15	10	20	15	10
Guar gum	-	30	-	10	15	20			
Xanthan gum	-	-	30	-	-	-	10	15	20
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
Magnessium state	2	2	2	2	2	2	2	2	2
PEG 400	5	5	5	5	5	5	5	5	5
Lactose	23	23	23	23	23	23	23	23	23
Total	100	100	100	100	100	100	100	100	100

Evaluation of granules

The granules were evaluated for their flow properties. Angle of repose of granules was determined by the funnel method. Loose bulk density (LBD) and tapped bulk densities (TBD) were determined, according to the method reported by Raghuram et al.[12], The Carr index (compressibility index) and Hausner ratio determined from the LBD and TBD.[13]

Evaluation of tablet

Prepared tablet were evaluated for quality control tests like weight variation test, hardness test, friability test and content uniformity study.[14-15]

Swelling Study.[16]

The tablets were weighed individually (W1) and placed separately in glass beaker containing 200 mL of 0.1 N HCl maintained at 37°C±1°C. At regular 1-h time intervals until 24 h, tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula.

SI = (W2-W1)/ (W1)

Floating property.[17]

Buoancy lag time (BLT) is the time required for tablet to rise to the surface of dissolution medium and total floating time (TFT) is the time the tablet constantly float on the water surface were evaluated in a dissolution vessel (dissolution apparatus, Lab India) filled with 900 ml of 0.1M HCL (pH 1.2) set at 37±0.5^{O}C with paddle rotation at 50 rpm.

***In vitro* drug release study**

The *in vitro* drug release study was performed using USP type II (Electrolab Tablet Dissolution tester – USP, Model No. TDT – 06P) at 50 rpm in 900 mL of 0.1M HCl (pH 1.2) maintained at 37±0.5°C. The samples were withdrawn at predetermined time intervals for period of 12 hr and replaced with the fresh medium. The samples were filtered through 0.45

μm membrane filter, suitably diluted and analysed at 286 nm using double beam UV-VIS spectrophotometer (Mode No. UV 2300, Techcomp). The content of drug was calculated using equation generated from calibration curve. The test was performed in triplicate and the mean value was used to construct the release profile.

Determination of release kinetics and release mechanism

The release data obtained were treated according to zero-order, first-order, Higuchi and Korsmeyer-Peppas equation models.[18-19]

RESULTS AND DISCUSSION

Drug polymer compatibility studies

The FT-IR specra of pure drug and its physical mixture with polymers eudragit RSPO, Guar gum, Xanthan gum revealed no considerable changes in IR peaks of Domperidone indicating absence of interaction between drug and polymer used. The results of DSC studies also confirmed that there was no appreciable change in the melting endotherm which further supports the IR spectroscopy results. . These results clearly indicate the usefulness of the utilized materials for preparation of Gastro retentive Floating Tablets.

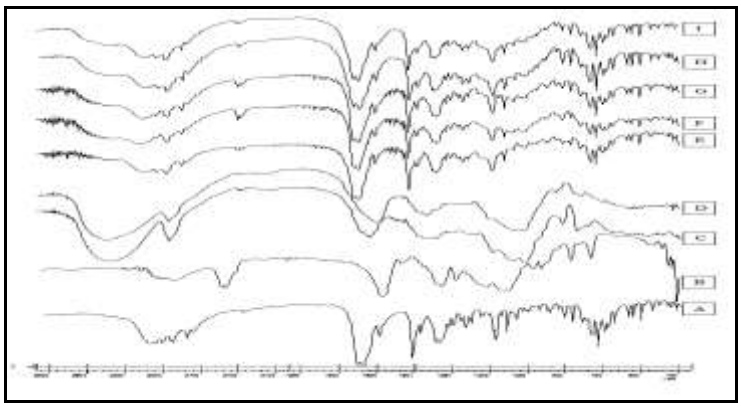

Figure 1: FTIR Spectra of pure drug and polymers. (A) Domperidone, (B) Eudragit RSPO, (C) Guar Gum, (D) Xanthan Gum, (E) Domperidone + Edragit RSPO, (F) Domperidone + Guar gum, (G) Domperidone + Xanthan Gum, (H) Domperidone + Edragit RSPO + Guar Gum, (I) Domperidone + Edragit RSPO + Xanthan Gum

Evaluation of granules

Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. All the batches of granules showed good flow properties since all batches had angle of repose of between 25°-35° which indicate good flow of granules. All batches had compressibility index between of between 12-15% and hausner ratio between

1.12-1.17 which indicates good flow character of granules. The results are as depicted in table 2.

Table 2: Pre compression properties of granules

Batch No.	Bulk density (g/mL)	Tapped density (g/mL)	Angle of Repose (°)	% compressibility	Hausner ratio
F2	0.439	0.505	27.35	12.96	1.14
F3	0.344	0.339	26.75	12.5	1.14
F4	0.317	0.364	26.2	12.94	1.14
F14	0.33	0.38	25.3	13.16	1.15
F15	0.317	0.364	26.2	12.94	1.14
F16	0.36	0.423	26.18	14.86	1.17
F17	0.422	0.482	26.77	12.5	1.14
F18	0.34	0.394	26.57	13.69	1.16
F19	0.405	0.468	26.95	13.46	1.15

Evaluation of tablet

Formulations were evaluated for the different physical evaluation parameters. The hardness of all the compression coated tablets was found to be within 6-6.5 kg/cm^2. The percent weight loss in the friability test was less than 1% in all the batches. All the batches contained drug within 100±5% of labeled amount. All the other physical parameters for tablet formulation were within the limits as shown in table3.

Table 3: Post-compression assessment of Domperidone floating tablets:

Batch No.	Friability	Hardness†	Thickness†	% Weight variation$^{\#}$
F2	0.166	6.8±0.38	3.96 ± 0.083	101±2.3
F3	0.227	6.3±0.43	3.83 ± 0.04	100 ± 3.1
F4	0.222	6.6±.82	3.98 ± 0.03	102 ± 3.9
F14	0.166	6.5±0.27	4.03 ± 0.025	101 ± 2.6
F15	0.167	6.5±.59	3.96 ± 0.021	100 ± 2.9
F16	0.166	6±1.3	3.93 ± 0.07	100 ± 2.38
F17	0.165	6.5±0.26	3.94 ± 0.05	102 ± 2.3
F18	0.221	6.0±0.5	3.94 ± 0.081	102 ± 2.7
F19	0.222	6.0±0.31	4.12 ± 0.01	101 ± 2.7

Swelling study

Swelling is an important factor to ensure floating and drug dissolution. Swelling study was performed on all the batches for 7 hrs. The rate and extent of swelling increased with an increasing concentration of polymer in the formulation. The swelling index of Batch F1-F9 formulations was in the range of 48.18±0.29 to 76.94±0.21%. The results of swelling index were depicted in Figure 2. The maximum swelling index was observed in formulations

containing Guar gum with their increasing concentration in formulation. Eudragit RSPO increases swelling index with their increases concentration. Eudragit RSPO when given in combination with Guar gum and xanthan gum showed more swelling. From the results, it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer.

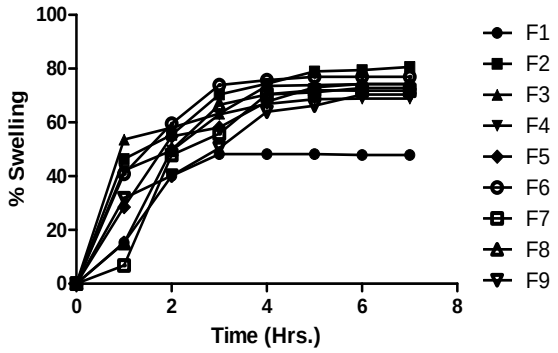

Figure 2: Swelling Study of Batch F1-F9

Floating Behaviors of Tablet

The tablets were floated and remained buoyant without disintegration thus it, maintains its dimensional stability during floating. The formulation F1, F2 and F3 containing Eudragit RSPO, Guar and Xanthan Gum Showed BLT 12, 10 and 8 minutes and TFT 4, 8 and 14 hours respectively. Batch F4-F9 batches showed BLT within the range of 11-14 minutes and TFT from 08-14 hrs respectively shown in the Table 4. The total buoyancy/floating time of batch containing plain natural gums shows good floating behavior. When Eudragit RSPO used with natural polymers it shows better floating behavior. Increased in concentration of natural polymer Xanthan and guar gum with Eudragit RSPO increases floating time as shown in table 4.

Table 4: Floating behavior of Batch F1-F9

B. No	BLT (min)	TFT (hr)
F1	12	4
F2	10	8
F3	8	14
F4	17	6
F5	20	7
F6	15	8
F7	15	6
F8	17	7
F9	18	6

***In vitro* drug release study**

The percentage of the drug released from the formulations F1, F2 and F3 was found to be 78.978 ± 0.74 %, 96.986 ± 0.32 % and 94.524 ± 0.16 %, respectively. The percentage of the drug released from the formulations F4, F5, and F6 was found to be 90.27 ± 0.31 %, 96.721 ± 0.12, and 95.142 ± 0.16 % respectively. The percentage of the drug released from the formulations F7, F8 and F9 was found to be 73.317 ± 0.36 %, 90.093 ± 0.32 and 95.188 ± 0.48 %, respectively as depicted in figure 2.

It was also observed that as the amount of polymer increases in the formulation there was decrease in drug release rate, which may be due to the drug entrapped in hydro gel by forming hydrophilic polymers. Xanthan gum and guar gum systems showed rapid drug release in first 6 h, so these systems cannot provide extended drug delivery over prolonged period of time, probably due to rapid partial tablet disintegration and slower swelling of these polymers resulting in a lack of contribution to hydrogel formation[20]. Combination of Eudragit RSPO with guar gum shows good sustained release properties than with Xanthan gum.

ANOVA was carried out using Bonfferroni post test between the drug release data of formulation, F1-F3 of plain polymer batches and combination of polymers batches F4 to F9, with their respective combinations are analyzed, ***p*** values were less than 0.001 indicating statistical significant difference existing between release profile of tablets containing different polymer-polymer combinations and different combination ratio.

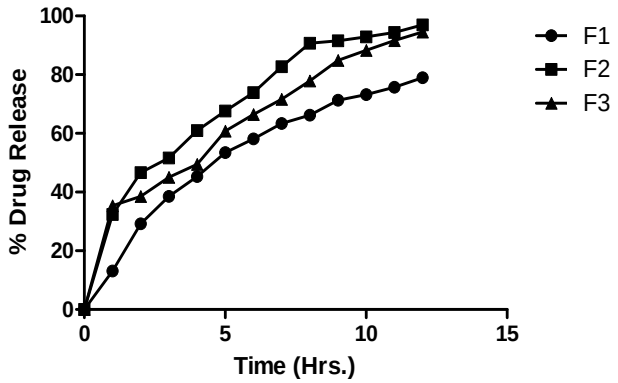

Figure 3: Cummulative % Release profile of Batch F1-F3

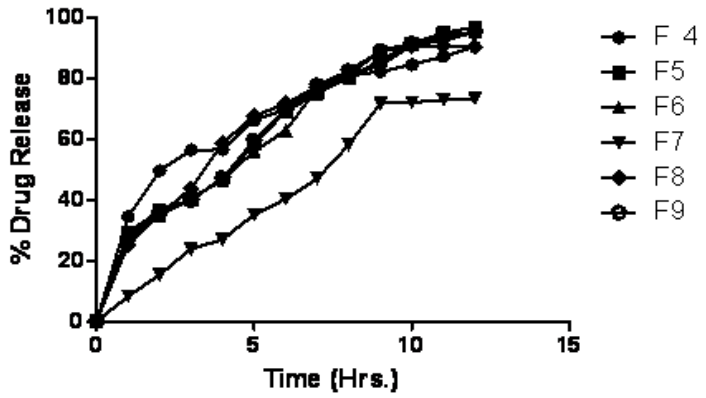

Figure 4: Cummulative % Release profile of Batch F4-F9

Determination of release kinetics and release mechanism

The best fitting model for all formulation was calculated. The plain polymer batches F1- F3, the best fitted models was found to be Higuchi release. The batch F4-F9 batches followed Korsmeyer peppas model as shown in Table 5. Analysis of the dissolution data using the equation proposed by Korsemeyer and Peppas gave values of n (release exponent) that lied between 0.45 and 0.89 in all the investigated formulae exhibiting a non-fickian release behavior controlled by a combination of diffusion and chain relaxation mechanisms. . Thus, the release of the drug from the prepared tablets is sustained by swelling of the polymer; followed by drug diffusion through the swelled polymer, slow erosion of the polymer

Table 5: Determination of release kinetics and release mechanism

Batch	Zero order		1st order		Matrix		Hix.Crow		Korsmeyer -Peppas		
	R	K	R	k	R	K	R	K	R	n	K
F1	0.8979	2.3471	0.9348	-0.0269	0.9859	7.3986	0.924	-0.0086	0.9854	0.5206	7.0418
F2	0.7956	10.1008	0.9883	-0.2693	0.9925	29.9332	0.9823	-0.0606	0.9943	0.4554	32.7919
F3	0.8618	9.3251	0.9798	-0.2133	0.9938	27.4423	0.9868	-0.0515	0.9763	0.4766	30.2693
F4	0.5718	9.1001	0.9262	-0.1791	0.9628	27.2872	0.8556	-0.0465	0.9865	0.5551	36.6152
F5	0.7564	11.3576	0.8325	-0.4044	0.8636	34.5758	0.7101	-0.0796	0.9163	0.695	52.4913
F6	0.8261	10.8074	0.8126	-0.2957	0.8491	32.9457	0.6433	-0.0664	0.9271	0.5628	53.242
F7	0.9861	6.884	0.9688	-0.113	0.9333	19.602	0.9799	-0.0315	0.9951	0.8221	8.152
F8	0.8552	9.5344	0.9882	-0.2156	0.9908	28.1065	0.9749	-0.0526	0.9897	0.553	25.3647
F9	0.8691	10.6263	0.8962	-0.2794	0.8914	32.2489	0.7632	-0.0639	0.9695	0.6744	50.8577

CONCLUSION

The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. The work was carried out using individual polymers and the

combination of Eudragit RSPO and natural polymers Xanthan and Guar gum in the different concentration. FTIR and DSC studies proved that no chemical interaction in Domperidone and polymers. The developed floating tablet of Domperidone used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient compliance. The *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer concentration and the polymer used. Analysis of the dissolution showed non-fickian release behavior controlled by a combination of diffusion and chain relaxation mechanisms. The sustained drug release with better floating was achieved with natural polymers.

ACKNOWLEDGMENTS

The authors are thankful to Dr Reddy's Laboratories Ltd, Hyderabad and Degussa , Mumbai for providing Domperidone and Eudragit RSPO as gift sample respectively and S.K.B. College of Pharmacy, Kamptee, Nagpur, India for providing necessary facilities to carry out this work.

REFERENCES

1. Patel A, Modasiya M, Shah D, Patel V. Development and in vivo floating behavior of verapamil HCl intragastric floating tablets. AAPS PharmSciTech, 2009; 10: 310-5.
2. Singh BN, Kim KH. Floating drug delivery systems – an approach to oral controlled drug delivery via gastric retention, J Control Release, 2000; 63(3): 235-59.
3. Arora S. Floating drug delivery system: a Review. AASP PharmSciTech. 2005; 6(3): E372-E383.
4. Prajapathi S, Patel L, Patel C. Floating Matrix Tablets of Domperidone Formulation and Optimization Using Simplex Lattice Design**.** Iranian J Pharm Res; 2011; 10(3): 447-455.
5. Abd Alaziz DM, Sammour OA, Elshamy AA and Neseem DI: Formulation and evaluation of binary and ternary solid dispersions of domperidone by solvent evaporation method. African journal of pharmacy and pharmacology 2014; 8: 66-80.
6. Savio CR, Soykan I and Richard WM, Domperidone: Review of pharmacology and clinical applications in gastroenterology. AJG; 2007; 102: 2036-2045.
7. Nokano M, Ogata A. In vitro release characteristics of matrix tablets: Study of Karaya gum and Guar gum as release modulators. Ind. J. Pharm; Sc. 2006; 68(6): 824-826.
8. Dhopeshwarkar V, Zatz J. Evaluation of xanthan gum in the preparation of sustained release matrix tablets. Drug Dev. Ind. Pharm, 1993; 19: 999-1017.

9. Khullar P, Khar RK, Agrawal SP. Evaluation of hydrogel-based controlled-release niacin tablets. Drug Dev. Ind. Pharm, 1998; 24(5): 479–483.
10. Jain NK, Kulkarni K, Talwar N. Controlled-release tablet formulation of isoniazid. Pharmazie, 1992; 47(4): 277–278.
11. Mehta KA, Kislaloglu MS, Phuapradit W, Malick AW, Shah NH. Release performance of a poorly soluble drug from a novel Eudragit-based multiunite erosion matrix. Int J Pharm, 2001; 213: 7– 12.
12. Raghuram RK, Srinivas M, Srinivas R. Once-daily sustained release matrix tablets of nicorandil: formulation and *in vitro* evaluation. AAPS PharmSciTech; 2003; 4(4): Article 61.
13. Lachman L, Lieberman HA. eds. The Theory and Practice of Industrial Pharmacy. Philadelphia, PA: Leas and Febiger, 1987: 317–318.
14. United States Pharmacopoeia XXX NF 25. United States Pharmacopoeial Convention, Rockville. 731.
15. Reddy KR, Mutalik S, Reddy S. Once-Daily Sustained-Release Matrix Tablets of Nicorandil: Formulation and In Vitro Evaluation. AAPS Pharm.Sci.Tech; 2003: 4-12.
16. Patel A. Devlopment and In Vivo Floating Behavior of Verapamil HCl Intragastric Floating Tablets. AAPS PharmaSciTech. 2009; 310-315.
17. Prajapati S, Patel L, Patel M. Studies on Formulation and in Vitro Evaluation of Floating Matrix Tablets of Domperidone. Int J. of Pharm; Res. 2009:19-23.
18. Higuchi T., Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci; 1963; 2: 1145 -1149.
19. Korsmeyer R.W, Gurny R ,and Peppas N.A., Mechanisms of solute release from porous hydrophilic polymers, Int J Pharm; 1983; 15: 25-35.
20. MurataY., et al., Use of floating alginate gel beads for stomach-specific drug delivery, European Journal of Pharmaceutics and Biopharmaceutics, 2000; 50: 221-226.