FORMULATION AND IN-VITRO EVALUATION OF GASTRO-RETENTIVE FLOATING TABLET OF FUROSEMIDE

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ABSTRACT

INTRODUCTION

4-chloro-2-(furan-2-ylmethylamino)-5-sulfamoylbenzoic acid (Furosemide) is high efficacious diuretic, used to treat edema and congestive heart failure. Gastro retentive floating tablets offer advantages by retaining in the stomach for a sufficient time against all physiological barriers. It improves bioavailability, reduces drug wastages, and improve the solubility of drug in high pH environment. The crucial aspect is to increase the dissolution time.

MATERIAL AND METHODS

An experimental design was done in the pharmaceutic laboratory of department of pharmacy from August 2022 to January 2023. Gastro-retentive floating tablets were prepared by direct compression method using different viscosity grades of polymers with sodium bicarbonate and were lubricated with magnesium stearate and talc. The parameters before and after compression were evaluated.

RESULTS

All the hydro-dynamically balanced system formulations showed good in-vitro floating properties. The tablet of F4 formulation was best which shows drug release up to 12 hours with percentage cumulative drug release up to 99.04%.

CONCLUSION

The preparation shows successful approach to maintain the sustain release of furosemide at different time interval. Among formulations, floating tablet formulated using 100 mg Hydroxypropyl methylcellulose K15 M (HPMC K15M) polymer was found to be best.

KEYWORDS

Furosemide, Gastro-retentive drug delivery system, Direct compression method.

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INTRODUCTION

Gastro-retentive dosage forms are the system which retains in the stomach for a sufficient time interval against all physiological barriers, releases active moiety in a controlled manner and finally is easily metabolized in the body.[1] The development of several formulations, including floating systems, mucoadhesive/ bioadhesive systems, expandable systems, and magnetic systems have the potential to increase drug effectiveness by extending the gastro-intestinal residence time.[2] Effective Gastro-retentive drug delivery system (GRDDS) depend on the rate at which the stomach empties, how quickly the dosage form moves through the digestive tract, how quickly the drug is released from the dosage form, and the location of the drug absorption.[3] Gastro-retentive drug delivery system are typically employed to extend the time that dosage forms remain in the stomach and avoid them from entering the lower intestinal environment.[4] Many strategies have been put up to produce a regulated extension of the stomach residence duration. Most of these systems fall under one of the following four categories: expansion, mucoadhesion, sedimentation and flotation.[5] In general, Gastro-retentive drug delivery system uses either hydrophilic polymer for hydrodynamically balanced systems or sodium bicarbonate and citric acid to create carbon dioxide.[6]

Floating dosage form stays on the contents of the stomach because they have a lower density than the stomach. The formulation floats due to the presence of hydrodynamic balanced systems.[7] This system has made use of both non-effervescent and effervescent technologies. Swellable polymers and gas-generating substances, like sodium bicarbonate and citric or tartaric acid are used in effervescent systems.[8] Hydroxy propyl methylcellulose (HPMC) is a polymer used in hydrophilic matrix system that is available in different viscosity grades like HPMC K4M, HPMC K15M and HPMC K100M. The drug will be released in desired manner that will increase gastric retention time and minimize fluctuations.

Furosemide acts on thick ascending limb of the loop of Henle and directly inhibits the Na+/K+/2Cl- cotransporter. It belongs to the class IV category as per the biopharmaceutical classification system (BCS). It has half-life less than 2 hours and is primarily absorbed in the upper gastrointestinal system. The traditional dose leads to poor bioavailability with 30–60% and needs dosing of three to four times per day.[9]

MATERIAL AND METHODS

Furosemide was provided as a gift sample from local pharmaceuticals company. All excipients were provided by the college laboratory. (Table 1). Ethical clearance was obtained from Institutional Review Committee having Reference No. UCMS/IRC/193/22 in November 22, 2022.

Table 1. List of chemicals

S.No.	Ingredients	Properties
1.	Furosemide	Active pharmaceutical ingredient
2.	Hydroxy propyl methylcellulose (HPMC) K4M, K15M, K100M	Synthetic Polymers
3.	Xanthan gum	Natural Polymer
4.	Sodium alginate	Natural Polymer
5.	Sodium bicarbonate	Effervescent
6.	Lactose	Diluent
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant

All equipments were provided by the college laboratory. (Table 2).

Table 2. List of instruments

S.No.	Equipments	Function	Manufacturers
1.	Dissolution test apparatus	For analysis of the tablet	Accurate
2.	UV visible spectrophotometer	For analysis of the tablet	Spectrochem-I
3.	Tablet compressing Machine	For converts granulated powder into pressed tablets by compression	Pharmatec
4.	Friability test apparatus	To test tablet strength when transporting	Biotec
5.	Desiccator	To absorb moisture	Bluefic
6.	Digital Vernier Caliper scale	To measure the thickness of the tablet	Accurate
7.	Digital weighing balance	For taking the uniform weight of material used for the formulation of the tablet	Sartorius
8.	Digital pH meter	To check the pH of the reagent	Slope
9.	Magnetic stirrer	For uniform solubility	Remi
10.	Sieve (#40, #80)	To make uniform size particle	RSH
11.	Hardness Tester	To check hardness of tablet	Monsanto
12.	Laboratory Glassware	To store, separate and heat a small amount of chemicals	Borosil

Preparation of chemical reagents

a. 0.1 N Hydrochloric acid preparation

It was prepared by taking 8.5 ml of conc. hydrochloric acid and diluted with distilled water to produce 1000 ml in a volumetric flask.

b. Standard stock solution preparation

20 mg of Furosemide was accurately weighted and transferred to the 100ml volumetric flask and dissolved in a 0.1N Hcl and diluted to 100ml which was 200µg/ml standard stock solution of furosemide.

c. Preparation of standard stock solution of furosemide for calibration curve

From above standard stock solution, different concentration solutions (1,2, 4, 6, 8, and 10µg/ml) were prepared in 0.1 N hydrochloric acid with appropriate dilution and analyzed in UV-visible spectrophotometer at 276 nm. Thus, measured

absorbance values and concentrations were plotted in excel and calibration curve was obtained with its equation and regression coefficient value.[10]

Preparation of floating tablet of furosemide

a. Direct compression method (Table 3)

Polymer and lactose were measured exactly, taken in a mortar and were mixed. Furosemide was added in the above mixture in appropriate amount and mixed by pestle. Sodium bicarbonate was weighed and taken separately in mortar and powdered by pestle. The powder was then passed through sieve #40, mixed with the drug blend and again sieve the content. The mixture was collected in plastic bag and mixed thoroughly for 3 minutes. Magnesium stearate was added and mixed for 5 minutes and then talc was added and mixed for 2 minutes. This final product was then compressed into tablets by using 8-station punching machine.[11]

Table 3. Formulation of gastro-retentive floating tablets of furosemide

Batch Code	Drug	HPMC K4M	HPMC K15M	HPMC K100M	Xanthan Gum	Sodium Alginate	Lactose	Sodium Bicarbonate	Magnesium Stearate	Talc	Total
F1	40	50	-	-	-	-	165	30	7	8	300
F2	40	100	-	-	-	-	115	30	7	8	300
F3	40	-	50	-	-	-	165	30	7	8	300
F4	40	-	100	-	-	-	115	30	7	8	300
F5	40	-	-	50	-	-	165	30	7	8	300
F6	40	-	-	100	-	-	115	30	7	8	300
F7	40	-	-	-	50	--	165	30	7	8	300
F8	40	-	-	-	100	-	115	30	7	8	300
F9	40	-	-	-	-	50	165	30	7	8	300
F10	40	-	-	-	-	100	115	30	7	8	300

Evaluation of Floating Tablet

a. Hausner's ratio

This is the parameter to measure flow of powder. The values below 1.25 indicate good and above indicates poor flow.

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Where, $\text{Tapped density} = \frac{\text{Mass of powder (g)}}{\text{Tapped volume (ml)}}$ and

$$\text{Bulk density} = \frac{\text{Mass of powder (g)}}{\text{Bulk volume (ml)}}$$

b. Carr's index

The value below 16% indicate good, above 23% indicate poor and in between indicate fair and passable flow of powder.

$$\text{Carr's index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped Density}} \times 100\%$$

c. Angle of repose

The frictional force in powder can be determined by angle of repose (Θ). The value below the 25 indicate excellent flow properties, above 40 indicate very poor whereas in between indicate good and passable flow properties.

$$\text{Tan } \Theta = \frac{\text{height of pile (h)}}{\text{radius of the base of pile (r)}}$$

d. Weight variation test

Take 20 tablets, weigh it individually and collectively. Then the average weight of one tablet was calculated from the collective weight.

e. Hardness test

This is the force given across the diameter of tablet to break the tablet.

f. Thickness

Six tablets were measured. The extent of deviation from standard value was also determined.

g. Friability

This was for mechanical strength of tablets. Initially weigh the tablets and placed it in the friabilator. The tablets were rotated for 4 minutes (100 rotations) at 25 rpm.

$$\text{Percentage friability} = \frac{\text{Initial weight - final weight}}{\text{Initial weight}} \times 100\%$$

h. In-vitro buoyancy studies

In-vitro buoyancy was determined by floating log time and total floating time. The tablets were taken in 100 ml beaker containing 0.1 N Hcl. The time required for the tablet to rise to the surface and float was the floating lag time and duration of time the tablet constantly floats on the medium was total floating time.

i. In-vitro drug release studies

Dissolution profile of these tablets can be determined by using dissolution apparatus with paddle, rotating at 50 rpm in 900 ml 0.1 N Hcl at 37°C. 10 ml of sample was withdrawn from test apparatus at 30 mins, 1, 2, 4, 6, 8, 10, and 12 hour time duration. Samples were filtered through a membrane filter. 1 ml from filtered solution was diluted to 10 ml with 0.1 N Hcl. Absorbance of these solutions was then measured at 276 nm using a UV/Visible spectrophotometer.

j. Assay

Tablets were weighed, average weight was determined and crushes in the mortar and pestle to make fine powder. The amount of sample equivalent to 20 mg of Furosemide was weighed and dissolve in 100 ml with 0.1 N Hcl and was filtered. Aliquot of 1 ml of solution was diluted to 10 ml with

solvent in separate volumetric flask. The drug content was measured at 276 nm using medium as blank solution. The assay percent of furosemide was calculated by using following formula.[12]

$$E(1\%, 1cm) = \frac{\text{Absorbance of standard}}{\text{Weight taken}} \times \frac{\text{Dilution Factor}}{\%\text{purity}}$$

$$\text{Content per tablet} = \frac{\text{Absorbance of sample}}{\text{Weight taken}} \times \frac{\text{Dilution Factor}}{E(1\%,1cm)} \times \frac{\text{Average weight}}{100}$$

$$\text{Assay}\% = \frac{\text{Content per tablet}}{\text{Claim per tablet}} \times 100\%$$

RESULTS

Pre-compression parameters (Table 4)

a. Angle of repose
The minimum angle of repose (25.84±1.69) was found in F2 formulation which was formulated with 100mg HPMC K4M and maximum angle of repose (29.03±0.93) was found in F7 formulation with 50mg xanthan gum.

b. Bulk density
The minimum bulk density (0.52±0.08) was found in F4 formulation and maximum bulk density (0.66±0.08) was found in F7 formulation.

c. Tapped density
The minimum tapped density (0.60±0.01) was found in F4 formulation and maximum tapped density (0.83±0.05) was found in F10 formulation.

d. Carr's index
The minimum Carr's index (12.8±1.12) was found in F5 formulation and maximum Carr's index (21.7±0.15) was found in F9 formulation.

e. Hausner's ratio:
The minimum Hausner's ratio (1.14±0.06) was found in F5 formulation and maximum Hausner's ratio (1.27±0.08) was found in F9 formulation.

Code	Angle of repose (Θ)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
F1	26.02±1.14	0.59±0.04	0.71±0.03	16.9±0.41	1.20±0.06
F2	25.84±1.69	0.55±0.09	0.67±0.06	17.9±0.78	1.21±0.04
F3	26.85±0.95	0.59±0.03	0.68±0.09	13.2±1.12	1.15±0.51
F4	27.01±1.66	0.52±0.08	0.60±0.01	13.3±0.87	1.15±0.09
F5	26.09±1.02	0.61±0.06	0.70±0.08	12.8±1.12	1.14±0.06
F6	26.76±0.68	0.62±0.03	0.72±0.05	13.9±0.89	1.16±0.60
F7	29.03±0.93	0.66±0.08	0.77±0.06	14.3±0.06	1.17±0.11
F8	28.87±1.32	0.54±0.05	0.65±0.03	16.9±0.13	1.20±0.24
F9	27.98±1.65	0.61±0.09	0.78±0.07	21.7±0.15	1.27±0.08
F10	28.87±1.54	0.66±0.07	0.83±0.05	20.5±0.67	1.25±0.31

Post-compression parameters (Table 5)

a. Weight variation
The minimum average weight (298±1.83) was found in F8 formulation and maximum average weight (307±1.18) was found in F1 formulation batch which satisfy the pharmacopeia requirement.

b. Thickness
The minimum thickness (2.36±0.016) was found in F8 and maximum thickness (2.50±0.011) was found in F1 formulation.

c. Hardness
From each formulation batch, 10 tablets were randomly selected. The minimum hardness (3.6±0.17) was found in F10 formulation and maximum hardness (5.5±0.13) was found in F6 formulation batch.

d. Friability
Friability test was carried out and minimum friability (0.16%) was found in F6 formulation and maximum friability (0.51%) was found in F10 formulation which was within pharmacopeia limit.

e. Drug content (Assay)
Assay was carried out for each formulation batch and minimum drug content (99.15%) was found in F8 formulation and maximum drug content (102.67%) was found in F1 formulation batch.

Table 5. Post-compression parameters

Batch code	Mean weight (mm)	Mean thickness (mm)	Hardness (kg/cm²)	Friability (%)	Drug content (%)
F1	307±1.18	2.50±0.011	5.0±0.38	0.21	102.67
F2	302±1.33	2.48±0.022	5.2±0.54	0.19	101.89
F3	301±0.98	2.44±0.015	5.3±0.14	0.25	101.23
F4	300±0.67	2.42±0.024	5.1±0.26	0.20	100.34
F5	303±1.07	2.44±0.019	5.4±0.31	0.17	102.06
F6	299±1.89	2.46±0.009	5.5±0.13	0.16	99.48
F7	304±0.76	2.41±0.015	3.8±0.15	0.48	102.16
F8	298±1.83	2.36±0.016	3.9±0.18	0.46	99.15
F9	300±1.52	2.39±0.021	3.7±0.21	0.48	99.86
F10	304±1.85	2.37±0.033	3.6±0.17	0.51	101.94

f. In-vitro buoyancy studies (Table 6)
In-vitro studies were carried out, the maximum floating lag time (48 sec) was found in formulation F6 and minimum (24 sec) was found in formulation F1 with HPMC K4M. The maximum total lag time (greater than 12 hours) was found in all batches and floating properties were also measured.

Table 6. In-vitro buoyancy studies

Batch code	Floating lag time (sec)	Total floating time (sec)
F1	24	More than 12 hours
F2	45	More than 12 hours
F3	26	More than 12 hours
F4	38	More than 12 hours
F5	31	More than 12 hours
F6	48	More than 12 hours
F7	47	More than 12 hours
F8	42	More than 12 hours
F9	45	More than 12 hours
F10	43	More than 12 hours

g. In-vitro drug release study (Table 7, Figure 1 & 2)
Dissolution study was performed at 37°C by 6-stations apparatus at 50 rpm. Absorbance of resulting solution was measured at 276 nm and the drug release was calculated from the standard calibration curve. The maximum percentage drug release (99.04%) was found in F4 batch.

Table 7. Percentage cumulative drug release for various formulations

	%Cumulative drug release in hours									
Batch Code / Time (hr.)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
0.5	35.64	29.43	31.35	18.01	14.96	10.27	8.45	6.31	9.58	8.02
1	57.02	39.89	45.26	27.24	23.35	18.63	12.45	8.98	16.25	14.62
2	76.96	45.34	55.76	36.71	34.27	27.98	15.01	13.02	31.89	29.52
4	81.56	58.76	67.21	48.43	46.43	38.01	18.04	16.33	44.99	41.33
6	88.24	69.80	80.59	61.65	59.43	46.67	22.89	19.98	61.63	59.41
8	99.86	79.54	91.42	74.41	68.94	57.15	27.32	25.02	66.31	63.28
10	-	97.88	98.65	87.06	79.84	67.98	32.66	30.31	71.49	69.25
12	-	-	-	99.04	90.21	78.32	35.92	34.18	77.86	75.93

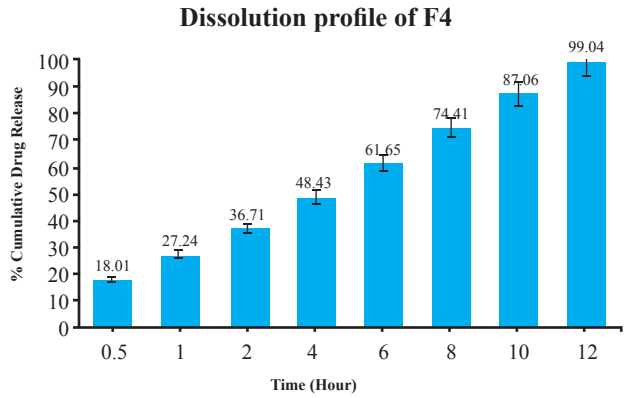

Figure 1. In-vitro dissolution profile of formulation F4

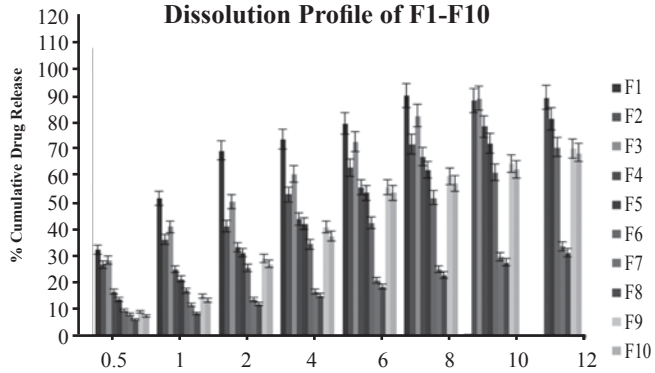

Figure 2. Comparison of in-vitro dissolution profile of formulation F1-F10

DISCUSSION

The pores are created in the tablet by production of carbon dioxide due to the reaction between sodium bicarbonate and hydrochloric acid. This results in wetting and swelling of the polymers that helps in upholding the buoyancy.[13]

Drug release is pH independent in HPMC. HPMC aqueous solutions are stable across a broad temperature range and resistant to enzymatic degradation. When a formulation containing HPMC is exposed to gastric fluid in aqueous solution, the surface polymer hydrates to produce viscous gel layer. The gel layer creates a diffusion barrier that slows down additional medication release and water uptake.[14]

HPMC is a hydrophilic polymer. In touch with water, it swells. In tablets containing HPMC of high viscosity grade, or HPMC K100M, the thickness of the swollen layer generated surrounding the matrix core was found to be higher, and the swelling was noticeably less in tablets containing HPMC K4M than in tablets containing HPMC K15M. High viscosity grade polymers have higher hydrodynamic volumes occupied by the hydrated polymer chains as a result, more swelling masses of matrices have been developed.[15]

The investigations were done using 50 and 100 mg concentrations of different synthetic polymer and natural polymer. The result of floating duration time of formulation prepared shows the minimum floating time of 8 hours which was found in formulation F1 and 10 hours of floating time which was found in F3 and F5 formulation with minimum floating lag time 24 sec, 26 sec, and 31 sec respectively which was due to less capacity to form hydrophilic barrier around the tablet.[16] All the formulation shows more than 12 hours of total floating time. The drug release from the formulation F4-F10 was controlled up to 12 hours than the formulation except F1, F2, and F3. This is due to matrix forming ability was more in case of formulation F4-F10 containing polymer likes HPMC K15M, HPMC K100M, and natural polymer xanthan gum and sodium alginate.[17] Formulation F1, F2 and F3 showed rapid burst release within 6-10 hours. This is due to low viscosity grade polymer containing in F1 and F2 formulation and low amount of polymer used in F3 formulation. Formulation F4 sustains the drug release and released the drug completely in 12 hours. Hence F4 was selected as optimized formulation. Formulation F6 released less than 90% of drug in 12 hours. This is due to high quantity of polymer used which retardation the drug release. Formulation F7, and F8 showed less than 40% the drug release for more than 12 hours. This is because xanthan gum has a high molecular weight and is a naturally occurring polysaccharide that has a slow rate of breakdown and a high degree of swelling in biological fluids.[18] Formulation F9, F10 released less than 80% drug.

CONCLUSION

It is concluded that the gastro-retentive floating tablet of furosemide is a successful approach to maintain the sustain released of the formulation. Selection of amount and nature of polymers in the dosage form play an important role in the enhancement of floating lag time and total floating time.

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CONFLICT OF INTEREST

None

REFERENCES

1 Bardonnet PL, Faivre V, Pugh WJ, Piffaretti JC, Falson F. Gastroretentive dosage forms: Overview and special case of Helicobacter pylori. Journal of Controlled Release. 2006 Mar 10;111(1–2):1–18.

2. Kanwar N, Kumar R, pharmacy AS, Preparation and evaluation of floating tablets of pregabalin. Taylor & Francis [Internet]. cited 2023 May 12;42(4):654–60.

3. Someshwar K, Chithaluru K, Ramarao T, Kumar KK. Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharmaceutica. 2011 Jun 1;61(2):217–26.

4. Kesarla RS, Ashwinbhai Vora P, Sridhar BK, Patel G, Omri A. Formulation and evaluation of floating tablet of H2-receptor antagonist. Taylor & Francis [Internet]. cited 2023 May 12;41(9):1499–511.

5. Neumann M, Heimhardt C. Development of a furosemide-containing expandable system for gastric retention. Elsevier [Internet]. cited 2023 May 12; 33(8):105-18

6. Mandal UK, Chatterjee B, Senjoti FG. Gastro-retentive drug delivery systems and in vivo success. Asian J Pharm Sci. 2016 Oct 1;11(5):575–84.

7. Özdemir N, Ordu S, Studies of floating dosage forms of furosemide: in vitro and in vivo evaluations of bilayer tablet formulations. Taylor & Francis [Internet]. 2010; 26(8):857–66.

8. Arza RAK, Gonugunta CSR, Veerareddy PR, Formulation and evaluation of swellable and floating gastroretentive ciprofloxacin hydrochloride tablets. AAPS Pharm SciTech [Internet]. 2009 Mar 10; 10(1):220–6.

9. Darandale SS, Vavia PR, Design of a gastroretentive mucoadhesive dosage form of furosemide for controlled release. Acta Pharm Sin B. 2012 Oct;2(5):509–17.

10. Naz A, Sadia S, Askari M, Zama H, Farheena S, Shah T, Design and Evaluation of Gastroretentive Floating Tablets of Diuretic Furosemide. World Journal of Pharmaceutical Research [Internet]. 2020; 9:1243.

11. Jagdale SC, Agavekar AJ, Pandya S V., Kuchekar BS, Chabukswar AR. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS PharmSciTech. 2009 Sep; 10(3):1071–9.

12. Gahandule, Mangal. and Banerjee, S.K. Development of UV spectrophotometric methods and validation for estimation of furosemide in bulk and tablet dosage form by absorbance maxima and area under the curve method. Int. J. of Advances in Pharmaceutics, 2016; 5(6):160-70.

13. Gutiérrez-Sánchez PE, Hernández-León A, Villafuerte-Robles L. Effect of sodium bicarbonate on the properties of metronidazole floating matrix tablets. Drug Dev Ind Pharm. 2008 Feb;34(2):171–80.

14. Siepmann J, Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Elsevier [Internet]. 2001 [cited 2023 May 12]; 48:139–57.

15. R.O. Williams III, T.D. Reynolds, T.D. Cabelka, M.A. Sykora, V. Mahaguna, Investigation of excipient type and level on drug release from controlled release tablets containing HPMC, Pharm. Dev. Tech. 2002,7(2);181–93.

16. Wan LSC, Heng PWS, Wong LF, The effect of hydroxypropyl methyl cellulose on water penetration into a matrix system, Int.J.Pharm., 1991; 73; 111-16.

17. Talukder MM, Michoel A, Rombaut P and Kinget R. Comaprative study on xanthun gum and hydroxypropyl methyl cellulose as matrices for controlled-release drug delivery. Int. J. Pharm., 1996; 129; 231-41.

18. Talukdar M.M. and Kinget R, Swelling and drug release behaviour of xanthan gum matrix tablets, Int. J. Pharm., 1995; 120; 63–72.