WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 6, Issue 1, 467-478. Research Article ISSN 2277– 7105

FORMULATION AND IN VITRO EVALUATION OF FLOATING MICROSPHERES OF AN ANTI DIABETIC DRUG

Donthureddy Sarika*, G. Rama Krishna[1] and Syed Munner[2]

Department of Pharmaceutics, K.C. Reddy Institute of Pharmaceutical Sciences, Jangamguntla Palem (V), Medikondur (Md), Guntur-522438, A.P, India.

Article Received on
12 Nov. 2016,

Revised on 02 Dec. 2016,
Accepted on 22 Dec. 2016

DOI: 10.20959/wjpr20171-7288

***Corresponding Author**
Donthureddy Sarika
Department of Pharmaceutics, K.C. Reddy Institute of Pharmaceutical Sciences, Jangamguntla Palem (V), Medikondur (Md), Guntur-522438, A.P, India.

ABSTRACT

The present study involved, preparation of Glipizide floating microspheres to improve the bioavailability by increasing residence time in stomach. In preformulation study the drug Glipizide was subjected to various preformulation studies namely solubility, melting point. Micromeritic properties of the prepared microspheres were evaluated for bulk density, Carr's index and angle of repose. Drug–polymer interaction was studied using FTIR analysis. The results showed that there were no changes in the IR spectra of pure Glipizide in the presence of Cellulose acetate and Cellulose acetate butyrate. Thus revealing compatibility of the selected drug with the polymer. Among the different Glipizide floating microspheres formulations, the formulation F1 was selected as the ideal formulation, based on its micromeritic properties, floating behavior, drug loading, drug entrapment efficiency and percentage of drug released for a prolonged period over 12h.

KEYWORDS: Glipizide floating microspheres, Bioavailability, Micromeritic properties, Drug–polymer interaction, floating behavior, Drug loading, Drug entrapment efficiency, Percentage of drug released.

1. INTRODUCTION

Oral controlled release dosage forms have been developed over the past three decades due to their considerable therapeutic advantages such as ease of administration, patient compliance and flexibility in formulation.[1] One requisite for successful performance of oral controlled drug delivery system is that drug should have good absorption throughout the gastrointestinal tract, preferably by passive diffusion.[2] These considerations have led to the development of

a unique oral controlled release dosage form with Gastro retentive properties. After oral administration, such a dosage form (DF) would be retained in the stomach and releases the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption sites in the upper gastrointestinal tract. Gastro retentive dosage forms (GRDFs) can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. It is also suitable for local drug delivery to the stomach and proximal small intestines.[3,4]

Gastro retentive dosage forms are designed to be retained in the stomach for a prolonged time and release their active ingredients and thereby enable sustained and prolonged input of the drug to the upper part of the gastrointestinal tract. This technology has generated enormous attention over the last few decades owing to its potential to improve the oral delivery of some important drugs for which prolonged retention in the upper GI tract can greatly improve their oral bioavailability and/or their therapeutic outcome.[5,6] Drugs delivered in this manner have a lower level of side effects and provide their therapeutic effects without the need for repeated dosages or with a low dosage frequency. Sustained release in the stomach is also useful for therapeutic agents that the stomach does not readily absorb, since sustained release prolongs the contact time of the agent in the stomach or in the upper part of the small intestine, which is where absorption occurs and contact time is limited.[7,8]

Types of Gastro retentive Dosage Forms[9, 10]

A. Expandable systems

B. Bio/Mucoadhesive systems

C. Floating drug delivery systems

a. Non-effervescent systems

i. Colloidal gel barrier system

ii. Microporous compartment system

iii. Alginate beads

iv. Hollow microspheres / Microballons

b. Gas-generating (Effervescent) systems

D. Combination of floating, mucoadhesion and swellable systems

Floating drug delivery systems: Floating drug delivery systems have bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system, after release of drug; the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and gas-generating system.

2. MATERIALS AND METHODS

Table-1-List of Chemicals and reagents

Sl. No	Materials	Source
1	Glipizide	Microlabs
2	Cellulose acetate	Sigma-Aldrich
3	Cellulose acetate	Biochemica reagent
	butyrate	
4	Dimethyl	SD Fine chemical Ltd
	sulfoxide	
5	Methanol	Spectrochem Pvt. Ltd. Mumbai.
6	Acetone	Spectrochem Pvt. Ltd. Mumbai.
7	Ethyl acetate	Fischer scientific Ltd
8	Polyvinylalcohol	SD Fine chemical Ltd
9	Tween 80	SD Fine chemical Ltd
10	Sodium	SD Fine chemical Ltd
	hydroxide pellets	
11	Potassium	Spectrum reagent and chemicals
	dihydrogen	Pvt. Ltd., India.
	Phosphate	
12	Potassium	Thomas Baker, Mumbai, India.
	chloride	
13	n-hexane	Merck

Table-2-Formula for Method A

Batch Code	Drug/polymer ratio	Stirring rate in RPM
F1	1:1	600
F2	1:2	600
F3	1:3	600
F4	1:4	600
F5	1:5	600
F1.1	1:1	400
F1.2	1:1	800

Table-3-Formula for Method B

Batch Code	Polymer	Stirring rate in RPM
F6	Cellulose acetate butyrate	600
F7	Cellulose acetate	600

Table-4-Formula for Method C

Batch Code	Polymer	Stirring rate in RPM
F8	Cellulose acetate butyrate	600
F9	Cellulose acetate	600

3. RESULTS

Table-5-Preparation of Standard solution

Weight of glipizide taken	100mg
Volume made up to	100ml
Concentration of standard solution	100µg/ml
Aliquots of volume made up to	25ml

Table-6-Data for standard graph of Glipizide in 1.2pH buffer at 276nm.

Concentration (g/ml)	Absorbance (nm)
2	0.064
4	0.123
6	0.193
8	0.245
10	0.318
12	0.379
14	0.431
16	0.510
18	0.563
20	0.625

Table-7-Data of characterization of glipizide floating microspheres F6 (CAB)-F7 (CA)

Batch Code	Mean Particle size (µm)	Bulk Density (gm/ml)	Carr's Index	Hausner's ratio	Angle of repose (θ)
F6	205.62±5.54	0.256 ±0.04	14.56±0.09	1.07 ±0.09	27.33±0.19
F7	212.44±3.72	0.255±0.01	14.47±0.17	1.11 ±0.06	26.47±0.58

Table-8-Data of characterization of glipizide floating microspheres F1-F5 (CA)

Batch Code	Mean Particle size (µm)	Bulk Density (gm/ml)	Carr's Index	Hausner's Ratio		Angle of repose (θ)
Glipizide	***	0.167 ±0.01	24.38±0.16	1.43	±0.07	***
F1	164.56±3.78	0.277±0.01	4.77±0.16	0.96 ±0.07		22.73±0.22
F2	169.43±4.27	0.270±0.02	6.15±0.12	0.98 ±0.02		22.81 ±0.62

F3	172.64±1.47	0.267±0.02	8.33 ±0.21	0.99	±0.08	21.27 ±0.56
F4	175.72±2.69	0.264 ±0.01	10.34±0.26	1.01	±0.06	23.64 ±0.45
F5	189.64±0.53	0.261 ±0.03	12.62±0.19	1.04 ±0.04		24.70 ±0.59

Table-9-Data of characterization of Glipizide floating microspheres F1.1(400rpm)-F1.2(800rpm) using Cellulose acetate

Batch Code	Mean Particle size (µm)	Bulk Density (gm/ml)	Carr's Index	Hausner's Ratio	Angle of repose (θ)
F1.1	170.73±5.63	0.275 ±0.03	4.18 ±0.26	0.95 ±0.02	23.41±0.26
F1.2	150.80±7.27	0.272 ±0.02	4.92 ±0.23	0.96 ±0.06	22.86±0.27

Table-10-Data of Percentage yield, drug loading and encapsulation efficiency of Glipizide microspheres for F1.1 (400rpm)-F1.2 (800rpm) using Cellulose acetate

Batch code	Percentage Yield (%)	Drug loading (%)	Encapsulation efficiency (%)
F1.1	93.33	42.01±0.56	84.46±0.23
F1.2	93.24	41.57±0.66	83.14±0.71

Table-11-Data of Percentage yield, drug loading and encapsulation efficiency of Glipizide microspheres for F1-F5 (CA)

Batch code	Percentage Yield (%)	Drug loading (%)	Encapsulation Efficiency (%)
F1	94.33	44.52±0.27	89.5±0.65
F2	93.24	27.46±0.02	82.66±0.35
F3	90.53	19.82±0.40	81.12±0.76
F4	87.55	15.51±0.85	77.74±0.62
F5	86.26	12.44±0.05	74.82±0.09

Table-12-Data of Percentage yield, drug loading and encapsulation efficiency of Glipizide microspheres for F6(CAB)-F7(CA)

Batch code	Percentage Yield (%)	Drug loading (%)	
F6	83.12	3.49±0.48	73.38±0.81
F7	82.06	3.27±0.19	70.48±0.38

Table-13-Results of buoyancy (%) for Glipizide floating microspheres F1-F5 (CA)

Batch code	Buoyancy (%)
F1	72.2±0.4
F2	73.3±1.5
F3	75.6±2.2
F4	76.7±3.4
F5	77.4±2.1

Table-14-Results of buoyancy (%) for glipizide floating microspheres F6 (CAB)-F7(CA)

Batch code	Buoyancy (%)
F6	88.8±4.8
F7	87.8±1.9

Table-15-Results of buoyancy (%) for glipizide floating microspheres F1.1 (400rpm)-F1.2 (800rpm) using Cellulose acetate

Batch code	Buoyancy (%)
F1.1	71.4±0.2
F1.2	72.1±0.3

Table-16-Cumulative percentage drug release profile of Glipizide floating microspheres F1-F5 (CA)

Time (hrs)	Batch code				
	F1	F2	F3	F4	F5
0.5	4.15±0.74	3.35±0.73	2.59±0.06	2.03±0.02	1.52±0.01
1	7.28±0.01	5.99±0.89	4.47±0.64	3.38±0.60	2.82±0.48
1.5	10.66±0.61	10.08±0.22	7.77±0.77	6.54±0.78	5.43±0.38
2	14.05±0.58	14.17±0.01	10.61±0.18	9.26±0.21	8.04±0.58
3	21.86±0.65	19.46±0.16	17.92±0.25	14.91±0.19	11.09±0.50
4	26.30±0.80	23.79±0.97	22.18±0.05	17.86±0.09	16.53±0.63
5	32.05±0.36	28.86±0.20	26.20±0.78	22.84±0.35	20.46±0.36
6	40.14±0.41	35.84±0.83	33.30±0.04	28.73±0.39	25.26±0.38
7	49.28±0.29	39.96±0.47	37.57±0.54	34.63±0.08	30.28±0.65
8	56.87±0.28	44.08±0.57	40.44±0.24	38.05±0.29	33.57±0.74
9	60.57±0.35	48.45±0.09	46.13±0.80	40.57±0.64	36.87±0.20
10	69.73±0.48	55.21±0.91	52.31±0.07	45.58±0.40	39.95±0.30
11	77.86±0.69	61.75±0.48	58.25±0.48	53.52±0.97	45.42±0.62
12	81.59±0.06	71.17±0.55	66.08±0.90	61.03±0.30	52.20±0.84
13	86.61±0.76	79.40±0.75	71.34±0.20	65.16±0.08	57.04±0.36
14	90.35±0.09	85.01±0.07	76.12±0.97	69.51±0.88	61.01±0.54

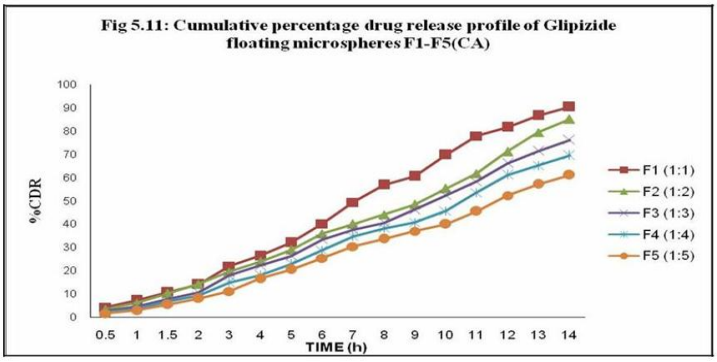

Fig-No-1: Cumulative percentage drug release profile of Glipizide floating microspheres F1-F5.

Table-17-Cumulative percentage drug release profile of Glipizide floating microspheres F6 (CAB)-F7(CA)

Time	Batch Code	
(hrs)	F6	F7
0.5	1.06±0.40	1.02±0.05
1	2.34±0.20	1.83±0.80
1.5	3.83±0.43	3.26±0.87
2	5.32±0.82	4.90±0.51
3	7.67±0.50	6.74±0.74
4	10.45±0.00	8.38±0.77
5	13.01±0.52	10.64±0.20
6	15.58±0.33	12.89±0.89
7	19.00±0.55	16.17±0.87
8	21.58±0.02	18.64±0.58
9	25.43±0.46	21.31±0.97
10	28.01±0.64	24.20±0.06
11	31.02±0.66	26.88±0.06
12	34.04±0.02	29.15±0.54
13	35.78±0.03	30.82±0.04
14	38.37±0.34	33.09±0.94

Table-18-Cumulative percentage drug release profile of Glipizide floating Microspheres F1.1 (400rpm)-F1.2 (800rpm) using Cellulose acetate

	Batch code	
Time	F1.1	F1.2
(hrs)		
0.5	2.21±0.05	1.68±0.88
1	4.42±0.35	4.10±0.33
1.5	7.62±0.14	7.72±0.67
2	11.76±0.59	11.35±0.41
3	17.46±0.77	15.95±0.06
4	21.90±0.81	20.55±0.22
5	25.86±0.22	24.91±0.76
6	31.29±0.43	30.25±0.29
7	34.76±0.75	35.83±0.53
8	41.68±0.32	40.94±0.14
9	47.62±0.40	45.32±0.94
10	52.83±0.45	49.96±0.34
11	58.54±0.20	54.12±0.00
12	64.74±0.70	58.52±0.24
13	70.46±0.76	64.37±0.72
14	76.19±0.44	70.23±0.84

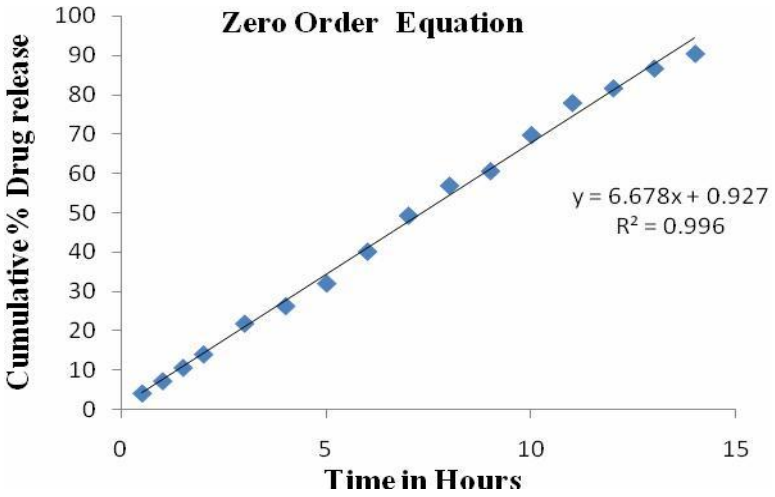

Fig-No-2: Zero order release kinetics of Glipizide microspheres from F1 (CA)

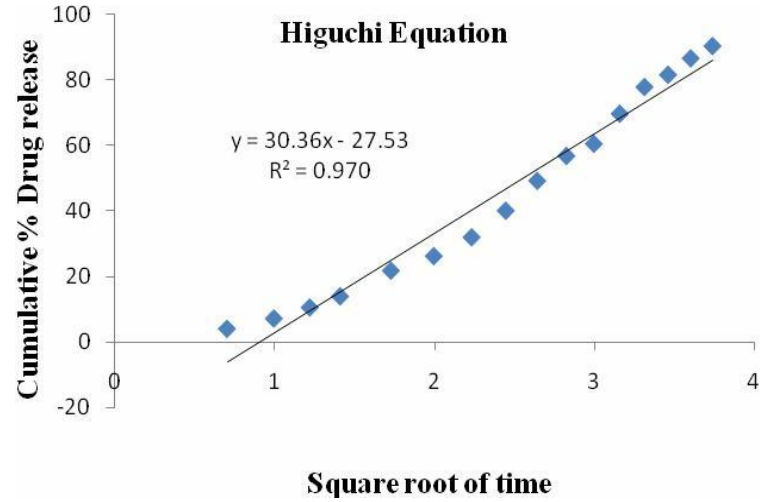

Fig-No-3: Higuchi model release kinetics of Glipizide microspheres from F1(CA)

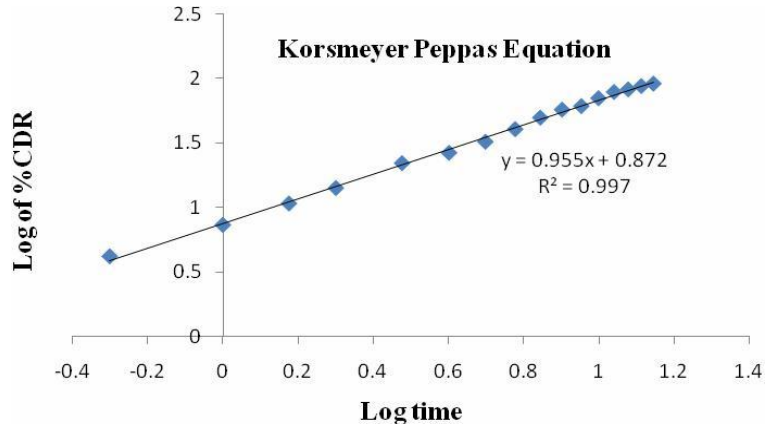

Fig-No-4: Korsmeyer-Peppas model release kinetics of Glipizide microspheres from F1 (CA)

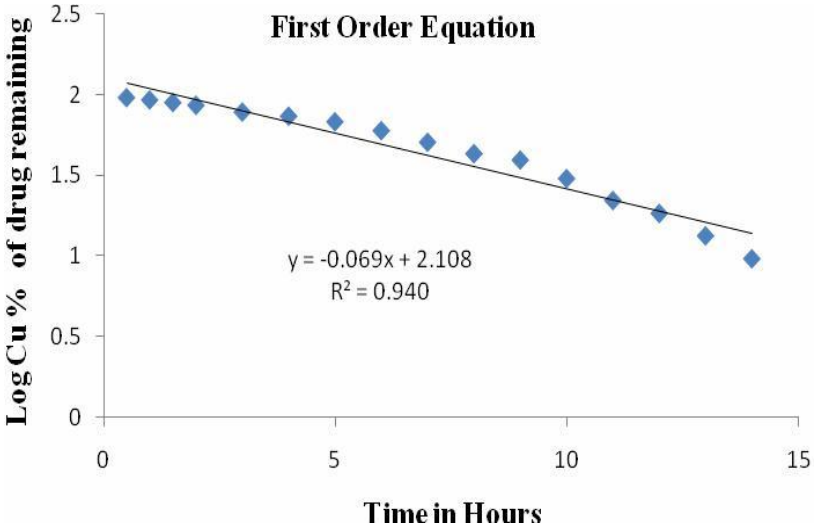

Fig-No-5: First order release kinetics of Glipizide microspheres from F1 (CA)

Table-19-Release kinetics of Glipizide microspheres from F1 (CA)

Time (h)	Square root of time	Log time	CDR	%CDR	Log of %CDR	Log Cu % of drug remaining
0.5	0.7071	-0.3010	3.48	4.15	0.6188	1.9815
1	1	0	5.81	7.28	0.8621	1.9671
1.5	1.2247	0.1760	8.42	10.66	1.0280	1.9510
2	1.4142	0.3010	11.05	14.05	1.14785	1.9342
3	1.7320	0.4771	16.28	21.86	1.3397	1.8928
4	2	0.6020	21.24	26.30	1.4200	1.8674
5	2.2360	0.6989	27.07	32.05	1.5058	1.8321
6	2.4494	0.7781	34.94	40.14	1.6036	1.7771
7	2.6457	0.8450	39.91	49.28	1.6926	1.7051
8	2.8284	0.9030	44.02	56.87	1.7549	1.6347
9	3	0.9542	48.71	60.57	1.7822	1.5957
10	3.1622	1	52.25	69.73	1.8434	1.4809
11	3.3166	1.0413	56.95	77.86	1.8913	1.3450
12	3.4641	1.0791	61.08	81.59	1.9116	1.2650
13	3.6055	1.1139	64.92	86.61	1.9376	1.1265
14	3.7416	1.1461	69.35	90.35	1.9559	0.9844

Table-20-Data of stability evaluation of glipizide microspheres of F1(CA)

Evaluation parameter		Observation in Day					
	Initial	Room temperature			45± 1°C / 75% RH		
		10	20	30	10	20	30
Physical appearance	Hard gelatin	No change	No change	No change	No Change	No change	No change

	capsules						
Average	0.177	0.181	0.185	0.191	0.183	0.187	0.194
weight of							
capsule(g)							
FTIR	Performed	---	---	No	---	---	No
pattern				change			change
Drug	100	99.72±	99.65±	99.58±	99.55	99.49	99.41±
content*		0.05	0.11	0.09	±0.09	±0.13	0.09
(%w/w)							
% CDR*	90.46	90.39±	90.27±	90.43±	90.32	90.17	89.86
	±0.72	0.04	0.35	0.54	±0.12	±0.3	±0.2

4. SUMMARY AND CONCLUSION

The present investigation was to prepare floating microspheres of Glipizide to improve the bioavailability by increasing residence time in stomach.

Glipizide floating microspheres were prepared by three methods. Method A: solvent evaporation method, Method B: o/w emulsification method and Method C: emulsion solvent evaporation, using different concentration of Cellulose acetate and Cellulose acetate butyrate as polymers. Liquid paraffin and Acetone-Ethyl acetate, Ethanol system were used for the preparation of microspheres. Polyvinyl alcohol and span 80 were used as surfactants and n-hexane was added as a non-solvent to the processing medium to solidify the microspheres. Method C led to formation of crystals. So, Method C could not be used for further studies.

The Preformulation parameters like melting point, solubility study were evaluated and FT-IR study was carried out to check any possible interactions between the drug and the excipients, thus confirming the compatibility between the selected range of the drugs and the polymers.

The microspheres were evaluated for percentage yield, Mean Particle size, Micromeritic properties, Drug loading and Drug entrapment efficiency. The mean particle size increased and the drug release rate, drug loading and drug entrapment efficacy decreased at higher polymer concentration. It also showed that as the particle size increased with the bulk density decreased.

FT-IR studies were carried out and there was no interaction between the selected drug and excipients under study. Scanning electron microscopy, showed good spherical geometry as evidenced by the photographs. The drug release studies were carried out using six basket dissolution apparatus USP type II. The cumulative percentage drug release from the microspheres decreased with increase in concentration of polymer.

The in vitro release data obtained from Formulations-F1 (CA), F1.1(CA), F1.2(CA) was fitted to zero order plot and Korsmeyer-Peppas equation. The drug release from the formulations F1 (CA), F1.1 (CA), F1.2(CA) was found to be non-Fickian diffusion.

A study was carried out to assess the stability of the formulations F1 (CA), F6(CAB), F7(CA) at room temperature and 40°C/75%RH over a period of 2 months. There were no significant changes in their physical appearance, average weight of capsule and FTIR pattern. The drug contents of the samples analyzed after 20, 40 and 60 days of storage was similar to the initial drug content.

From all the prepared formulations, the ideal formulation F1 (CA) was selected based on micromeritic properties, drug loading, drug entrapment efficiency, floating behavior and *in vitro* release studies.

5. REFERENCES

1. Garg R, Gupta GD. Progress in Controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research.* 2008; 7: 1055-1056.
2. Patil JM, Hirlekar RS, Gide PS and Kadam VJ. Trends in Floating Drug Delivery Systems. *Journal of Scientific and Industrial Research*. 2006; 65: 11-21.
3. Furquan Khan N, Mohamed Dehghan HG. Gastroretentive drug delivery systems: A patent perspective. *International Journal of Health research*. 2009; 2: 23-44.
4. Shweta Arora, Javed Ali, Alka Ahuja, Roop Khar K and Sanjula Babooota. Floating Drug Delivery Systems: A Review. *AAPS Pharm Sci Tech.* 2005; 6: E372-390.
5. Mayavanshi AV, Gajjar SS. Floating drug delivery systems to increase gastric retention of drugs: A Review. *Research J.Pharm and Tech.* 2008; 1: 345-348.
6. Tortora and Grabowski. Principles of Anatomy and Physiology: 866.
7. Ramesh Putheti R and Mahesh Patil C. Pharmaceutical Formulation and Development of Floating and Swellable Sustained Drug Delivery Systems: A Review. *e-Journal of Science and Technology*. 2009; 4: 1-12.
8. Vyas SP. Khar. "Targeted and Controlled Drug Delivery Novel Carrier System", Ist Ed., CBS Publishers and Distributors. 2002; 417-54.
9. Tanwar YS. Floating Microspheres: Development, Charecterisation and Applications. Pharmainfo.net.
10. Kumaresh Soppimath S, Anandrao Kulkarni R and Tejraj Aminabhavi M. Development of Hollow Microspheresas Floating Controlled-Release Systems For Cardiovascular

Drugs: Preparation and Release Characteristics. *Drug Development and Industrial Pharmacy*. 2001; 27: 507–515.