International Journal of Farmacia

Journal Home page: www.ijfjournal.com

Development and invitro evaluation of gastroretentive floating effervescent matrix tablets of Enalapril

Syeda Ahmedi Aqsa[*1], Pamu Sandhya[1]

Shadan Women's College of Pharmacy, Khairatabad, Hyderabad, Telangana 500004

Corresponding Author: Syeda Ahmedi Aqsa

***Email: s.aqsa_hussaini@yahoo.com**

ABSTRACT

Enalapril is a potent ACE inhibitor which is rapidly metabolized in the liver.It is rapidly converted by ester hydrolysis to Enalaprilat on oral administration. It may be used to treat renovascular hypertension, symptomatic congestive heart failure and hyperglycaemia. It may be used alone or in combination with thiazide diuretic. However its absorption is erratic in diabetic patients due to impaired gastric motility so, to overcome this the present study gastric retentive controlled release dosage form of the drug was formulated with different polymers like HPMC K15M, sodium bicarbonate, magnesium stearate, MCC, talc in different ratios. In this direct compression method has been employed to prepare floating matrix tablets. The formulations F1-F12 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. From the dissolution data it was evident that formulation F11 was found to be best formulation with maximum % drug release of 99.92 % in 12 hours.

Keywords: Enalapril, Floating matrix tablets, Renovascular hypertension.

INTRODUCTION

Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation [1]. Gastro retentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects [2]. Gastro retentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastro retentive drug delivery approaches being designed and developed [3]. Enalapril is a potent, competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I (ATI) to angiotensin II [4]. Its molecular weight is 376.447 g/mol. Its IUPAC name is (2s)-1-[(2s)-2-{[(2s)-1-ethoxy-1-oxo-4-phenylbutan-2-yi] amino}propanoyl Pyrollidine-2-carboxylic acid. Enalapril may be used to treat essential or renovascular hypertension and symptomatic congestive heart failure. Enalapril is a prodrug that is rapidly metabolized by liver esterases to Enalaprilat following oral administration [5]. Enalaprilat, the active metabolite of enalapril, decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure [6]. Enalaprilat lowers blood pressure by antagonizing the effect of the RAAS. The GFDDS of Enalapril prepared from all the polymers were found to be of good quality fulfilling all the official and other requirements of compressed tablets [7]. The

concentration of the effervescent agent greatly influenced the floating lag time [8]. The GFDDS of Enalapril prepared from HPMC remained intact and the compactness of the tablet was not affected during the *in vitro* dissolution test [9]. It was found that the drug release from the GFDDS of Enalapril mainly depended upon the concentration of polymer present in the GFDDS for all the twelve formulations [10].

MATERIALS AND METHODS

Formulation of Enalapril floating tablets using different polymers: HPMC K15M, HPMC 4M, HPMC K100M, Sodium Bicarbonate, Magnesium stearate and Talc in different ratios [11].

Table 1: Materials

Name of the materials
Enalapril
HPMC K4M
HPMC K15M
HPMC K100M
Sodium bi carbonate
Lactose
Magnesium stearate

Methods

Formulation (or) preparation of floating tablets of enalapril

In this work, direct compression method has been employed to prepare floating matrix tablets of Enalapril with HPMC K15M, HPMC K4M & HPMC K100M [12].

Table 2: Formulation chart of floating tablets of Enalapril

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Enalapril	10	10	10	10	10	10	10	10	10	10	10	10
Xanthan gum	15	20	25	30	--	--	--	--	--	--	--	--
Guar gum	--	--	--	--	15	20	25	30	--	--	--	--
HPMC K15M					--	--	--	--	15	20	25	30
$NaHCO_3$	10	10	10	10	10	10	10	10	10	10	10	10
Citric acid	5	5	5	5	5	5	5	5	5	5	5	5
MCC	106	101	96	91	106	101	96	91	106	101	96	91
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150	150	150

Procedure

All the ingredients were accurately weighed and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 minutes. Micro crystalline cellulose, sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 40mesh. Tablets were compressed by direct compression method on a multi punch12 station Rotary tablet compression machine using 8mm flat round punches.

Evaluation of floating tablets

Tablets are evaluated for both pre-compression parameters like bulk density, Carr's index, Hausner's ratio as well as their post compression parameters like various quality control tests such as tablet Thickness and Diameter,Hardness, Friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for FDDS like floating lag time and total floating time & release rate of drug.

Evaluation of Post Compression Parameters of Floating Tablets

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. Thickness and diameter were measured using vernier calipers.

Hardness

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability

The friability test was carried out to evaluate the hardness and stability instantly to withstand abrasion in packing, handling and transporting. In Roche Friabilator in which twenty tablets were weighed (W_o) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations, the tablets were again weighed (w).

Uniformity of weight

This test is performed to maintain the uniformity of weight of each tablet this is done by sampling and weighing 20 tablets at random and average weight is calculated.

Content Uniformity

This test is performed to maintain the uniformity of weight of each tablet This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 15 mg of Enalapril was dissolved in 0.1 N HCL in 100ml volumetric flask.

In vitro buoyancy determination

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviours of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication [13].

In vitro dissolution studies

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Lab India) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium 900ml and was maintained at 37 ± 0.5^0C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the Enalapril at 274 nm by using a double beam UV spectrophotometer (Lab India). Each dissolution study was performed for three times and the mean values were taken [14].

RESULTS AND DISCUSSIONS

Compatibility studies by FTIR

The drug and excipient compatibility studies were carried out by FTIR study. The study showed peaks for the corresponding functional groups in Enalapril .When the study was carried out with Enalapril and polymers, there was no major changes in the peaks.Hence there was no interaction with the polymers.

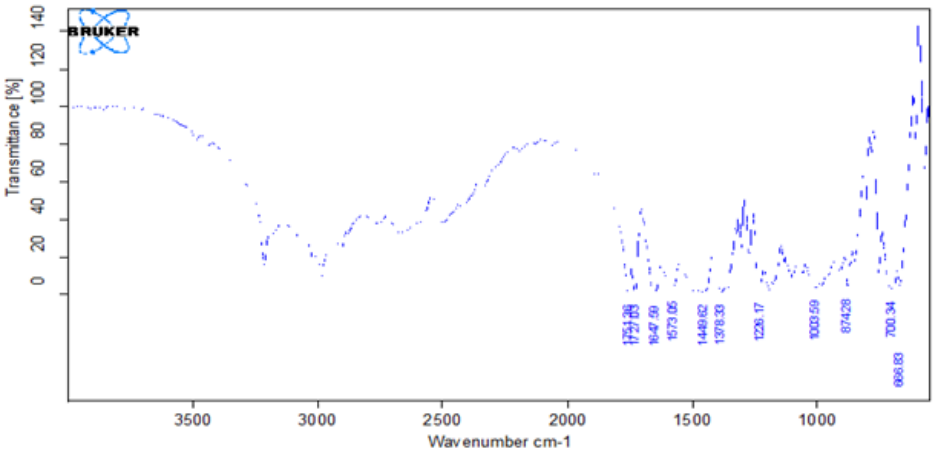

Fig 1: FTIR of pure drug

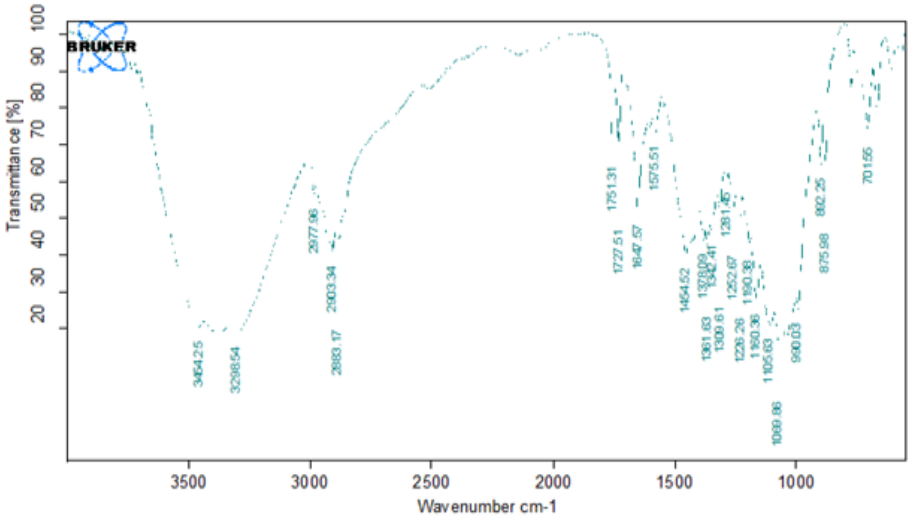

Fig 2: FT-IR of optimized formula

Determination of λ_{max}

Enalapril was dissolved in 10 ml of methanol solution and further diluted with 0.1N HCI. Then the solution was scanned for maximum absorbance in UV double beam spectrophotometer (Shimadzu 1700) in the range from 200 to 400 nm, using 0.1N HCI as blank. The λ_{max} of the drug was found to be 221 nm.

Pre-compression parameters

Table 3: Evaluation of the flow properties of powder blend for formulation F1to F12

Formulation	Compressibility Index	Angle of repose	Hausner ratio
F1	13.25±0.34	22.25±0.12	1.18±0.82
F2	18.59±0.12	21.16±0.31	1.38±0.54
F3	15.52±0.14	36.52±0.93	1.24±0.78
F4	17.86±0.25	28.56±0.34	1.18±0.56
F5	14.29±0.32	22.85±0.67	1.23±0.38
F6	17.84±0.54	21.43±0.89	1.16±0.32
F7	19.58±0.43	23.45±0.41	1.32±0.93

F8	15.56±0.61	22.47±0.62	1.16±0.26
F9	14.78±0.28	26.89±0.64	1.15±0.46
F10	17.42±0.32	27.45±0.15	1.27±0.62
F11	18.56±0.36	22.51±0.41	1.35±0.39
F12	14.28±0.53	21.85±0.62	1.26±0.20

Post compression studies

The physical characteristics of Enalapril floating tablets (F1 to F9) such as weight variation, thickness, hardness, friability and drug content were determined and results of the formulations (F1 to F9) found to be within the limits.

Table 4: Evaluations of physical parameters of tablets

Batch No.	Average weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	148.23±0.72	4.23±0.271	0.20	99.1
F2	149.62±0.56	4.61±0.268	0.12	99.7
F3	150.71±0.76	4.52±0.36	0.18	98.23
F4	149.25±1.42	4.73±0.361	0.16	99.62
F5	151.43.±0.96	4.76±0.213	0.13	97.27
F6	150.70±0.37	5.85±0.301	0.23	99.5
F7	148.52±0.18	4.88±0.310	0.20	101.4
F8	149.96±1.21	4.52±0.213	0.19	97.9
F9	150.95±1.32	4.36±0.403	0.20	98.8
F10	149.91±1.44	4.95±0.415	0.18	99.97
F11	151.84±1.51	4.11±0.353	0.18	99.2
F12	148.77±1.67	5.17±0.347	0.17	101.2

In vitro buoyancystudies

Table 5: Evaluations of physical parameters of tablets

Formulation	Buoyancy lag time (Seconds)	Duration of floating (Hours)
F1	80 Sec	8.2
F2	60 Sec	7.5
F3	50 Sec	8.
F4	60 Sec	12.6
F5	1 min 3 Sec	8
F6	3 min 10 sec	6
F7	45 Sec	7
F8	2 min 5 sec	5
F9	80 sec	10.5
F10	40 **Sec**	>12
F11	30 **Sec**	>12
F12	1 min 6 **Sec**	>12

Invitro drug release studies

The in-vitro dissolution studies of floating tablets

Table 6: Cumulative % release of formulations F1-F4

Time (hrs.)	F1±SD	F2 ±SD	F3±SD	F4±SD
0.25	38.93±0.51	24.96±0.65	19.87±1.23	6.76±0.54
0.50	45.34±0.45	32.32±.84	24.05±1.98	18.86±0.84
0.75	55.87±0.95	40.02±0.94	38.45±0.98	24.67±0.38
1	65.08±0.45	54.98±0.97	42.99±0.76	39.97±0.32
2	81.90±0.62	65.04±0.76	59.94±0.46	52.45±0.39
4	98.56±0.72	85.43±0.49	62.54±0.59	60.66±0.76
6	---	97.67±0.39	78.09±0.93	77.76±0.49
8	---	---	99.86±0.49	86.12±0.96
10	---	---	---	98.34±0.67
12	---	---	---	---

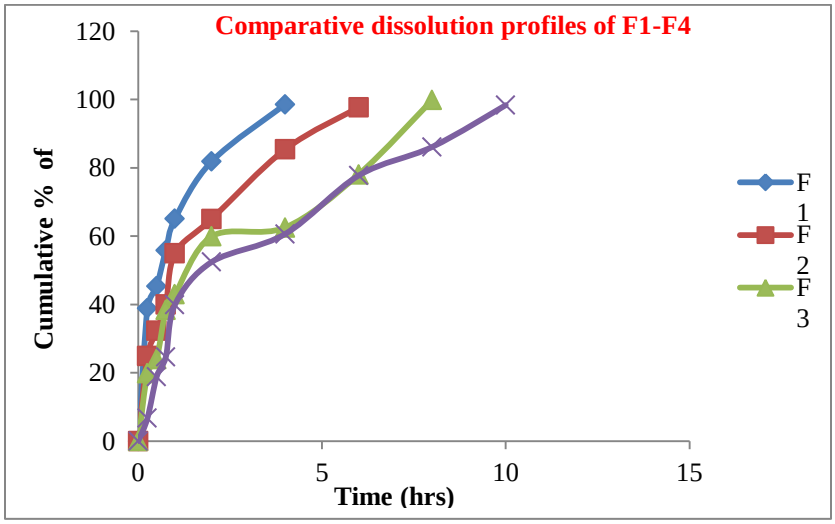

Fig 3: Comparative profiles of dissolution F1-F4

Table 7: Cumulative % release of formulations F5-F8

Time (hrs)	F5±SD	F6 ±SD	F7±SD	F8±SD
0.25	35.92±0.31	26.26±0.18	15.82±1.13	9.27±0.88
0.50	9.74±0.73	30.52±0.52	20.05±1.98	12.26±0.18
0.75	55.14±0.35	49.20±0.25	26.24±0.98	29.47±0.52
1	69.10±0.25	63.18±0.24	39.18±0.76	35.92±0.32
2	72.70±0.23	70.04±0.76	58.84±0.24	47.25±0.49
4	97.15±0.45	89.29±0.19	68.52±0.62	52.33±0.54
6	---	96.77±0.32	89.10±0.45	70.25±0.60
8	---	---	97.82±0.29	78.69±0.72
10	---	---	---	88.24±0.56
12	---	---	---	97.23±0.66

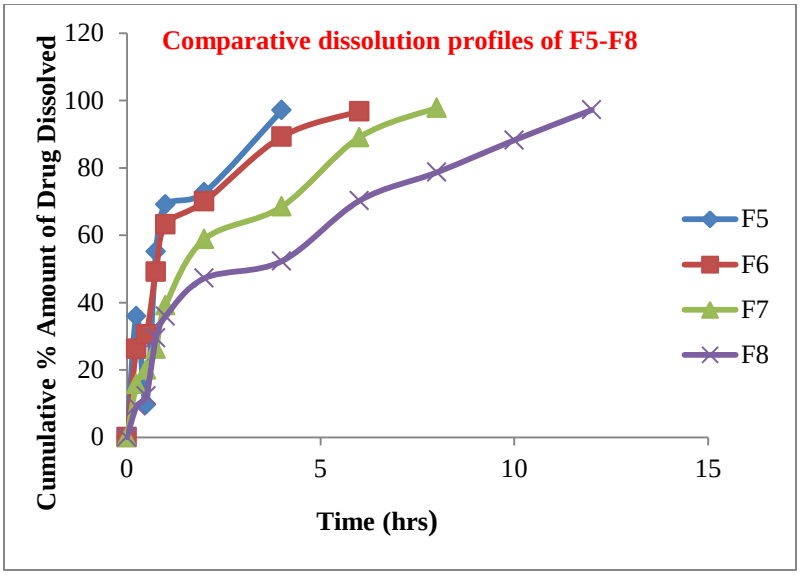

Fig 4: Comparative dissolution profiles of F5-F8

Table 8: Cumulative % release of formulations F9-F12

Time (hrs)	F9±SD	F10 ±SD	F11±SD	F12±SD
0.25	13.47±0.47	10.96±0.65	5.87±1.52	3.76±0.32
0.50	20.34±0.45	19.32±0.84	15.25±1.92	9.86±0.58
0.75	36.87±0.95	32.02±0.94	28.45±0.48	20.67±0.88
1	40.08±0.45	39.98±0.97	36.99±0.82	29.97±0.93
2	63.90±0.62	58.04±0.76	45.94±0.46	32.45±0.48
4	78.56±0.72	69.43±0.49	58.54±0.59	39.66±0.77
6	84.96±0.23	79.67±0.39	69.09±0.93	49.76±0.29
8	96.29±0.54	85.0±0.59	76.86±0.49	59.12±0.71
10	---	97.03±0.98	89.02±0.58	67.34±0.52
12	---	---	99.92±0.69	75.56± 0.95

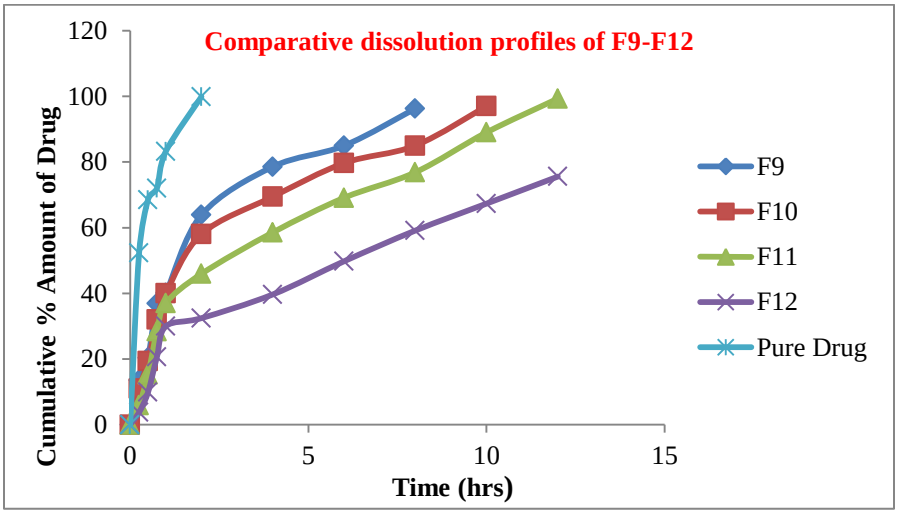

Fig 5: Comparative dissolution profiles of F9-F12 & Pure Drug

Drug release kinetics

Table 9: Drug release kinetics of prepared floating formulations (dependent model method

	Correlation Co-efficient (r) value				Korsemeyer - Peppas	
Formulation	**Zero order**	**First order**	**Higuchi's**	**Erosion**	**r value**	**n value**
F1	0.744	0.983	0.596	0.733	0.984	0.353
F2	0.835	0.97	0.613	0.826	0.853	0.345
F3	0.863	0.936	0.615	0.855	0.954	0.441
F4	0.891	0.894	0.709	0.886	0.911	0.630
F5	0.703	0.946	0.638	0.698	0.441	0.558
F6	0.759	0.949	0.590	0.826	0.921	0.427
F7	0.899	0.952	0.694	0.893	0.973	0.549
F8	0.903	0.924	0.703	0.898	0.925	0.569
F9	0.840	0.967	0.671	0.834	0.943	0.556
F10	0.850	0.935	0.667	0.844	0.935	0.547
F11	**0.992**	**0.874**	**0.726**	**0.898**	**0.900**	**0.618**
0.906	0.883	0.646	0.734			
0.921	0.986	0.311	0.700			

Drug-polymer compatibility studies

IR spectroscopic studies

Enalapril pure drug and Enalapriland polymer physical mixture, optimized tablet formulation were subjected to IR spectroscopic studies to check the compatability among them.No prominent difference was observed in the IR peaks of Enalapril+ HPMC 100 K physical mixtures and optimized formulations upon comparison with the peaks of drug and polymer alone, which may considered that Enalapriland HPMC K100M are compatible enough without any interactions.

SUMMARY AND CONCLUSION

Various approaches have been developed to retain the dosage form in the stomach. Gastric floating drug delivery systems offer numerous advantages over other gastric retention systems. There are no reports on the formulation of gastric floating drug delivery systems of enalapril. Hence, in the present investigation, GFDDS of Enalapril were developed with hydrophilic polymers like HPMC K100M, xanthan gum and guar gum to deliver Enalaprilto the upper parts of the small intestine in a controlled manner to improve its bioavailability. The GFDDS of Enalapril were developed in the form of tablets comprising of an effervescent agent. The concentration of the effervescent agent greatly influenced the floating lag time. The GFDDS of Enalapril prepared from HPMC remained intact and the compactness of the tablet was not affected during the *in vitro* dissolution test. It was found that the drug release from the GFDDS of Enalapril mainly depended upon the concentration of polymer present in the GFDDS for all the twelve formulations. By increasing the concentration of the polymer, decreased dissolution rates were obtained for the all the polymers. The slow rate of polymer hydration and the presence of effervescent agent caused a burst release initially. By increasing the proportion of the effervescent agent the porosity produced by the entrapped gas increased and dissolution rate was increased. The dissolution data were fitted to four popular release models such as zero-order, first-order, diffusion and erosion equations to determine the release mechanism. The correlation coefficients and the slope values from Higuchi plots indicated that the release mechanism followed diffusion and erosion with zero order kinetics. The results of the present study thus clearly indicated that GFDDS for Enalapril were successfully formulated by using different grades of hydrophilic polymers such as HPMC K100, xanthan and guargum. From the results it can be concluded that F11 with HPMC K100M, and sodium bicarbonate as gas generating agent provides the 99.92 % of drug release up to 12hours.

CONCLUSION

The objective of the present work was preparing floating tablets to achieve controlled drug release pattern. The gas generating agent sodium bicarbonate was added in specific concentration (15%) in all formulations to attain desired floatability and total floating time. Different polymers like guar gum,

xanthan gum and HPMC K15M were used in three different ratios (1:1, 1:1.5, 1:2 %) as retarding polymers. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F12 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. From the dissolution data it was evident that formulation F11 was found to be best formulation with maximum % drug release of 99.90% in 12 hours. The drug release pattern from optimized formulation F11 followed zero order kinetics that is drug release rate is independent of its concentration of dissolved substance.

REFERENCES

[1]. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery system. Expert Opin Drug Deliv. 3(2), 2006, 217- 33.

[2]. Iannucelli V, Coppi G, Bernabei MT, Camerorni R. Air compertment multiple-unit system for prolonged gastric residence. Part-I. Formulation study. Int J Pharm. 174(1-2), 1998, 47-54.

[3]. Rouge N, Buri P, Doelker E. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Int J Pharm.136(1-2), 1996, 117 -139

[4]. T. Higuchi. Mechanism of sustained action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. ***J. Pharm.Sci.*** 52, 1963, 1145-9.

[5]. N.A. Peppas,. Analysis of Fickian and non-Fickian drug release from polymers. ***Pharm.Acta.Helv***. **60,** 1985, 110–111.

[6]. C .Mahesh, J. Paras, C. Sachin, S. Rajesh, V. Pradeep. Development of sustained release gastro retentive drug deliverysystem for ofloxacin: In vitro and in vivo evaluation. **Int.J.Pharma.** 304, 2005, 178–184.

[7]. G. Penners, K. Lustig and P.V.G. Jorg. Expandable pharmaceutical forms, US ***patent*** 5, 1997, 651 985.

[8]. L. Whitehead, J.H. Collett, and J.T. Fell. Amoxycillin release from a floating dosage form based on alginates. ***Int.J.Pharm.*** 210(1-2), 2000, 45-49.

[9]. S. Li, S. Lin, T.W. Chien, B.P. Daggy and H.L. Mirchandani. Statistical optimization of gastric floating system for oral controlled delivery of calcium. ***AAPS Pharm.Sci.Tech.*** 2(1), 2001.

[10]. B.S. Dave, A.F. Amin and M.M. Patel. Gastroretentive drug delivery system of ranitidine hydrochloride: formulation and in vitro evaluation. ***AAPS Pharm.Sci.Tech.*** 5(2), 2004, 1-6.

[11]. British Pharmacopoeia, 1, 2005, 367-368.

[12]. Remington, the Science and Practice of Pharmacy, 21, 2009, l-11.

[13]. Goodman and gilman, The Pharmacology Basis Of Therapeutics, 9, 1996, 831- 832.

[14]. Martindale. The Complete Drug Reference. 838 CIMS, OCT2009- 32, 2010, 88-89.