Research Paper

International Journal of Pharmaceutical Sciences and Nanotechnology
Volume 10 • Issue 4 • July – August 2017
MS ID: IJPSN-5-10-17-KOTA

Development and Evaluation of Olmesartan Medoxomil Controlled Release Floating Microspheres using Natural Gums

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Received March 6, 2017; accepted June 5, 2017

ABSTRACT

The present research was aimed to prepare Olmesartan medoxomil floating microspheres for controlled release using polymers such as sodium alginate, sodium bicarbonate, calcium chloride, Hydroxy propyl methyl cellulose (HPMC K4M, K15M), Olibanum gum and Xanthan gum by ionotropic gelation method. The prepared microspheres were evaluated for the percent drug content, entrapment efficiency, percentage buoyancy and *in vitro* dissolution studies. Among all the formulations F14 was selected as optimized formulation based on the micromeretic and physico-chemical parameters including drug release studies. Percentage buoyancy of optimized formulation was found to be 96.45%. *In vitro* release study of formulation F14 showed 98.11% drug release after 12 h in a controlled manner, which is desired for disease like Hypertension. The reference standard shows the drug release of 94.12% within 12 h. Drug and excipient compatibility studies were carried out by FT-IR and no interactions were observed. The SEM of microspheres show a hollow spherical structure with a rough surface morphology. Some of microspheres showed dented surface structure but they showed good floating ability on medium indicated intact surface. The shell of microspheres also showed some porous structure which might be due to release of carbon dioxide. F14 followed zero order, Higuchi and Korsmeyer Peppas kinetics indicating diffusion controlled with non-fickian (anomalous) transport, projecting that its active ingredient are delivered by coupled diffusion and erosion. From these results, it can be concluded that the polymer proportion controlled the drug release from the olmesartan floating microspheres.

KEYWORDS: Olmesartan, Buoyancy, HPMC, Floating microspheres, Hypertension.

Introduction

Since the past three decades, the population of the GERD patients has been increasing. These situations are demanding the intake of drug for prolonged period as multiple doses may causes non-compliance. To overcome this problem, a sustained or controlled release dosage forms which will deliver the drug for upto 12 hrs and many drug molecules formulated as Gastroretentive Drug Delivery System (GRDDS) have been patented keeping in view of its commercial success. To overcome this restriction and to increase the bioavailability of these drugs, controlled drug delivery systems with a prolonged residence time in the stomach can be used (Mohamed et al., 2009).

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period than conventional dosage forms (Shweta et al., 2005). Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices (Dave Brijesh et al., 2004). Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach (Gattani et al., 2009). Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms (Arora Shweta et al., 2005).

Floating drug delivery system (FDDS) promises to be a potential approach for gastric retention. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach (Singh et al. 2010). Floating microspheres have emerged as an efficient means of enhancing the bioavailability and controlled delivery of many drugs the increasing sophistication of delivery technology will ensure the development of increasing number of gastro-retentive drug delivery systems to optimize the delivery of molecules that exhibit absorption window, low bioavailability, and extensive first pass metabolism (Gattani et al., 2009).

Olmesartan Medoxomil is a non-peptide angiotensin II receptor antagonist use in the treatment of mild to moderate hypertension. This drug is weakly basic, lipophilic and having very less oral bioavailability of about 26%. Olmesartan Medoxomil inhibits type I angiotensin II receptor in the rennin angiotensin system, there by producing best antihypertensive action (Najm, 2011, Abhijith and Amrish, 2013). The aim of present work is to design an *in vitro* evaluation of Olmesartan floating microspheres to enhance its bioavailability and prolonged residence time in stomach.

Materials and Methods

Floating Microspheres

Formulation of olmesartan floating microspheres – formulation design: Olmesartan floating microspheres were prepared using polymers sodium alginate, HPMC K4M, HPMC K15M and sodium bicarbonate using Ionotropic gelation method. Different formulation trials were made using different concentrations of hydrophilic and hydrophobic polymers along with sodium bicarbonate summarized in the Table 1.

Procedure: Fourteen formulations of Olmesartan medoxomil floating microspheres were prepared by ionotropic gelation technique using different proportion of polymers as shown in Table 1. A solution of sodium alginate was prepared by weighed quantity of drug (Dose is 40mg of Olmesartan) and HPMC K4 or HPMC K15 with other polymers were added and was triturated to form fine powder, and then added to above solution. Sodium bicarbonate, a gas-forming agent was added to this mixture. Resultant solution was extruded drop wise with the help of syringe and needle into 100 mL aqueous calcium chloride solution and stirred at 100 rpm. After stirring for 10 minutes the obtained microspheres were washed with water and dried at 60° -2 hours in a hot air oven and stored in dessicater (Ranjith Kumar et al., 2017).

Evaluation of Olmesartan medoxomil floating microspheres: Micromeretic properties like particle size, angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio and evaluation parameters like swelling index, drug entrapment efficiency and percentage yield, *in vitro* dissolution studies and percentage buoyancy studies were performed (Pavan Kumar et al., 2014).

In vitro drug release studies: *In vitro* drug release studies for developed Olmesartan medoxomil microspheres were carried out by using dissolution apparatus II paddle type (Electrolab TDL-08L). The drug release profile was studied in 900 mL of 0.1 N HCl at 37 ± 0.5 °C temperature at 100 rpm. The amount of drug release was determined at different time intervals of 0, 1, 2, 3, 4, 6, 8, 10 & 12 hours by UV visible spectrophotometer (Shimadzu UV 1800) at 271nm.

Kinetic modeling of drug release: In order to understand the kinetics and mechanism of drug release, the result of the *In vitro* dissolution study of floating microspheres were fitted with various kinetic equations like Zero order as cumulative percentage released Vs. time, First order as log percentage of drug remaining to be released Vs. time, Higuchi's model cumulative percentage drug released Vs. square root of time. r^2 and K values were calculated for the linear curves obtained by regression analysis of the above plots. To analyze the mechanism of drug release from the tablets the *in vitro* dissolution data was fitted to zero order, first order, Higuchi's release model and Korsmeyer – Peppas model.

Drug Excipient Compatibility Studies

The drug excipient compatibility studies like Fourier Transmission Infrared Spectroscopy (FTIR) and SEM were performed.

Stability Studies

The stability study of the optimized formulation was carried out under different conditions according to ICH guidelines. The optimized microspheres were stored in a stability chamber for stability studies (REMI make). Accelerated stability studies were carried out at 40 ^{0}C / 75 % RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency and cumulative percentage drug released during the stability study period.

TABLE 1

Formulation trials of olmesartan floating microspheres.

Formulation code	Olmesartan (mg)	Sodium alginate	HPMC K 4M (mg)	Sodium bi carbonate (mg)	Calcium chloride	OLIBANUM GUM (mg)	XANTHAN GUM (mg)
F1	40	1%	150	25	2%	0.5	10
F2	40	1%	200	50	2%	0.75	15
F3	40	1%	250	75	2%	1	20
F4	40	1%	300	100	2%	1.5	25
F5	40	1%	350	125	2%	1.75	30
F6	40	1%	400	150	2%	2	35
F7	40	1%	450	175	2%	2.5	40
F8	40	1%	150	25	2%	0.5	10
F9	40	1%	200	50	2%	0.75	15
F10	40	1%	250	75	2%	1	20
F11	40	1%	300	100	2%	1.5	25
F12	40	1%	350	125	2%	1.75	30
F13	40	1%	400	150	2%	2	35
F14	40	1%	450	175	2%	2.5	40

TABLE 2

Micromeretic properties of Olmesartan floating microspheres.

Formulation code	Particle size (µm)	Bulk density g/cc^3	Tapped density g/cc^3	Angle of repose	Carr's index	Buoyancy%
F1	67.45 ± 0.04	0.60	0.56	25°.93	13.56%	93.20%
F2	62.12 ± 0.08	0.65	0.60	28°.74	10.34%	85.50%
F3	64.29 ± 0.13	0.73	0.64	29°.67	11.34%	82.30%
F4	71.43 ± 0.04	0.77	0.71	25°.03	14.36%	91.10%
F5	75.35 ± 0.04	0.78	0.76	29°.74	11.12%	80.64%
F6	80.67 ± 0.09	0.82	0.82	32°.15	7.23%	88.40%
F7	83.45 ± 0.09	0.86	0.84	25°.54	13.91%	87.10%
F8	64.23 ± 0.14	0.87	0.65	30°.91	10.32%	71.50%
F9	88.21 ± 0.11	0.67	0.68	26°.91	10.03%	74.80%
F10	74.34 ± 0.10	0.74	0.75	25°.24	12.34%	75.40%
F11	79.45 ± 0.21	0.76	0.77	25°.70	11.90%	90.50%
F12	92.67 ± 0.13	0.90	0.85	25°.91	11.94%	92.20%
F13	89.23 ± 0.19	0.82	0.80	26°.54	11.34%	86.40%
F14	63.45 ± 0.09	0.73	0.88	22°.66	9.90%	96.45%

Results and Discussion

All the formulations were evaluated for their various physical parameters like particle size, bulk density, tapped density, angle of repose, Carr's index and percentage buoyancy and found to be within the results. The formulation F14 shows best results like particle size 63.45 ± 0.09µm, bulk density of 0.73g/cc^3, angle of repose 22°.66, compressibility index 9.90% and percentage buoyancy of 96.45% (Table 2, Figure 1).

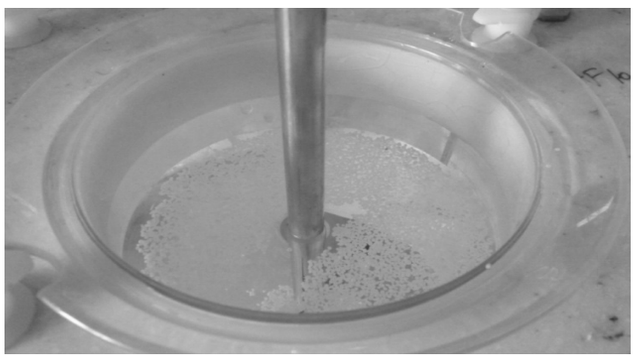

Fig. 1. *In vitro* buoyancy study of Olmesartan floating microspheres (F14).

The results of percentage yield, entrapment efficiency and swelling index-floating microspheres of all formulations were within the limits as shown in Table 3. The percentage yield, entrapment efficiency and swelling index of F14 was found to be 96.30%, 97.88% and 95.90% respectively.

TABLE 3

Percentage yield, entrapment efficiency and swelling index of Olmesartan microspheres.

Formulation code	Percentage Yield	Entrapment efficiency	Swelling index
F1	85.09%	78.09%	76.76%
F2	80.12%	83.23%	79.78%
F3	82.23%	82.56%	83.34%
F4	87.87%	88.30%	85.23%
F5	88.30%	91.20%	88.34%
F6	91.30%	90.10%	89.78%
F7	92.10%	97.30%	95.12%
F8	85.42%	83.30%	82.23%
F9	93.50%	94.56%	91.10%
F10	90.76%	86.78%	88.45%
F11	82.56%	85.89%	84.34%
F12	93.50%	92.56%	92.10%
F13	84.30%	82.30%	83.89%
F14	96.30%	97.88%	95.90%

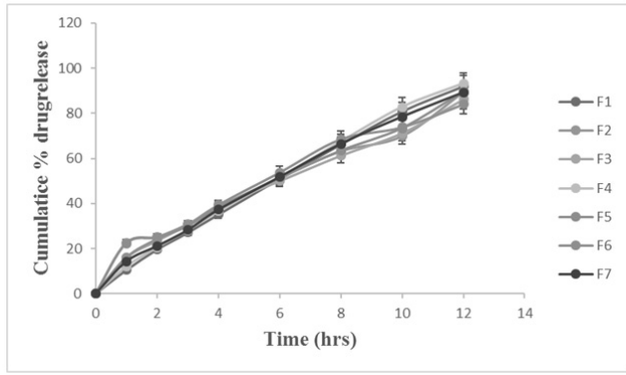

Fig. 2. *In vitro* cumulative % drug release of Olmesartan floating microspheres F1-F7.

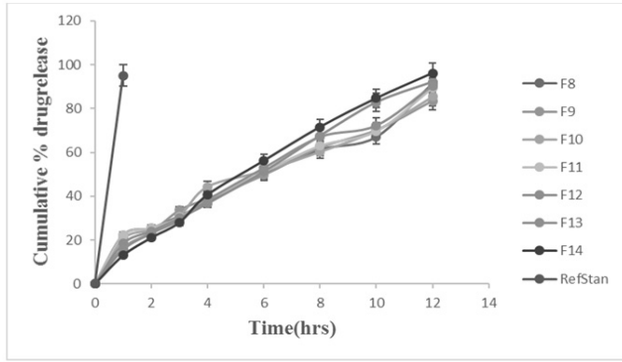

Fig. 3. *In vitro* cumulative % drug release of Olmesartan floating microspheres F8-F14 with reference standard.

The *in vitro* drug profile of Olmesartan from different formulations was carried and the results are depicted in Table 4 & 5. The highest drug release was found in the formulation F14 i.e 96.11% within 12hrs. F14 was found to be optimized formulation based on the dissolution and

other evaluation parameters. The *in vitro* drug release profile from reference standard conventional tablet was found to be 94.12% within 60 min.

TABLE 4

In vitro cumulative % drug release of Olmesartan floating microspheres F1-F7.

Time (h)	F1	F2	F3	F4	F5	F6	F7
0	0%	0%	0%	0%	0%	0%	0%
1	10.45%	22.67%	15.89%	12.10%	22.34%	16.10%	14.31%
2	19.5.7%	25.23%	23.41%	20.50%	25.12%	24.30%	21.15%
3	27.06%	30.10%	30.56%	28.03%	30.78%	30.20%	28.19%
4	35.08%	38.20%	38.95%	36.50%	38.28%	39.40%	37.23%
6	50.92%	51.34%	49.95%	51.60%	51.36%	53.80%	51.73%
8	66.25%	63.33%	61.26%	67.49%	63.38%	68.60%	66.46%
10	80.90%	69.99%	71.21%	82.80%	73.39%	73.90%	78.45%
12	92.03%	89.52%	86.15%	93.22%	89.54%	84.07%	89.23%

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.977 indicates that the drug release follows a zero order mechanism (Table 6). This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsemeyer-Peppas plots.

The mass transfer with respect to square root of the time has been plotted, revealed a linear graph with regression value close to one i.e. 0.973 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.715 suggest that the drug release from floating tablet was anomalous Non fickian diffusion which are shown in Figure 4.

TABLE 5

In vitro cumulative % drug release of Olmesartan floating microspheres F8-F14 with Reference standard.

Time in (h)	F8	F9	F10	F11	F12	F13	F14	Reference standard
0	0%	0%	0%	0%	0%	0%	0%	0
1	22.32%	16.43%	20.55%	22.09%	18.40%	15.62%	13 .40%	94.12%
2	25.45%	23.55%	24.85%	25.48%	24.05%	23.01%	21.05%	
3	31.01%	33.65%	31.03%	30.33%	30.02%	29.11%	28.02%	
4	37.25%	38.89%	44.43%	38.26%	36.66%	38.24%	40.66%	
6	50.33%	49.69%	51.6%	51.13%	51.18%	52.83%	56.18%	
8	61.35%	62.24%	60.35%	63.03%	67.58%	67.03%	71.58%	
10	67.09%	70.18%	70.06%	69.69%	82.79%	72.22%	84.79%	
12	91.56%	83.56%	85.45%	89.42%	92.11%	90.36%	98.11%	

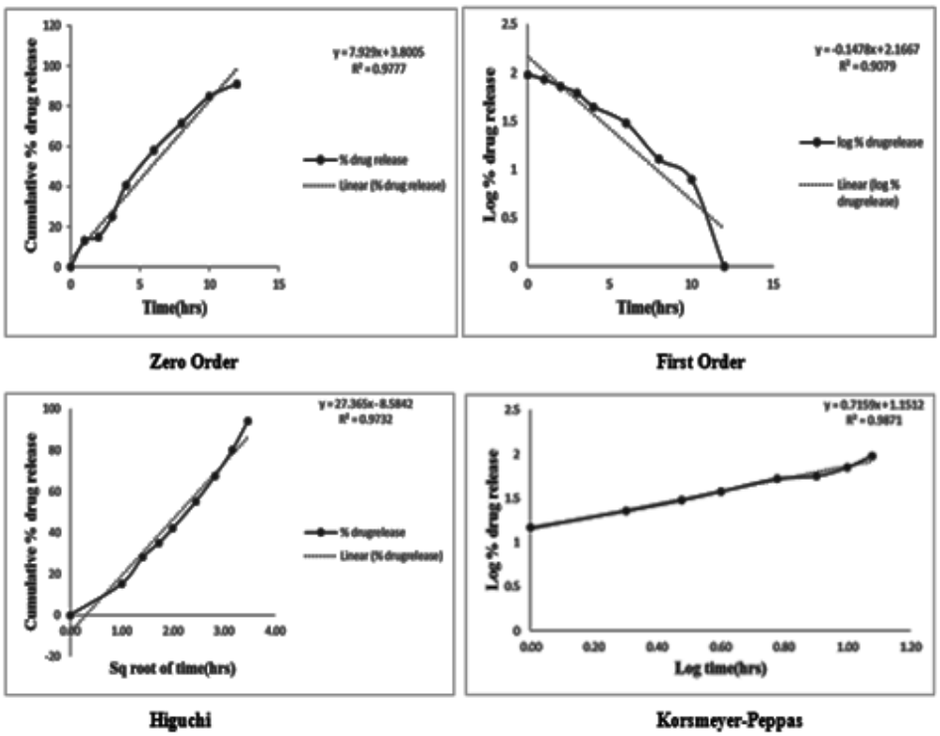

Fig. 4. Release order kinetics of Olmesartan optimized floating microspheres (F14).

TABLE 6

Release order kinetics of optimized floating microspheres (F14).

Formulation code	Zero order	First order	Higuchi	Korsmeyer-Peppas	
	R^2	R^2	R^2	R^2	n
F14	0.977	0.907	0.973	0.987	0.715
Reference standard	0.894 ± 0.0216				

Drug Excipient Compatibility Studies

Fourier transform infrared spectroscopy (FTIR): Possible interactions between drug and polymer were investigated by FT-IR. FT-IR of pure Olmesartan characteristic sharp peaks of alkene stretching (=C–H and CH_2) vibration at 3398.32–3039.48 cm^{-1} and alkane stretching (–CH_3, –CH_2 and –CH) vibration at 2860.73 cm^{-1}. Also exhibited C ⎯ O stretch at 1739.2 cm^{-1} due to saturated ketone and C ═ O–NH stretching at 1638.90 cm^{-1}. A selective stretching vibration at 1552.57 cm^{-1} and 1529.80 cm^{-1} for primary and secondary amine was also observed (Figure 5). Overall there was no alteration in peaks of Olmesartan pure drug and optimized formulation (Figure 6), suggesting that there was no interaction between drug & excipients.

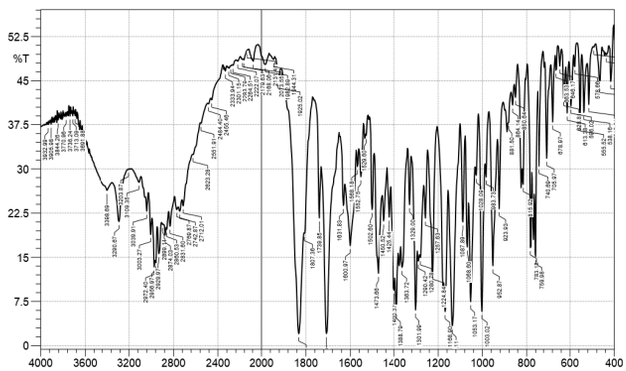

Fig. 5. FT-IR spectrum of pure drug Olmesartan medoxomil.

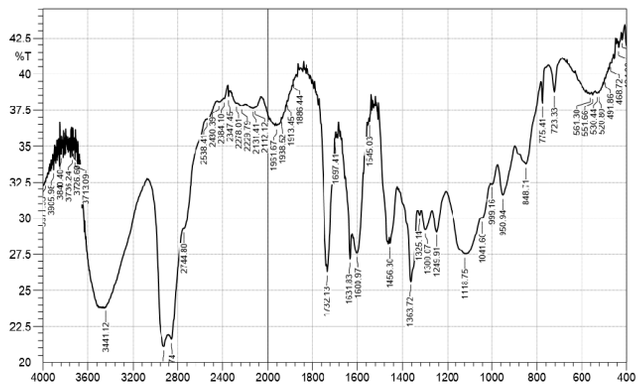

Fig. 6. FT-IR spectrum of Olmesartan medoxomil optimized formulation F14.

Scanning Electron Microscopy Studies

SEM of Olmesartan medoxomil floating microspheres: The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. Some of microsphere showed dented surface structure but they showed good floating ability on medium indicated intact surface (Figure 7). The shell of microspheres also showed some porous structure it may be due to release of carbon dioxide.

Stability studies: Optimized formulation F14 was selected for stability studies on the basis of high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From the results it was concluded that, optimized formulation is stable and retained their original properties with minor differences.

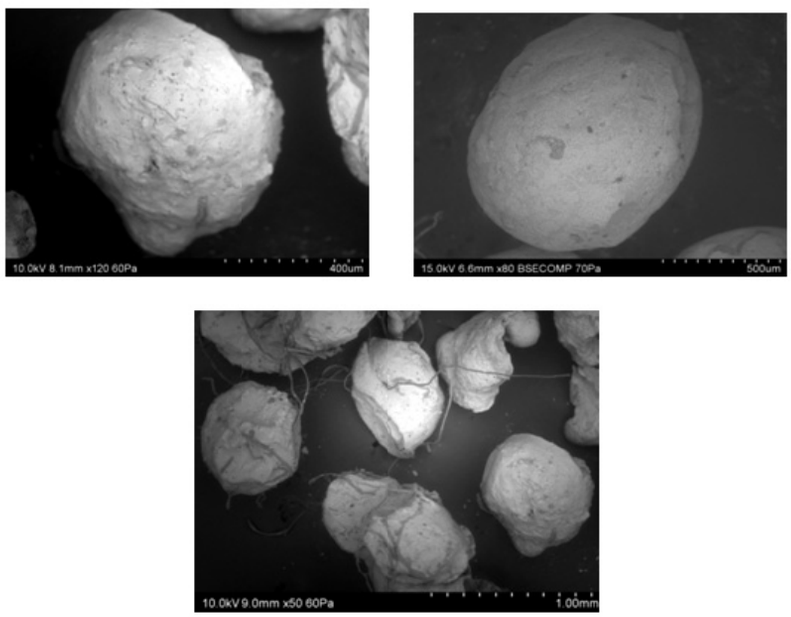

Fig. 7. Scanning electron micrograph of Olmesartan medoxomil floating microspheres.

Conclusions

In the present study, an attempt was made to prepare different types of Olmesartan medoxomil floating microspheres, which were characterized for particle size, percentage yield, percentage drug entrapment, stability studies and found to be within the limits. Among all the formulations F14 was selected as optimized formulation. *In vitro* release study of formulation F14 showed 96% release after 12 h in a controlled manner. The *in vitro* release profiles from optimized formulations were applied on various kinetic models suggest that the drug release from floating tablet was anomalous Non-fickian diffusion. FT-IR analyses confirmed the absence of drug-polymer interaction. The SEM of microspheres shows a hollow spherical structure with a rough surface morphology. The shell of microspheres also showed some porous structure it might be due to release of carbon dioxide. Optimized formulation F14 was selected for stability studies on the basis of high cumulative % drug release. F14 was stable and retained their original properties with minor differences. From these results, it can be concluded that the polymer proportion controlled the drug release from the floating microspheres. Prepared Olmesartan medoxomil floating formulation showed best appropriate balance between buoyancy and drug release rate.

References

Abhijith S. and Amrish C., (2013). Formulation and Evaluation of Pulsatile Tablet in Capsule Device. *IJPPS.* **5(2):** 125-129.

Arora Shweta., Ali Javed.., Ahuja Alka. and Khar Roop K., (2005). *AAPS Pharm Sci Tech* **6(3):** E372-E390.

Dave Brijesh S., Amin Avani F. and Patel Madhabhai M., (2004). Gastroretentive Drug Delivery System of Ranitidine Hydrochloride: Formulation and *In vitro* Evaluation. *AAPS Pharm Sci Tech* **5 (2):** 1-6.

Gattani Y. S., Kawtikwar P. S. and Sakarkar D. M., (2009). Formulation and evaluation of Gastro retentive Multiparticulate Drug delivery system of Aceclofenac. *Int J Chem Tech Res.* **1(1):** 1-10.

Mohamed H.G. and Dehghan Furquan N Khan., (2009). Gastroretentive Drug Delivery Systems: A Patent Perspective. *Int J Health Res.* **2(1):** 23-44

Najm, W I., (2011). Peptic ulcer disease. *Primary care.* **38 (3):** 383-94.

Pavan Kumar P. and Priya S., (2014). Formulation and *In vitro* evaluation of floating microspheres of dextromethorphan hydrobromide, *IJPPS.* **6(4):** 206-210.

Ranjith Kumar K., Bhikshapathi D.V. R. N. and Haarika B., (2017). Design and *In vitro* evaluation of floating microspheres using misoprostol, *IJPAR.* **6 (1):** 108-117.

Shweta A., Javed A., Ahuja A., Khar Roop K. and Baboota S., (2005). Floating Drug Delivery Systems: A Review, *AAPS Pharm Sci Tech.* **6(3):** 372-390.

Singh B., Kanoujia J., Pandey Manisha. and Saraf Shubhini A., (2010). Formulation and Evaluation of Floating Microspheres of Famotidine. *Int J Pharm Tec*h Res. **2(2):** 1415-1420.

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