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Development and Characterization of Alginate Microspheres Containing Olmesartan by Ionotropic Gelation Method

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ABSTRACT

The present study was designed to formulate and evaluate the Olmesartan sodium alginate microspheres. Fourteen formulations batches of microspheres (S1-S14) were prepared by using ionotropic gelation method. Sodium alginate, calcium chloride, ethyl cellulose, HPMC K15M was selected in the formulations. The effect of polymer and cross-linking agent on particle size (68.18 ± 0.06), % yield (98.34%), entrapment efficiency (97.36%), and drug release were studied. From the evaluation parameters S11 was found to be optimized and the highest drug release 96.98 ± 5.28 with in 12 h in controlled manner when compared with other parameters. From release order kinetics the drug release from microspheres was followed zero order with anomalous Non fickian diffusion. The prepared microspheres compatibility studies and morphological studies were investigated by Fourier-transform infrared spectroscopy (FTIR) and scanning electron microscopy (SEM), found to be compatible with the polymers. Thus, Olmesartan microspheres could be the best choice in the effective management of hypertensive with better patient compliance for prolonged period of time.

Keywords: Olmesartan, hypertension, microspheres, ionotropic gelation technique, release order kinetics.

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INTRODUCTION

A controlled release drug delivery system is usually designed to deliver the drug at rate-controlled release properties can also be imparted to oral dosage formulations through the formation of resin-drug complexes coated with polymers. [1] As multiarticulate drug delivery lead to wide and uniform distribution throughout GIT, a localized high concentration at a specific point may be avoided. [2] Microspheres have been explored extensively for their use in the field of drug delivery and various polymers have been utilized for the formulation of the microspheres, which in turn have been assessed for different purposes. [3] Microspheres are one of the multiple unit dosage forms. Eventually the total dose and few adverse reactions may be reduced since a steady plasma

concentration is maintained. Microspheres are potential drug delivery carrier systems in the segment of novel drug delivery and are prepared using assorted polymers. [4]

Olmesartan medoxomil (OLM) is an orally active nonpeptide angiotensin II receptor antagonist. It is approved by the US FDA in 2002 for the treatment of hypertension, either alone or in combination with another anti-hypertensive. [5] It is a pro drug that is rapidly converted in vivo to the pharmacologically active metabolite, Olmesartan due to an endogenous esterase. It simply acts by inhibiting the vasoconstrictor effects of angiotensin II by selectively blocking angiotensin II type 1 receptor sites in vascular smooth muscle. [6-7]

Sodium alginate is an anionic natural polysaccharide, prepared by mixture of D-mannuronic acid and L-glucuronic acid. [8] Sodium alginate is extensively used as carrier for drug delivery due to its biocompatibility and low toxicity. The widely used method for olmesartan microspheres preparation is an ionotropic gelation method. This technique offers several advantages such as simple method of preparation no need to use of organic solvent, and, also easier to control. Sodium alginate could form gel in the presence of multivalent cations such as Ca^{2+}, Zn^{2+}, Ba^{2+} and Al^{3+} etc... by ionic cross-linking to form microspheres, it has been widely used in sustained drug release. Hence in this study calcium chloride is selected as cross-linking agent and also because of its nontoxic and biocompatibility. [9]

Ethyl cellulose and HPMC K15M l also acts as a good control or modified release polymers. The objective of the present study was to develop Olmesartan microspheres by ionotropic gelation method. The results indicate that the optimized formulation of Olmesartan microspheres can be successfully used for the treatment of Hypertension.

MATERIALS AND METHODS

Materials

Olmesartan was gifted by Arbro Pharmaceuticals, New Delhi. Ethyl cellulose and HPMC K15M were purchased from S. Kant. Healthcare Ltd Vapi, Gujarat. Sodium alginate was purchased from Pruthvi Chemicals, Mumbai. Calcium chloride and all other chemicals and solvents were of analytical grade.

Methods

Formulation of Olmesartan Microspheres

The microspheres of sodium alginate were prepared by using ionotropic gelation technique. In this method weighed quantity of Olmesartan and other polymers listed in Table 1 was added to 100 ml sodium alginate solution and thoroughly mixed at 500 rpm. 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 degrees - 2 hours in a hot air oven and stored in desiccators. [10]

Evaluation of olmesartan microspheres

Particle size

The 100 microspheres were evaluated with respect to their size and shape using optical microscope fitted with an ocular micrometer and a stage micrometer. The particle diameter was measured randomly by optical microscope. [11] Angle of repose [12], Bulk density, tapped density [13], Compressibility index [14] and Hausner's ratio [15] were evaluated according to the reported procedure.

Drug entrapment efficiency and % yield

To determine the incorporation efficiency, 10 mg of formulated microspheres were thoroughly crushed by triturating and suspended in required quantity of methanol followed by agitation to dissolve the polymer and extract the drug. After filtration, suitable dilutions were made and drug content assayed spectrophotometrically at 259 nm. Each batch should be examined for drug content in a triplicate manner. [16]

% Drug entrapment = Calculated drug concentration /Theoretical drug concentration × 100

% yield = [Total weight of microspheres / Total weight of drug and polymer] × 100

In vitro drug release studies

Release rate of drug from sodium alginate microspheres was carried out using USP type II dissolution apparatus with 900 ml of 0.1N HCl (pH 1.2) as dissolution medium. Accurately weighed amount of microspheres from each batch were subjected to dissolution studies in triplicate manner. At appropriate intervals up to 12 h, specific volume of aliquots was withdrawn and the same volume was replaced analyzed for the concentration of drug by UV spectrophotometer at 259 nm. [17]

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 microspheres were fitted with various kinetic equations like Zero order as cumulative percentage drug release 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. [18-20]

Drug Excipients Drug Compatibility Studies

The drug excipients compatibility studies were carried out by Fourier Transmission Infrared Spectroscopy (FTIR) method, SEM and Differential Scanning Colorimetry.

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectra for pure drug, physical mixture and optimized formulations were recorded using a Fourier transform Infrared spectrophotometer. The analysis

was carried out in Shimadzu-IR Affinity 1 Spectrophotometer. The samples were dispersed in KBr and compressed into disc/pellet by application of pressure. The pellets were placed in the light path for recording the IR spectra. The scanning range was 400-4000 cm^{-1} and the resolution was 1 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Samples were accurately weighed and heated in sealed aluminum pans at a rate of 10°C/ min between 25 and 350°C temperature rang under nitrogen atmosphere. Empty aluminum pan was used as a reference.

SEM studies

The surface and shape characteristics of pellets were determined by scanning electron microscopy (SEM) (HITACHI, S-3700N). Photographs were taken and recorded at suitable magnification.

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°C / 75% RH for the best formulations for 6 months. The microspheres were characterized for the percentage yield, entrapment efficiency & cumulative % drug released during the stability study period.

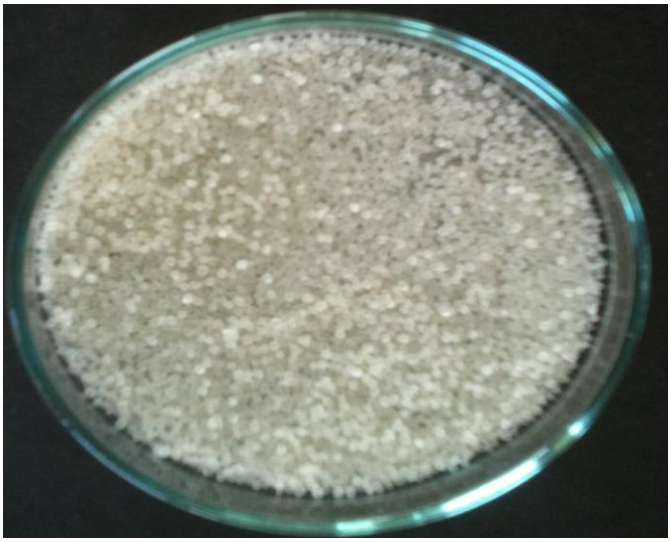


Fig. 1: Normal microspheres of Olmesartan

RESULTS AND DISCUSSION

Formulation of Microspheres of Olmesartan

Micromeritic properties of formulated Olmesartan sodium alginate microspheres (Figure 1) were shown in Table 2; all the formulations were evaluated and found to be within the IP limits. Percentage yield and entrapment efficiency of all the fourteen formulations were evaluated and depicted in Table 3. The formulation S11 shown the good percentage yield and entrapment efficiency when compared with other formulations of 98.34% and 97.36%.

Table 1: Formulation trials for Olmesartan microspheres

Formulation Code	Olmesartan (mg)	Sodium Alginate	HPMC K15M (mg)	Ethyl cellulose (mg)	Calcium Chloride
S1	40	1.0%	100	-	6 %
S2	40	1.25%	150	-	6 %
S3	40	1.5%	200	-	6 %
S4	40	1.75%	250	-	6 %
S5	40	2.0%	300	-	6 %
S6	40	2.25%	350	-	6 %
S7	40	2.5%	400	-	6 %
S8	40	1.0%	-	100	10%
S9	40	1.25%	-	150	10%
S10	40	1.5%	-	200	10%
S11	40	1.75%	-	250	10%
S12	40	2.0%	-	300	10%
S13	40	2.25%	-	350	10%
S14	40	2.5%	-	400	10%

Table 2: Micromeritic properties of formulated Olmesartan sodium alginate microspheres

Formulation code	Particle size (µm)	Bulk density (g/cc^3)	Tapped density (g/cc^3)	Angle of repose	Carr's index
S1	71.88 ± 0.01	0.59 ± 0.07	0.65 ± 0.04	25°.67 ± 0.02	11.82
S2	70.98 ± 0.01	0.60 ± 0.01	0.64 ± 0.02	24 °.68 ± 0.02	11.96
S3	72.66 ± 0.01	0.62 ± 0.01	0.63 ± 0.02	25 °.66 ± 0.02	12.98
S4	73.49 ± 0.02	0.61 ± 0.01	0.69 ± 0.07	26 °.09 ± 0.03	13.19
S5	71.98 ± 0.01	0.59 ± 0.07	0.65 ± 0.04	23 °.60 ± 0.01	12.21
S6	70.60 ± 0.01	0.58 ± 0.06	0.66 ± 0.05	24 °.98 ± 0.02	11.23
S7	72.81 ± 0.01	0.62 ± 0.01	0.64 ± 0.02	25 °.60 ± 0.02	14.06
S8	73.49 ± 0.02	0.59 ± 0.07	0.69 ± 0.07	22 °.90 ± 0.01	13.09
S9	70.66 ± 0.01	0.57 ± 0.05	0.68 ± 0.06	23 °.45 ± 0.01	13.46
S10	71.40 ± 0.01	0.61 ± 0.01	0.65 ± 0.04	22 °.96 ± 0.01	12.59
S11	68.18 ± 0.06	0.56 ± 0.05	0.62 ± 0.01	21 °.46 ± 0.01	10.18
S12	69.29 ± 0.07	0.58 ± 0.06	0.63 ± 0.02	23 °.98 ± 0.01	11.96
S13	72.18 ± 0.01	0.60 ± 0.01	0.66 ± 0.05	25 °.67 ± 0.02	11.58
S14	73.67 ± 0.02	0.59 ± 0.07	0.64 ± 0.02	26 °.48 ± 0.03	12.01

Table 3: Percentage drug yield and entrapment efficiency of Olmesartan microspheres.

Formulation code	Percentage yield (%)	Entrapment efficiency (%)
S1	90.18	93.66
S2	95.60	90.78
S3	86.49	91.64
S4	89.67	92.18
S5	91.42	89.67
S6	97.67	88.46
S7	91.80	96.78
S8	93.78	91.14
S9	95.44	94.70
S10	96.63	96.56
S11	98.34	97.36
S12	90.16	92.14
S13	89.24	93.17
S14	91.47	89.21

Table 4: *In vitro* cumulative % drug release of Olmesartan sodium alginate microspheres formulations

Time (h)	S1	S2	S3	S4	S5	S6	S7
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	15.29 ± 0.95	17.39 ± 0.97	16.45 ± 0.96	21.45 ± 1.02	19.32 ± 0.99	14.23 ± 0.94	18.45 ± 0.98
2	20.45 ± 1.28	21.45 ± 1.30	23.13 ± 1.31	30.29 ± 2.01	26.89 ± 1.34	20.68 ± 1.02	35.90 ± 2.24
4	33.78 ± 2.19	30.87 ± 2.01	32.20 ± 2.10	48.74 ± 2.69	35.47 ± 2.24	37.60 ± 2.28	46.46 ± 2.65
6	49.21 ± 2.75	48.36 ± 2.69	45.74 ± 2.65	59.98 ± 2.96	46.36 ± 2.65	48.29 ± 2.69	59.37 ± 2.96
8	58.74 ± 2.95	59.23 ± 2.96	56.69 ± 2.89	60.47 ± 2.97	59.24 ± 2.96	57.26 ± 2.89	69.18 ± 3.32
10	79.63 ± 3.95	75.78 ± 3.88	79.28 ± 3.95	78.64 ± 3.95	69.74 ± 3.32	63.27 ± 2.98	72.97 ± 3.80
12	89.45 ± 4.98	91.01 ± 5.01	89.57 ± 4.98	90.91 ± 5.01	90.89 ± 5.00	89.46 ± 4.99	93.60 ± 5.03

Table 5: *In vitro* cumulative % drug Olmesartan sodium alginate release of microspheres formulation

Time (h)	S8	S9	S10	S11	S12	S13	S14	Marketed product
0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
1	18.06 ± 0.98	20.67 ± 1.30	17.21 ± 0.97	28.67 ± 1.39	21.20 ± 1.05	22.78 ± 1.08	19.20 ± 0.99	9.46 ± 0.78
2	26.97 ± 1.33	32.67 ± 2.23	26.47 ± 1.36	39.45 ± 2.40	32.67 ± 2.23	35.49 ± 2.15	28.67 ± 1.36	15.42 ± 0.95
4	33.69 ± 2.23	40.67 ± 2.45	35.29 ± 2.15	52.16 ± 2.85	48.24 ± 2.40	50.12 ± 2.81	37.89 ± 2.19	22.98 ± 1.30
6	61.23 ± 3.10	52.19 ± 2.85	58.91 ± 2.95	67.84 ± 3.18	60.26 ± 3.10	62.98 ± 3.12	47.23 ± 2.40	36.78 ± 2.18
8	78.47 ± 3.92	64.23 ± 3.15	75.84 ± 3.81	74.67 ± 3.88	70.29 ± 3.79	71.48 ± 3.80	59.60 ± 2.95	54.98 ± 2.89
10	82.98 ± 4.55	77.68 ± 3.84	85.27 ± 4.68	86.98 ± 4.69	81.28 ± 4.68	84.29 ± 4.62	74.99 ± 3.81	79.80 ± 3.90
12	91.20 ± 5.01	89.36 ± 4.99	92.18 ± 5.02	96.98 ± 5.28	92.63 ± 5.02	93.67 ± 5.03	89.41 ± 4.99	91.28 ± 5.00

Table 6: Release order kinetics of optimized microspheres (S11)

Formula Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	K	R^2	K	R^2	K	R^2	N
S11	0.991	5.690	0.712	0.129	0.9863	25.949	0.986	0.470
Marketed product	0.957	7.155	0.758	0.114	0.868	26.622	0.922	0.500

Table 7: Stability studies of optimized microspheres

Retest Time for Optimized formulation	Percentage yield	Entrapment efficiency	*In-vitro* drug release profile (%)
0 days	98.34	97.36	96.98
30 days	96.45	96.14	95.13
60 days	94.23	95.20	94.76
120 days	91.06	94.98	93.49
180 days	90.47	93.74	92.41

In vitro drug release studies

In vitro drug release studies were carried out and depicted in Table 4 & 5 and Figure 2 & 3. Among all the formulations S11 showed best drug release of 96.98 ± 5.28% within 12 h when compared with other formulations.

Mathematical modeling of optimized formula of microspheres

In the view of establishment of release mechanism and quantitatively interpreting and translate mathematically the dissolution date being plotted (Figure 4, 5, 6 & 7 and Table 6).

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e. 0.991 indicates that the drug release follows a zero-order mechanism. 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 Korsmeyer 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. 0.9863 starting that the release from the matrix was through diffusion. Further the n value obtained from the Korsmeyer plots i.e. 0.470 suggest that the drug release from microspheres was anomalous Non fickian diffusion.

Drug Excipients Compatibility Studies

FT-IR studies

There was no alteration in peaks of Olmesartan pure drug (Figure 8) and optimized formulation (Figure 10), also shown Olmesartan physical mixture in Figure 9, suggesting that there was no interaction between drug & excipients. There is additional peaks appeared or disappeared hence no significant changes in peaks of optimized formulation was observed when compared to pure drug, indicating absence of any interaction.

Scanning Electron Microscopy

The external and internal morphology of controlled release microspheres were studied by Scanning Electron Microscopy.

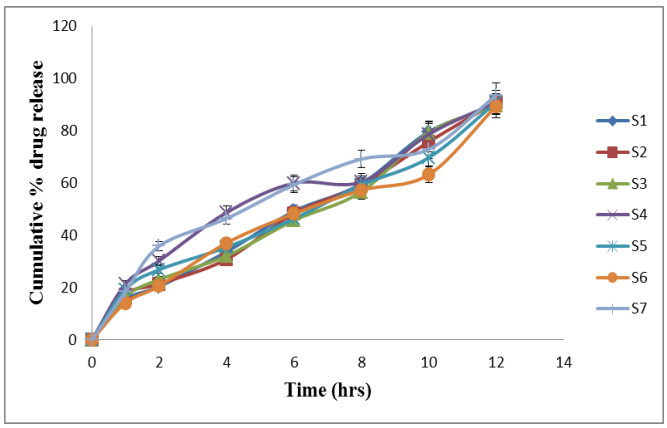


Fig. 2: *In vitro* cumulative % drug release of Olmesartan sodium alginate microspheres formulation

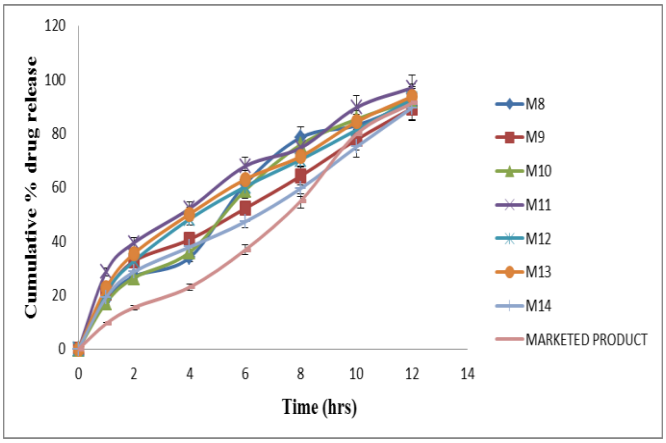


Fig. 3: *In vitro* cumulative % drug Olmesartan sodium alginate release of microspheres formulations

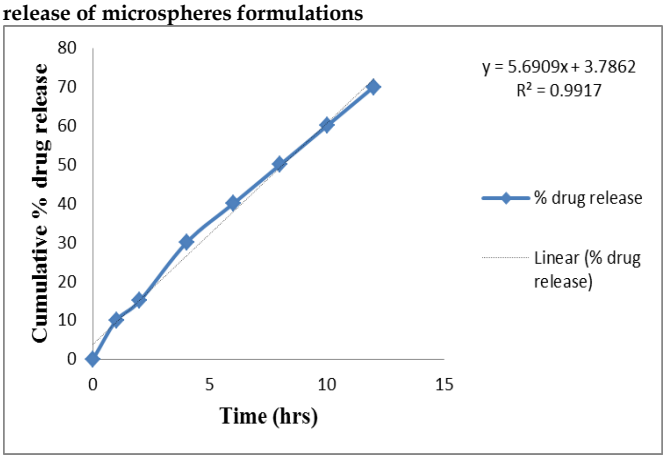


Fig. 4: Zero order plot for the optimized formulation of Olmesartan micropsheres S11

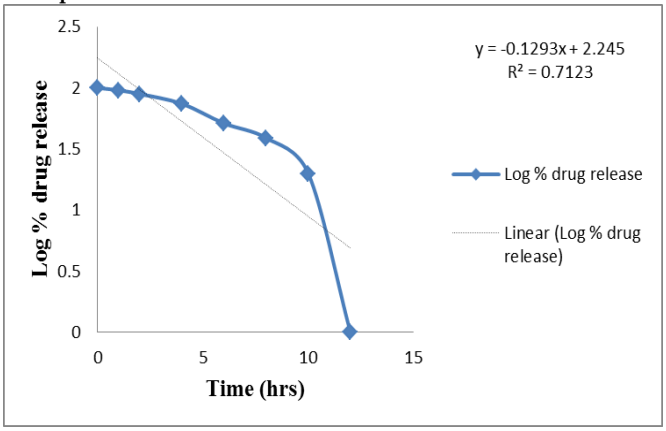


Fig. 5: First order plot for the optimized formulation of Olmesartan microspheres S11

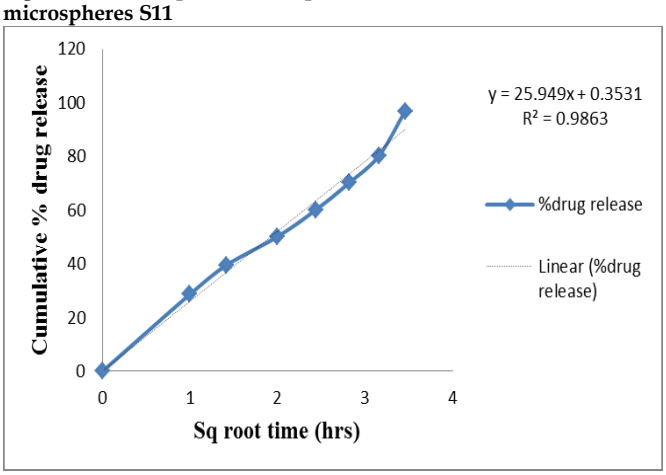


Fig. 6: Higuchi plot for the optimized formulation of olmesartan microspheres S11

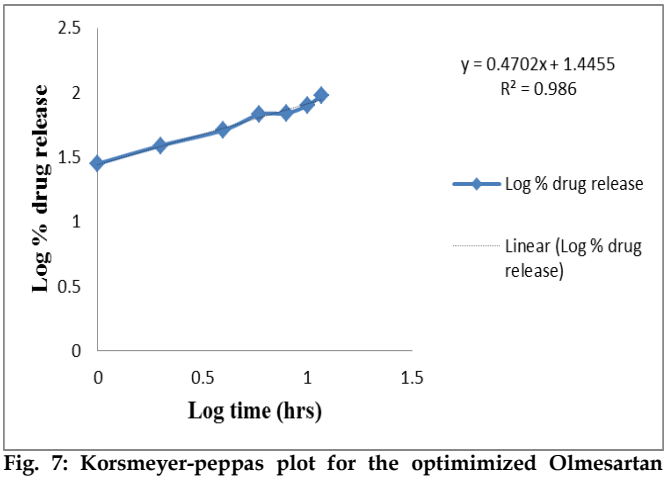


Fig. 7: Korsmeyer-peppas plot for the optimimized Olmesartan microspheres S11

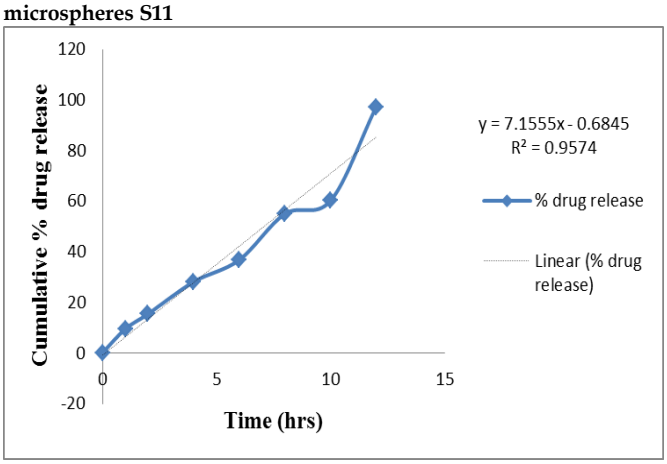


Fig. 8: Zero order plot for the Marketed product

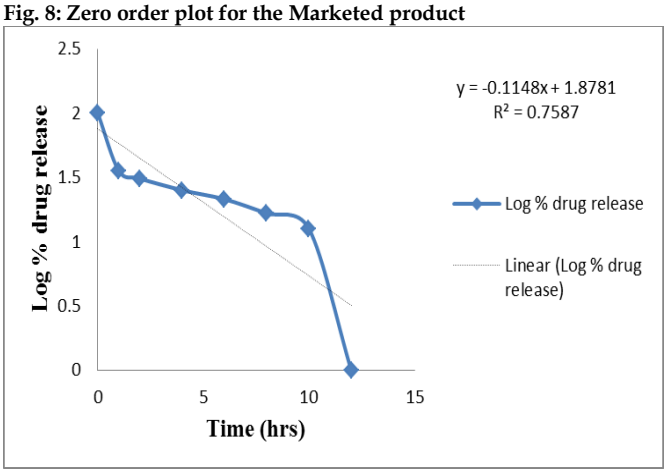


Fig. 9: First order plot for the Marketed product

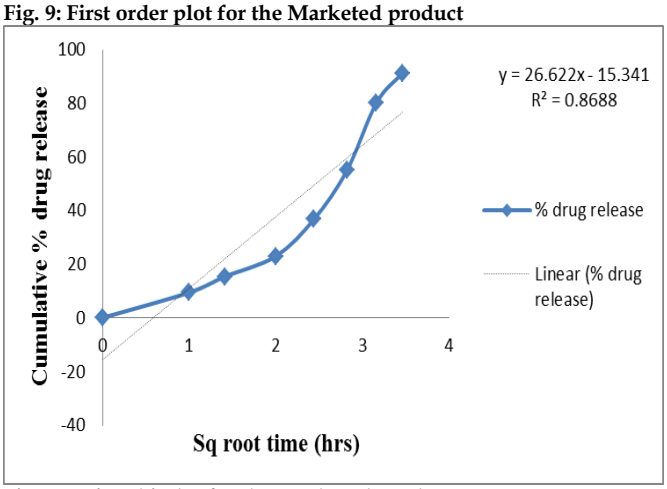


Fig. 10: Higuchi plot for the Marketed product

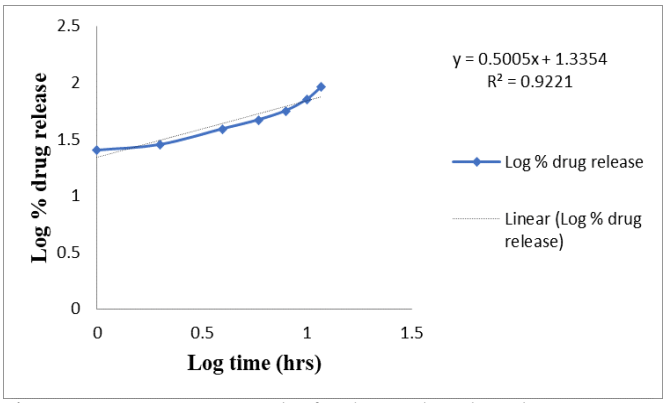


Fig. 11: Korsmeyer-peppas plot for the Marketed product

Morphology of the various formulations of Olmesartan microspheres prepared was found to be discrete and spherical in shape (Figure 11). The surface of the Olmesartan microspheres was rough due to higher concentration of drug uniformly dispersed at the molecular level in the sodium alginate matrices. There are no crystals on surface which states that is drug is uniformly distributed.

Stability studies

Optimized formulation was selected for stability studies since high cumulative % drug release. Stability studies were conducted for 6 months according to ICH guidelines. From these results it was concluded that, optimized formulation is stable and retained their original properties with minor differences which depicted in Table 7.

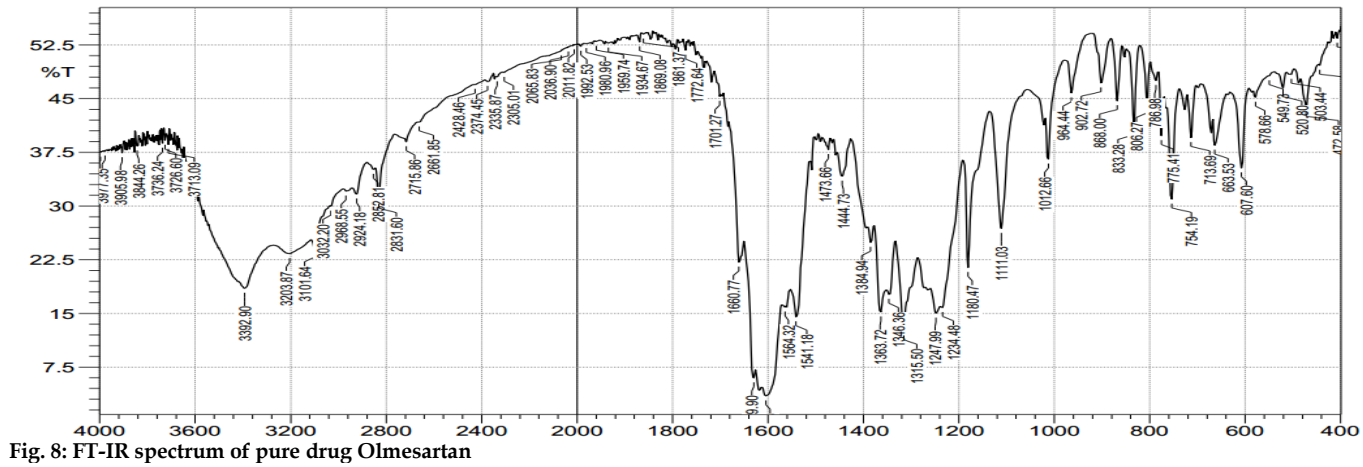


Fig. 8: FT-IR spectrum of pure drug Olmesartan

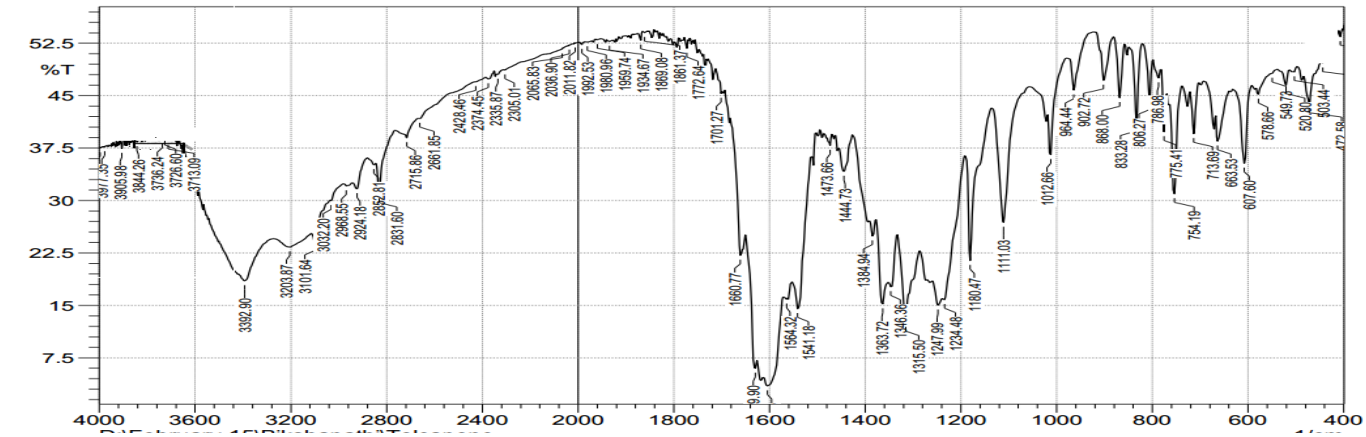


Fig. 9: FT-IR spectrum of Olmesartan physical mixture

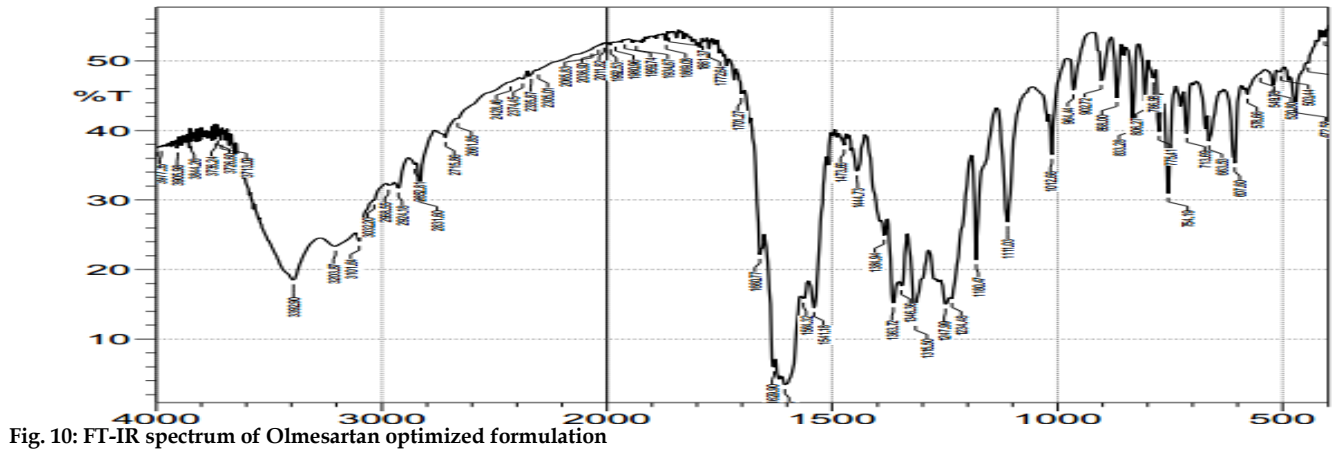
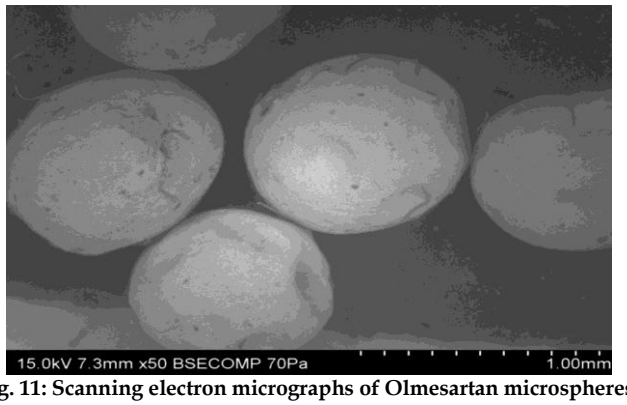


Fig. 10: FT-IR spectrum of Olmesartan optimized formulation



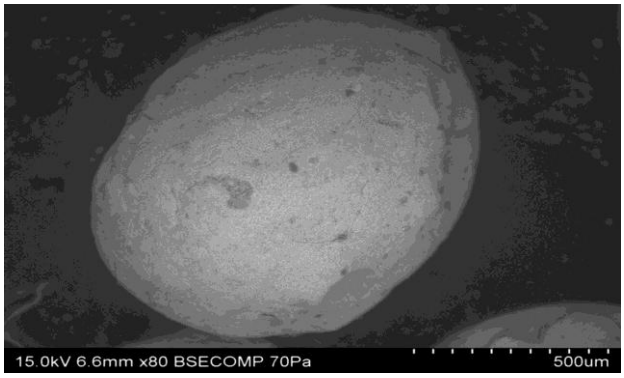


Fig. 11: Scanning electron micrographs of Olmesartan microspheres

Olmesartan loaded microspheres were prepared by ionotropic gelation method. From the results it concluded that formulation S11 was found to be satisfactory results in terms of excellent Micromeretic properties, particle size, yield of microsphere, entrapment efficiency, swelling index and highest *in vitro* drug release of in a sustained manner with constant fashion over extended period for 12h compared with marketed product in 12 h. The drug and excipients were compatible studied by using FTIR. Drug release from olmesartan microspheres followed Zero order and Higuchi model. It was suggested that mechanism of drug release from microspheres was diffusion controlled. The prepared microspheres were spherical in shape studied by SEM studies. The optimized formulation S11 was stable. Hence the formulated and prepared floating Olmesartan microspheres may establish to be potential candidate for safe and effective sustained drug delivery and improve the bioavailability.

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