Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206**
Sch. Acad. J. Pharm., 2013; 2(5):365-372

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Research Article

Development and Evaluation of Floating Pulsatile Microspheres of Metoprolol Tartrate Using Emulsification-Solvent Evaporation Technique

Shivhare U. D.*, Rathod H. D., Mathur V. B.
Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road, Nagpur - 441 110, India.

***Corresponding author**
Shivhare U. D
Email: udshivhare@gmail.com

Abstract: The purpose of present work was to develop Metoprolol tartrate microspheres for floating pulsatile release intended for chronopharmacotherapy. Floating pulsatile concept was applied to increase the gastric residence of the dosage form having lag phase followed by a burst release. The floating pulsatile microspheres were prepared by emulsification solvent evaporation technique. The best batch exhibited excellent floating time as well as release at desired time. The particle size was controlled by changing polymer concentration and emulsifier concentration. Polymers used for the preparation were Eudragit L 100 and Eudragit S 100. The floating microspheres provided two phase release pattern with initial lag time during floating in acidic medium followed by rapid release in phosphate buffer. This approach suggested the use of floating pulsatile microsphere as promising drug delivery for site and time specific release of Metoprolol tartrate for chronotheraphy of hypertension.
Keywords: Microspheres, Metoprolol tartrate, Eudragit L 100, Eudragit S 100, Emulsification-solvent evaporation technique, hypertension

INTRODUCTION

Various diseases like asthma, hypertension and arthritis show circadian variation that demand time-scheduled drug release for effective drug action, for example, inflammations associate with morning body stiffness, asthma and heart attack in the early hours of the day. In this principle, an "ideal" dosage form ought to be taken at a convenient time before sleep, providing maximum drug release in the morning hours [1].

A pulsatile drug delivery system that can be administered at night before sleep but that releases drug early morning would be a promising chronopharmaceutics system. The combinations of floating- pulsatile principle are very suitable for above mentioned diseases.

Floating pulsatile drug delivery system concept was applied to increase the gastric residence of the dosage form, thereby targeting site specific drug release in the upper gastrointestinal tract. Pulsatile drug delivery system (PDDS) is characterized by a time period of no release (lag time) followed by a rapid (burst) and complete drug release. A pharmaceutical dosage form capable of delivering therapeutic agents into the body in a time-controlled or position-controlled pulsatile release fashion, is composed of a single unit system (tablet, capsule) or multiple unit system having multitude of multicoated particulates [2-5].

Metoprolol tartrate is a β adrenoreceptor blocking agent used for the treatment of angina pectoris, hypertension and in myocardial infaraction.

Therefore, the objective of the present study was the development and evaluation of floating pulsatile microspheres containing Metoprolol tartrate. Here the content of the dosage form or the dosage form is retained in stomach in the floating condition by suitable mechanism and after a predetermined lag time release the drug. In the present study suitable polymer and excipients were selected to keep the microspheres in the floating condition and formulation is designed to provide the effective drug delivery after a predicted time lag.

MATERIALS AND METHODS

Metoprolol tartrate was a generous gift sample obtained from ZIM Labs, Nagpur, India and Eudragit S 100 and Eudragit L 100 were received as gift samples from Vikram Thermo India Ltd, Gandhinagar and Evonik Degussa, Mumbai respectively.

Preparation of microspheres

Accurately weighted amount of Eudragit L-100 and S-100 were dissolved in 25 ml of acetone to form a homogenous polymers solution. Core material, i.e. Metoprolol tartrate was dispersed in it and mixed thoroughly. Sodium bicarbonate and 5% crosscarmilose was added to this solution. This organic phase was slowly poured at 50-60°C into liquid paraffin (100 ml) containing Span-80 for 2 h with stirring to form a

uniform emulsion. Thereafter, it was allowed to attain room temperature and stirring was continued until residual acetone evaporated and smooth-walled, rigid and discrete microspheres were formed. The microspheres were collected by decantation and the product was washed with n-hexane and dried at room temperature for 3 hrs [6].

Particle size analysis

Particle size of microspheres was determined by using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [7-8].

Determination of encapsulation efficiency

About 10 mg of accurately weighed drug loaded microspheres were added into 10 ml of methanol and the drug concentration were determined spectrophotometrically at 223 nm in UV-visible spectrophotometer [9]. Encapsulation efficiency was calculated by the following formula:

$$\text{Encapsulation efficiency (\%)} = \frac{\text{Experimental drug content x100}}{\text{Theoretical drug content}}$$

Floating ability of microspheres:

Floating microspheres (100 mg) were placed in 0.1 N HCl (100 ml) containing 0.02% Tween 80. The mixture was stirred at 100 rpm using a magnetic stirrer and the floating times were recorded [10].

***In vitro* drug release studies:**

The dissolution studies of the microspheres equivalent to 100mg of metoprolol tartrate were performed using Dissolution Apparatus USP Type II. Volume of the dissolution medium was 900 ml with a stirring speed of 100 rpm and the temperature was maintained at 37 ºC ± 0.5^0C. These conditions were kept constant for all studies.The drug release study was carried out in 0.1 N HCl (pH 1.2) for a time period equivalent to floating time which varied for each batches of microspheres, followed by dissolution in phosphate buffer, pH 7.4 till complete release of drug. During dissolution 10 ml sample was withdrawn at different time intervals of 1 to 12 h and same was replaced with equal volume of fresh medium. The withdrawn samples were filtered through Whatmann filter paper no.42 and absorbance was measured at 223 nm using UV–Visible Spectrophotometer [11].

Cumulative percent drug released was found out at each time interval and graph was plotted between cumulative % drug released and time in h.

Treatment of drug release data with different kinetic equations:

Analysis of drug release from microspheres was performed with a flexible model that can identify the contribution to overall kinetics, mechanism of drug release and the dissolution data obtained for optimized formulation was treated with the different release kinetic equations [12].

RESULTS AND DISCUSSION

Floating pulsatile microspheres were prepared using emulsification solvent evaporation technique. Table 1 shows the composition of various formulations.

Table 1: Formulation Composition of Floating Pulsatile Microspheres of Metoprolol Tartrate

Sl. No.	Formulation code	Drug	Polymer	Sodium Bicarbonate	Span 80
1.	A1	200	200	0.5	1
2.	A2	200	200	0.5	1.5
3.	A3	200	200	0.5	2
4.	A4	200	200	0.5	2.5
5.	B1	200	200	1	1
6.	B2	200	200	1	1.5
7.	B3	200	200	1	2
8.	B4	200	200	1	2.5
9.	C1	200	200	1.5	1
10.	C2	200	200	1.5	1.5
11.	C3	200	200	1.5	2
12.	C4	200	200	1.5	2.5
13.	D1	200	200	2	1
14.	D2	200	200	2	1.5
15.	D3	200	200	2	2
16.	D4	200	200	2	2.5
17.	E1	200	400	0.5	1
18.	E2	200	400	0.5	1.5
19.	E3	200	400	0.5	2
20.	E4	200	400	0.5	2.5

21.	F1	200	400	1	1
22.	F2	200	400	1	1.5
23.	F3	200	400	1	2
24.	F4	200	400	1	2.5
25.	G1	200	400	1.5	1
26.	G2	200	400	1.5	1.5
27.	G3	200	400	1.5	2
28.	G4	200	400	1.5	2.5
29.	H1	200	400	2	1
30.	H2	200	400	2	1.5
31.	H3	200	400	2	2
32.	H4	200	400	2	2.5
33.	I1	200	600	0.5	1
34.	I2	200	600	0.5	1.5
35.	I3	200	600	0.5	2
36.	I4	200	600	0.5	2.5
37.	J1	200	600	1	1
38.	J2	200	600	1	1.5
39.	J3	200	600	1	2
40.	J4	200	600	1	2.5
41.	K1	200	600	1.5	1
42.	K2	200	600	1.5	1.5
43.	K3	200	600	1.5	2
44.	K4	200	600	1.5	2.5
45.	L1	200	600	2	1
46.	L2	200	600	2	1.5
47.	L3	200	600	2	2
48.	L4	200	600	2	2.5

The effects of polymer concentration, emulsifier concentrations and sodium bicarbonate on the particle size, angle of repose aother properties of microspheres were studied (Table 2)

Table 2: Characterization of Prepared Microspheres

Code	Mean Particle size (µm)	Angle of repose (θ)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's Index (%)	Hausner's ratio	Encapsulation Efficiency (%)	Floating Time (min)	Drug Content (%)
A1	712.9±18.4	35.52	0.285	0.322	11.49	1.12	73.12	135	36.56
A2	696.1±12.5	32.00	0.294	0.338	13.01	1.14	72.98	145	36.49
A3	679.4±11.2	29.03	0.298	0.363	17.90	1.21	72.22	150	36.11
A4	655.8±15.8	27.74	0.303	0.370	18.10	1.22	71.34	160	35.67
B1	722.3±23.3	34.56	0.289	0.350	17.42	1.21	73.35	200	36.67
B2	706.8±19.3	31.21	0.294	0.392	25.00	1.33	72.86	215	36.43
B3	687.0±13.7	28.36	0.317	0.392	19.13	1.23	72.42	230	36.21
B4	632.5±8.3	27.11	0.327	0.425	23.05	1.26	71.55	245	35.77
C1	783.6±9.2	33.66	0.298	0.363	17.90	1.21	73.85	255	36.92
C2	752.1±8.1	30.45	0.303	0.370	18.10	1.22	73.19	265	36.59
C3	724.0±18.8	27.74	0.333	0.392	15.05	1.17	72.78	270	36.39
C4	712.5±19.9	26.56	0.338	0.434	22.11	1.28	71.41	285	35.70
D1	747.0±19.6	32.82	0.317	0.392	19.13	1.23	73.22	260	36.61
D2	718.2±23.7	29.72	0.327	0.392	16.58	1.19	72.86	275	36.43
D3	682.0±33.6	27.74	0.370	0.434	14.74	1.17	72.64	280	36.32
D4	664.8±15.8	25.96	0.392	0.465	15.69	1.18	71.29	295	35.64
E1	889.6±11.5	31.21	0.327	0.425	23.05	1.26	74.84	195	24.94
E2	864.1±16.4	29.72	0.384	0.454	15.41	1.18	74.12	205	24.70
E3	851.6±7.9	28.74	0.392	0.465	15.69	1.18	73.52	220	24.50
E4	794.5±15.7	27.11	0.408	0.487	16.22	1.19	73.46	235	24.48
F1	882.3±21.9	30.45	0.333	0.392	15.05	1.17	75.12	230	25.03

F2	839.5±12.3	29.03	0.357	0.416	14.18	1.16	74.92	255	24.97
F3	791.7±19.6	28.36	0.377	0.425	11.29	1.12	74.32	270	24.77
F4	776.2±27.1	26.56	0.384	0.454	15.41	1.18	73.74	285	24.57
G1	893.5±18.7	29.72	0.312	0.384	18.75	1.23	75.36	295	25.11
G2	868.1±22.2	27.74	0.317	0.392	19.13	1.23	74.89	320	24.96
G3	803.3±10.8	25.96	0.327	0.392	16.58	1.19	74.35	335	24.78
G4	767.4±22.3	23.02	0.333	0.392	15.05	1.17	73.82	435	24.60
H1	923.6±25.6	26.56	0.327	0.377	16.58	1.19	75.66	315	25.21
H2	876.8±15.3	24.93	0.384	0.454	15.41	1.18	74.92	325	24.97
H3	827.3±16.1	23.46	0.392	0.465	15.69	1.18	74.48	345	24.82
H4	812.5±18.9	22.58	0.408	0.487	16.22	1.19	73.94	390	24.64
I1	984.3±21.2	30.45	0.384	0.454	15.41	1.23	74.94	245	18.73
I2	979.6±11.5	28.36	0.392	0.465	15.69	1.23	74.42	255	18.60
I3	962.8±9.8	24.93	0.416	0.487	14.57	1.19	73.78	265	18.44
I4	955.3±15.7	23.94	0.434	0.487	10.80	1.17	73.55	270	18.38
J1	974.5±29.3	29.03	0.357	0.416	14.18	1.19	75.36	270	18.84
J2	959.3±17.9	27.11	0.370	0.434	14.74	1.18	74.84	305	18.71
J3	921.4±15.3	25.45	0.392	0.465	15.69	1.18	74.36	310	18.59
J4	898.2±19.7	23.46	0.408	0.487	16.22	1.19	73.88	335	18.47
K1	981.3±21.5	28.36	0.416	0.476	12.60	1.14	75.72	320	18.93
K2	964.5±32.1	27.74	0.434	0.487	10.80	1.12	74.94	330	18.73
K3	939.8±19.7	23.02	0.465	0.540	18.56	1.22	74.48	350	18.62
K4	915.3±10.9	22.58	0.476	0.571	11.85	1.13	73.96	365	18.49
L1	979.1±19.3	27.74	0.392	0.465	15.69	1.18	75.62	375	18.90
L2	955.3±11.9	25.96	0.408	0.487	16.22	1.19	75.42	395	18.85
L3	939.8±21.8	24.41	0.434	0.487	10.80	1.12	75.34	410	18.83
L4	903.0±17.3	22.19	0.465	0.571	18.56	1.22	74.18	445	18.54

The mean diameter of the microspheres significantly decreased with increasing the concentration of surfactants. The more emulsifier added, the less irregular were the microspheres, and the size of the microspheres was reduced. This appears to have resulted from a tightening of polymeric network, leading to microsphere shrinkage as the concentration of emulsifier is increased. On increasing the concentration of drug – polymer ratio,the particle size was increased. This increase in particle size of the microspheres can be attributed to an increase in viscosity with increasing polymer concentrations, which resulted in larger emulsion droplets and finally in greater microsphere size.

On increasing the concentration of drug – polymer ratio,the particle size was increased. This increase in particle size of the microspheres can be attributed to an increase in viscosity with increasing polymer concentrations, which resulted in larger emulsion droplets and finally in greater microsphere size.

The effects of various process and formulation parameters on the drug content and entrapment efficiency of microspheres are shown in Tables 2. As the ratio of drug-polymer increases, encapsulation efficiency increased ; this is due to higher ratio of drug to polymer,which would produce large size droplets with decrease surface area, here diffusion of drug from such microspheres will be slow, resulting in higher encapsulation efficiency.

The higher drug loading typically results in lower encapsulation efficiency due to higher concentration gradients, which ultimately leads to diffusion of drug out of the polymer/solvent droplets to the external processing medium. Also the viscosity of the polymer solution at higher drug loading was very high and is responsible for the formation of larger polymer/solvent droplets. It caused a decrease rate of entrapment of drug due to slower hardening of the larger particles, allowing time for drug diffusion out of the particles, which tends to decrease encapsulation efficiency. Keeping the drug-polymer ratio constant, there was a significant decrease in encapsulation efficiency of Metoprolol tartrate with increasing the concentration of surfactant for emulsification. This may be due to the fact that the increase in surfactant concentration proportionally increases miscibility of solvents with light liquid paraffin, which may increase the extraction of drug into the processing medium.

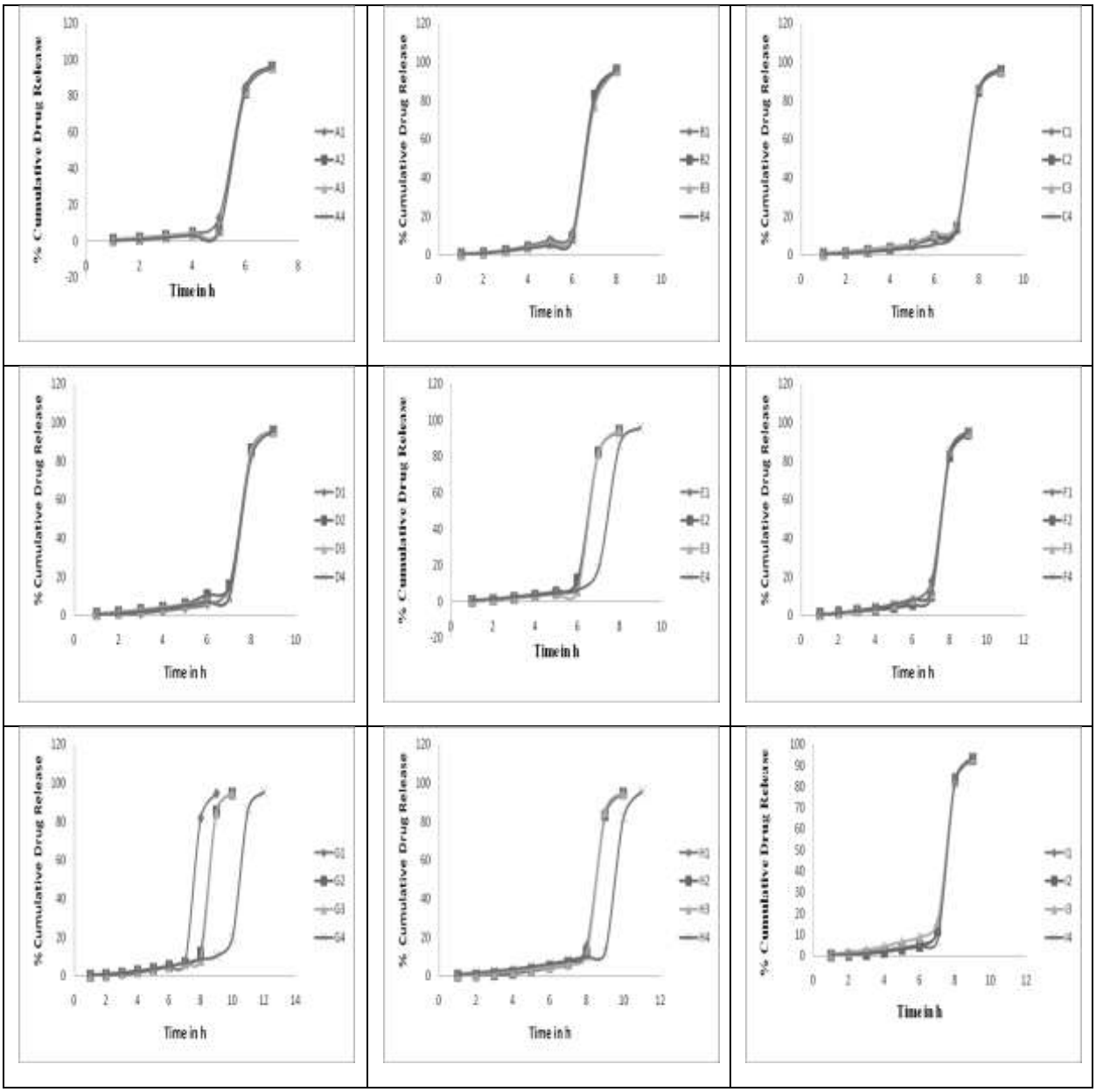
The floating test was carried out to investigate the floating ability of the prepared microspheres. Floating microspheres were dispersed in 0.1 N HCl containing Tween 80 (0.02%w/v). Tween 80 was added to stimulate the floating condition of microspheres. Floating ability of different formulations was found to

be differed according to the polymer ratio and concentration of sodium bicarbonate.

Dissolution studies (Fig.1) were performed first at pH 1.2 for time equivalent to floating time (round figure-hours) and then subsequently medium was replaced with fresh pH 7.4 having maintained temperature of 37±0.2ºC. In pH 1.2 the formulation A1 showed 4-5% cumulative drug release, A2 showed 5-6% cumulative drug release ,A3 showed 6-7 cumulative drug release,A4 showed 5-6% cumulative drug release. The low amount of drug release at gastric pH is also advantageous to reduce gastric irritation. After this lag time, complete drug was released within 60-120 minutes about 95.69, 95.80, 96.06, 96.14 for A1,A2,A3 and A4 respectively in phosphate buffer pH 7.4 this is due to the acidic groups of eudragit L100 and S100 gets converted in the salt form hence dissolution in neutral and alkaline condition

The results might also be explained by the fact that the higher polymer content resulted in larger particles with proportionately less drug. As the concentration of Span 80 increased, the faster drug release was observed. This may be attributed to the presence of free drug on the surface of the microspheres with increasing the concentration of Span 80 for emulsification process. The desired drug release with predetermined lag time about 95.00 % was found to be in formulation G3 with desired floating time and hence was designated as optimized batch.

Similar observations were found in the further formulations having drug to polymer ratio 1:2 and 1:3 with increasing concentration of span 80.



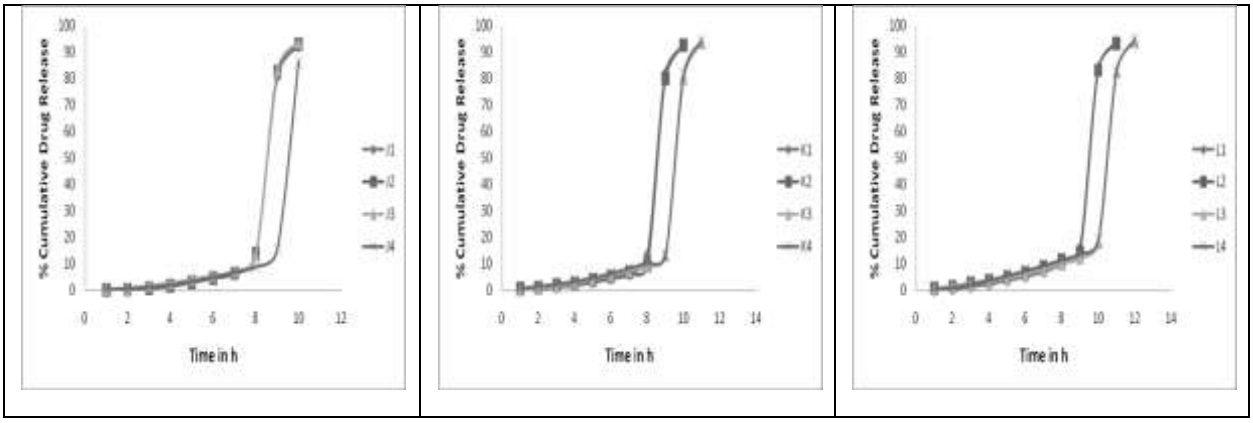


Figure 1: *In vitro* Drug release from various formulations

The *in vitro* release profiles were applied on various kinetic models in order to find out the mechanism of drug release. The best fit with the highest correlation coefficient was shown in zero-order, Higuchi, and followed by first order equations. The rate constants were calculated from the slope of the respective plots. The data obtained were also put in Korsmeyer-Peppas model in order to find out n value, which describes the drug release mechanism. The n value of microspheres of different drug to polymer ratio was ranged between 0.619 and 0.702, indicating that the mechanism of drug release was Non-Fickian or anomalous transport.

Table 24 : Kinetic Treatment of Drug Release Data of Various Batches

Formulation Code	Zero order equation	First order equation	Higuchi's equation	Korsmeyer Peppas equation	n
	R^2				
A1	0.932	0.986	0.980	0.997	0.688
A2	0.986	0.975	0.944	0.989	0.649
A3	0.989	0.984	0.946	0.992	0.648
A4	0.971	0.995	0.972	0.993	0.679
B1	0.955	0.983	0.960	0.991	0.686
B2	0.967	0.969	0.941	0.989	0.674
B3	0.933	0.972	0.953	0.969	0.694
B4	0.974	0.984	0.960	0.994	0.655
C1	0.954	0.993	0.985	0.998	0.668
C2	0.960	0.992	0.964	0.995	0.685
C3	0.988	0.992	0.946	0.985	0.692
C4	0.990	0.966	0.912	0.973	0.684
D1	0.975	0.978	0.937	0.985	0.624
D2	0.984	0.960	0.895	0.990	0.665
D3	0.956	0.952	0.935	0.978	0.689
D4	0.980	0.914	0.966	0.991	0.619
E1	0.975	0.978	0.937	0.985	0.624
E2	0.982	0.934	0.945	0.992	0.621
E3	0.968	0.945	0.941	0.990	0.693
E4	0.970	0.987	0.976	0.978	0.639
F1	0.964	0.913	0.964	0.977	0.686
F2	0.973	0.963	0.966	0.983	0.702
F3	0.959	0.981	0.925	0.961	0.673
F4	0.984	0.950	0.962	0.972	0.642
G1	0.986	0.975	0.944	0.989	0.649
G2	0.967	0.969	0.941	0.989	0.674
G3	0.933	0.972	0.953	0.969	0.694
G4	0.954	0.993	0.985	0.998	0.668
H1	0.988	0.992	0.946	0.985	0.692
H2	0.990	0.966	0.912	0.973	0.684

H3	0.932	0.986	0.980	0.997	0.688
H4	0.955	0.983	0.960	0.991	0.686
I1	0.947	0.973	0.958	0.935	0.658
I2	0.983	0.969	0.955	0.973	0.675
I3	0.964	0.939	0.992	0.942	0.663
I4	0.975	0.957	0.976	0.938	0.697
J1	0.963	0.998	0.976	0.993	0.688
J2	0.949	0.959	0.985	0.955	0.692
J3	0.989	0.966	0.952	0.963	0.635
J4	0.983	0.996	0.965	0.971	0.629
K1	0.966	0.967	0.958	0.974	0.684
K2	0.976	0.988	0.974	0.983	0.639
K3	0.991	0.981	0.983	0.995	0.683
K4	0.985	0.975	0.973	0.958	0.642
L1	0.994	0.982	0.965	0.986	0.665
L2	0.987	0.964	0.952	0.953	0.651
L3	0.953	0.972	0.986	0.981	0.682
L4	0.968	0.965	0.973	0.994	0.694

Stability studies as per the ICH guidelines for the G3 formulations was performed for a period of 90 days to ascertain whether the drug undergoes any change or degradation during its shelf-life. These samples were checked for changes in physical appearance and drug content at regular intervals (Tables 15 and figures 29). The formulation G3 exhibited no change in physical appearance. Maximum drug was retained by formulation G3 under all storage conditions.

CONCLUSION

Metoprolol tartrate possesses all requisite qualities required for sustained drug delivery system in the form of microspheres.The results proved that prepared microspheres exhibited excellent floating time as well as release at the desired time. In the present work the particle size can be controlled by changing polymer concentration and emulsifier concentration. The drug/polymer mass ratio can dramatically affect the drug content and encapsulation efficiency.Among the various formulation, the formulation G3 was found to be optimum formulation. The formulation G3 containing drug:polymer ratio (1:2), span 80 (2% w/v) and Sodium bicarbonate (1.5%w/v) fulfilled all desirable requirements for formulation of microspheres. Formulation G3 was found to release the drug for 9 h (95.00%) and had particle size of 803.3 µm and follow Korsmeyer-Peppas model in dissolution studies. The batch was stable for 90 days at 40^0C and 75% RH.

REFERENCES

1. Shaji J and Shinde A; Formulation and optimization of floating pulsatile microspheres using response surface methodology. International Res J of Pharm., 2012; 3(1): 166-169.
2. Somani VG, Shahi SR, Udavant YK, Atram SC, Satpute R and Shinde NM; A floating pulsatile drug delivery system based on hollow calcium pectinate beads. Asian J of Pharmaceutics, 2009; 3:120-124.
3. Badve SS, Sher P, Korde A and Pawar AP; Development of hollow/porous calcium pectinate beads for floating-pulsatile drug delivery. European J of Pharmaceutics and Biopharm., 2007; 65: 85-93.
4. Shaji J and Patole V; Novel floating pulsatile approach for chronotherapeutic release of indomethacin. Dhaka University J of Pharm Sci., 2007; 6: 37-41.
5. Sharma S and Pawar A; Low density multiparticulate system for pulsatile release of meloxicam. International J of Pharmaceutics, 2006; 313:150-158.
6. Ramdas M, Dileep KJ, Anitha Y, Willi P, Chandra PS; Alginate encapsulated bioadhesive chitosan microspheres for intestinal drug delivery. J Biomater Appl., 1999;13(4): 290-296.
7. Kamel AH; Alginate-diltiazem hydrochloride beads: optimization of formulation factors, *in vitro* and *in vivo* bioavailability. J Microenacapsul., 2003; 20(2): 211-255.
8. Chowdary KPR, Rao S; Preparation and evaluation of mucoadhesive microcapsules of indomethacin. Saudi Pharmaceutical Journal, 2003; 11(3): 97-103.
9. Sambathkumar R, Venkateswaramurthy N, Vijayabaskaran M, Perumal P; Formulation of clarithromycin loaded mucoadhesive microspheres by emulsification-internal gelation technique for anti *helicobacter pylori* therapy. Int J Pharm and Pharmaceutical Sci., 2011; 3(2):173-179.
10. O'Neil MJ, Smith A, Heckelman PE, editors; The Merck Index. 13th edition, Whitehouse station, NJ: Merck and Co. Inc; 2001: 1771, 954, 563, 850.

11. Sweetman SC, Martindale; The complete drug reference. 33rd edition, Pharmaceutical Press; London: 2000: 1421, 1321, 1265, 1305.

12. Rowe RC, Sheskey PJ, Weller PJ. Editors; Handbook of Pharmaceutical Excipients. 6th edition, Pharmaceutical Press, London. 2001: 624, 326, 110.