RESEARCH ARTICLE

Development and Characterization of Olmesartan Medoxomil-Loaded Microspheres for Hypertension Management

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ABSTRACT

Our aim is to develop and assess microspheres loaded with olmesartan medoxomil, the antagonist of angiotensin II receptor which is used in hypertension treatment, for their efficacy. The microspheres were fabricated through a solvent evaporation process employing eudragit L100 and chitosan as the inner phase and liquid paraffin as the outer phase. Optimization was done according to the results of entrapment efficiency and *in-vitro* drug release. Fourier-transform infrared (FTIR) analysis indicated negligible interaction, which clarifies the suitability of the drug and excipients. The resulting microspheres exhibited a pale yellow hue and free-flowing characteristics, as confirmed by micromeritics experiments. Scanning electron microscopy (SEM) revealed smooth and spherical microspheres. Particle size, ranging from 187.44 to 358.75 µm, increased with polymer concentration, as determined by optical microscopy. Formulation F9, with a ratio of eudragit L100 to chitosan at 7:1, demonstrated the highest drug entrapment percentage (97.82%). *In-vitro* release studies demonstrated a reduction in olmesartan medoxomil release with increasing polymer content, with formulation F9 sustaining release for 12 hours. Furthermore, short-term accelerated stability testing indicated the physicochemical stability of the microsphere formulations throughout the stability period.

Keywords: Olmesartan medoxomil, Microspheres, Solvent evaporation, Eudragit L100, Chitosan.

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INTRODUCTION

Olmesartan medoxomil functions by inhibiting substances that constrict blood vessels, facilitating smoother blood flow and enhancing the heart's pumping efficiency. Angiotensin II, derived from angiotensin I through the angiotensin system, stimulates aldosterone synthesis, cardiac activity, and kidney sodium reabsorption. Olmesartan is known for its ability to selectively inhibit the vasoconstrictive effects of angiotensin II by blocking its interaction with the AT1 receptor located in vascular smooth muscle. This inhibition occurs regardless of the pathway through which angiotensin II is produced. Importantly, olmesartan demonstrates a notable affinity towards the AT1 receptor compared to AT2 receptor.[1-3] Given its efficacy, olmesartan has gained popularity for hypertension management.

Microspheres, which are solid particles with spherical shapes and sizes up to 1000 µm, have diverse applications in the field of pharmaceuticals. Whether polymeric, waxy, or other compositions, microspheres hold promise for enhancing patient compliance by providing sustained therapeutic responses with minimal side effects. Recognizing this potential, the current study endeavors to develop and assess olmesartan medoxomil-loaded microspheres for hypertension management.[4-7]

MATERIALS AND METHODS

Olmesartan medoxomil was gifted by Yarrow Chem produced, Maharshtra. Methanol and chloroform were acquired from Molychem in Mumbai, and sodium dihydrogen phosphate from Finar Chemical Ltd in Ahmedabad, India. In addition, ethanol was acquired from Molychem in Mumbai. All additional materials and chemicals utilized are of the highest quality.

Infrared Spectroscopy using Fourier Transform

Infrared spectroscopy was conducted using an Agilent Cary-630 FTIR instrument, with spectra collected in the range of

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4000 to 400 cm^{-1}. Methodology entailed 200 to 400 mg sample in KBr and compacting using a hydraulic press at a pressure of 5 tonnes for 5 minutes. IR-spectral experiments revealed the interaction between drugs and excipients by analyzing any shift in peaks.[8]

Melting Point Determination

Olmesartan medoxomil melting point was assessed employing the open capillary tube technique. In this procedure, a tube was sealed and filled with olmesartan medoxomil by tapping it multiple times. A computerized melting device was used to position the capillary tube. The gadget was programmed to automatically increase the heating temperature at a rate of 1ºC per minute. The temperature rise was observed with a magnifying lens. The temperature at which the medication began to melt was recorded.[9]

Preparation of Olmesartan Microspheres

Olmesartan microspheres were created utilizing a solvent evaporation process with Eudragit L100 and chitosan as a polymer. One of the most common microsphere preparation processes for controlled-release applications is solvent evaporation. In brief, varying ratios of drugs and polymers (1:1, 1:2, 1:3) taken in methanol with vigorous stirring to achieve a uniform drug-polymer sample. This mixture was then slowly added to a liquid paraffin having 0.2% Span 80. To ensure complete evaporation of the solvent, the sample was stirred in a magnetic stirrer at 500 rpm for 2 to 3 hours at room temperature. Following the removal of the liquid paraffin, appropriate filtration was done.[10-13] Different concentrations and ratios of polymers are shown in Table 1.

Evaluation of Olmesartan Microsphere

Micromeritic evaluation

The micromeritic characteristics of the formulated microspheres were analyzed as per the reported parameters.[14]

Determination of angle of repose

A powdered blend was assessed at a predetermined height. The height and circumference were traced. Area counted within its boundary. Measurement is calculated using the following formula:

$$\tan \theta = h/r$$

Bulk density and tapped density determination

About 20 grams of blended powder (W) were placed in 100 mL graduated cylinder, and the starting volume was recorded. Further procedures were carried out as per the reported methodology.[15,16]

Hausner's ratio

Hausner's ratio is calculated by dividing both densities, tapped and bulk.[15]

Compressibility index

The compressibility index (CI) provides insight into compressibility and flowability. A compressibility index below 20% suggests that the material has favorable flow characteristics.[15] CI was computed using the formula:

Table 1: Concentration and ratios

Batch	*Olmesartan (mg)*	*Eudragit L100 (mg)*	*Gum (mg)*	*Methanol (mL)*	*Liq parapaffin(mL)*	*Span 80 (%)*
F1	20	10	10	50	20	0.2
F2	20	10	30	50	20	0.2
F3	20	10	50	50	20	0.2
F4	20	10	70	50	20	0.2
F5	20	10	90	50	50	0.2
F6	20	30	10	50	20	0.2
F7	20	50	10	50	20	0.2
F8	20	70	10	50	20	0.2
F9	20	90	10	50	50	0.2

$$CI = \frac{(\text{Tapped Density} - \text{Bulk Density})}{\text{Tapped Density}} X100$$

Particle size determination

This analysis was performed via microscopy. A calibrated optical microscope was used to measure the sizes of approximately 100 microspheres.[15]

Percentage yield

The %yield is determined by accurately weighing microspheres and dividing weight.[15] % yield was then calculated using the following formula:

$$\%\text{yield} = \frac{\text{actual wt of product}}{\text{total wt of excipients with drug}} X100$$

Drug loading and drug entrapment

For the evaluation, microspheres containing an equivalent of 40 mg drug were used. Entrapment was assessed by processing them repeatedly with buffer 6.8 pH. The extracts were then combined and diluted with buffer. After appropriate dilution, the absorbance was recorded to 257 nm.[15] Results of the microspheres were calculated using specific formulas:

$$\%\text{Drug loading} = \frac{\text{Wt of the drug (DC)}}{\text{Total wt}} X\ 100$$

$$\%\text{Drug entrapment} = \frac{\text{drug actually present (DC)}}{\text{drugload expected}} X\ 100$$

Scanning electron microscope study

Prepared microspheres were subjected to morphological analysis using a scanning electron microscope (SEM). JEOL1100E Ionsputter was utilized for examination. Samples were loaded and carbon-coated with ion sputtering.[15]

Differential scanning analysis

Differential scanning calorimetry analysis (DSC) thermograms of microspheres as well as the pure drug were calculated using V2.5HTA instrument over 20 to 550°C at 20°C/minute heating rate.[15]

X-ray diffraction study

X-ray diffraction (XRD) spectra of prepared microspheres and olmesartan drug were obtained using an X-ray generator

(Make: Phillips, Model: PW 1830) coupled with a diffractometer (Model: PW 1710).[15]

In-vitro release study

On olmesartan medoxomil microspheres, the dissolution test was conducted. To the 900 mL of 0.1N HCL dissolution media (pH 1.2), a sample equivalent to 20 mg of olmesartan medoxomil was added at 100 rpm and 37 ± 0.5°C. At the end of 2 hours, the dissolution medium was changed to 6.8 pH buffer. Reading was taken at fixed intermissions over 12 hours, filtered, diluted, and assayed on a spectrophotometer at 257 nm. Using standard calibration curve, cumulative %drug release was determined.[15,17]

Stability studies

Stability studies for the drug substance under normal storage conditions are detailed in Table 2.

As per ICH, a test was performed on the selected formulation. Carefully chosen formulations were securely enclosed in aluminum foil within strongly locked containers and stored under specified conditions. After time period, the formulations were assessed for their percentage of drug entrapment and drug release characteristics.[15,18]

Table 2: Drug substance intended for regular storage

Study	*Storage conditions (Temp: ± 2°C, RH: ± 5% RH)*	*Minimum time period (year)*
Longterm	with 25°C /60% RH	1
Intermediate	with 30°C /65%RH	
accelerated	with 30°C /65%RH	
	with 40°C /65%RH	½

Table 3: Physical parameters of the API

Sr.No.	*Parameters*	*Remark*
1	Physical state	Solid
2	Color	White
3	Odor	Odourless

Table 4: Solubility of olmesartan medoxomil in various solvents

Solvents	*Solubility (mg/mL)*
Distilled water	0.089 ± 0.0012
0.1N HCl	20.53 ± 0.0640
Phosphate buffer pH 6.8	11.09 ± 0.0371
Methanol	52.11 ± 0.0418
Ethanol	39.26 ± 0.0256

RESULTS AND DISCUSSION

Preformulation Study

Physical appearance

The physical properties of the API was depicted (Table 3).

Melting point

Using capillary method, the melting point of olmesartan medoxomil was measured and was observed to be 177°C, which corresponds to USP standards (175–180°C), showing the purity of the sample.

Solubility analysis

Olmesartan medoxamil solubility tests were conducted with different solvents as well as phosphate buffer 6.8 pH. Table 4 displays data from solubility investigations in various solvents. The result revealed the highest solubility in methanol and ethanol was soluble in hydrochloric acid and 6.8 pH buffer, and so these solvents were chosen for calibration curve determination.

Compatibility study using FTIR

FTIR special analysis was used to characterize the physical mixture of medicine (Olmesartan medoxomil) and polymer for any physical or chemical changes in drug properties. Interpretations of the IR-spectrum are depicted in Table 5 and spectra are shown in Figure 1.

The results showed no functional group interference, as the principal peaks of olmesartan medoxomil remained unaffected in the drug-excipient physical combinations, indicating chemical compatibility.

Micromeritics studies

The micrometric properties depicted in Table 6. Properties assessed included Hausner's ratio (HR), percentage compressibility index, and densities. The percentage CI ranged from 11.26 to 18.75 across F1 to F9, showing required flow characteristics. The angle of repose (AR) of F1 to F9 microsphere formulations were between 18.09 and 26.94°, suggesting that the prepared microspheres exhibit excellent to required flow behavior.

Particle size analysis

The size for all formulations was found to be between 187.44 and 358.75 µm. The size of formulation F1, which contained eudragit L100 and chitosan in a 1:1 ratio, was 187.44 µm. The formulation F9, which contained eudragit L100 and chitosan in a 7:1 ratio, had the largest particle size (358.75 µm). As the concentration of eudragit L100 in the formulation was enhanced, which could be attributed to the high viscosity of eudragit L100. This leads to an increase in droplet size and, hence, particle size. The formulation using a 1:1 blend of eudragit L100 and chitosan revealed reduced particle size (F1; 187.44 µm), which could be due to the lower viscosity of chitosan compared to eudragit L100. The mean particle size of olmesartan medoxomil microspheres is depicted in Table 7 and Figure 2.

Drug loading, drug entrapment and percentage yield

Table 8 displays the results of drug load capacity and entrapment efficiency. The entrapment efficiency was lower in formulation F1, which contained a 1:1 ratio of eudragit L100 to chitosan. The formulation F9 with a 7:1 eudragit L100:chitosan ratio had the maximum entrapment, 97.82%. The formulation comprising more eudragit L100 than chitosan had a higher drug entrapment efficiency and drug loading capacity. It could be because hydrophobicity increased as the concentration of eudragit L100 increased, resulting in improved polymer precipitation in the

Table 5: Interpretations of IR-specta

Functional group	*Wave number (cm^{-1})*			
	Olmesartan medoxomil (Drug)	*Drug - Eudragit L100*	*Drug- chitosan*	*Microsphere mixtures*
-OHalcohol groups (Stretched)	3360.11	3362.04	33354.32	3365.90
C=O ketonic group	1668.48	1668.48	1668.48	1662.69
C-H (Stretch)	2929.97	2928.04	2926.11	2928.04
C-N secondary amine	1134.18	1134.18	1132.25	1130.32
C-O bending	1035.81	1003.02	977.94	1047.38

Table 6: Micromeritics of microspheres

Batches	*HR*	*CI (%)*	*AR (degree)*	*Bulk densities (g/cm^{3})*	*Tapped densities (g/cm^{3})*
F1	1.158 ± 0.023	12.05 ± 0.21	21.93 ± 0.23	0.5422 ± 0.045	0.6166 ± 0.019
F2	1.166 ± 0.051	14.24 ± 0.32	24.74 ± 0.24	0.4986 ± 0.027	0.6884 ± 0.024
F3	1.193 ± 0.011	11.26 ± 0.27	18.09 ± 0.17	0.5233 ± 0.019	0.7203 ± 0.028
F4	1.131 ± 0.019	11.94 ± 0.34	23.81 ± 0.14	0.4811 ± 0.065	0.6446 ± 0.015
F5	1.141 ± 0.020	12.36 ± 0.74	24.67 ± 0.36	0.5418 ± 0.023	0.6183 ± 0.031
F6	1.156 ± 0.087	13.59 ± 0.82	25.08 ± 0.15	0.5166 ± 0.025	0.7176 ± 0.013
F7	1.142 ± 0.031	18.75 ± 0.21	26.94 ± 0.64	0.4571 ± 0.019	0.7248 ± 0.028
F8	1.119 ± 0.026	14.38 ± 0.79	21.86 ± 0.33	0.4819 ± 0.076	0.6852 ± 0.042
F9	1.184 ± 0.032	15.44 ± 0.68	19.69 ± 0.41	0.5361 ± 0.044	0.7210 ± 0.039

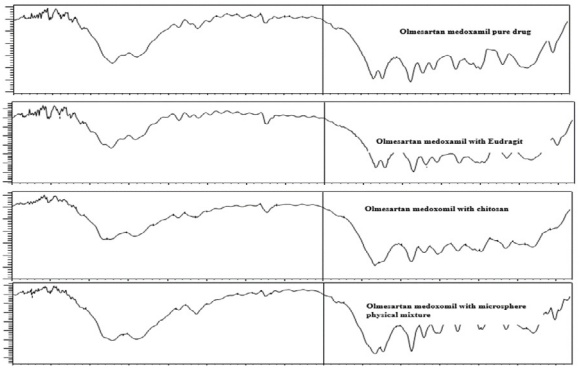

Figure 1: Infrared spectra for olmesartan medoxomil with microsphere physical mixture

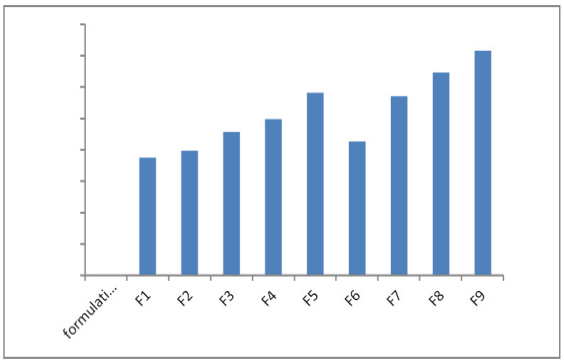

Figure 2: Comparison of mean particle size of F1 to F9 formulations

droplet's border layer. As a result, medication partitioning to the As a result, medication partitioning to the continuous phase (liquid paraffin) will be limited.

The percentage drug loading for F1 to F9 ranged from 48.54 to 98.78%, while the entrapment efficiency ranged from 68.30 to 97.82%. The yield of different formulations F1 through F9 was computed and found to be in the range of 78.14 to 93.28%. Percentage drug loading of the prepared microspheres is depicted in Figure 3.

Morphological study using SEM

To assess the shape and surface morphology of the olmesartan medoxomil microsphere, SEM was used. This study indicated that all microspheres generated were non-porous, spherical in form and smooth in nature.

When compared to the microspheres of olmesartan medoxomil with greater amounts of chitosan having higher concentrations of eudragit L00 were found optimum. Figure 4 shows photographs of the formulations F5 and F9.

DSC analysis

The DSC profile clearly showed that pure drug olmesartan exhibited a pronounced endothermic peak at 189.81°, which corresponded to the medication's reported melting temperature, but no such peak was detected for the drug-loaded microsphere. DSC thermogram of pure drug olmesartan was indicated in Figure 5.

XRD analysis

Several prominent peaks in the XRD of olmesartan at diffraction angles of 2; 11, 13, 15.5, 16.5, 17.5, 19, 22.5, 26, 28.5, and 32° confirmed the presence of crystalline olmesartan. These peaks, however, were not seen in the XRD pattern of olmesartan-loaded microspheres, demonstrating that

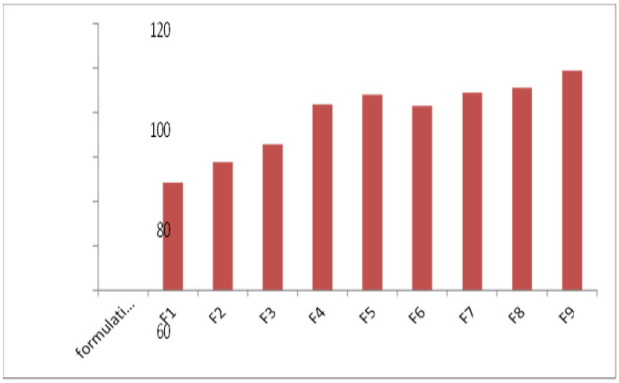

Figure 3: Percentage drug loading of the prepared microspheres

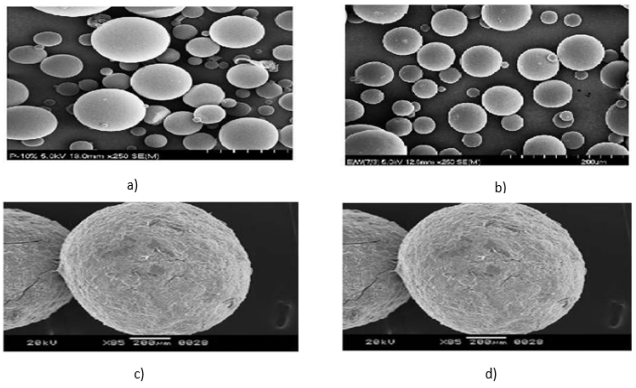

Figure 4: SEM images of olmesartan medoxomil microsphere formulation

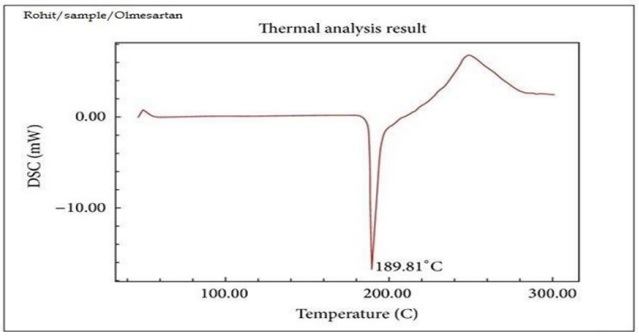

Figure 5: DSC thermogram of olmesartan (pure)

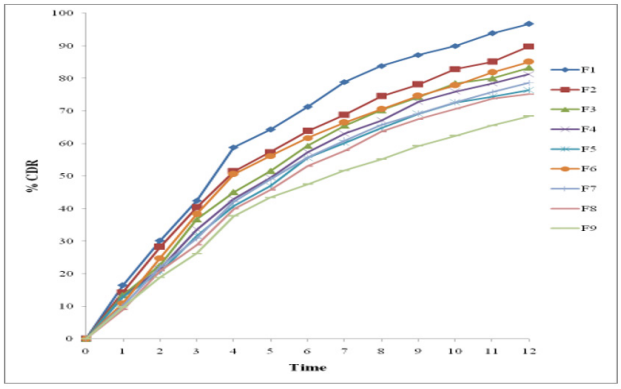

Figure 6: Comparative cumulative percentage drug profile

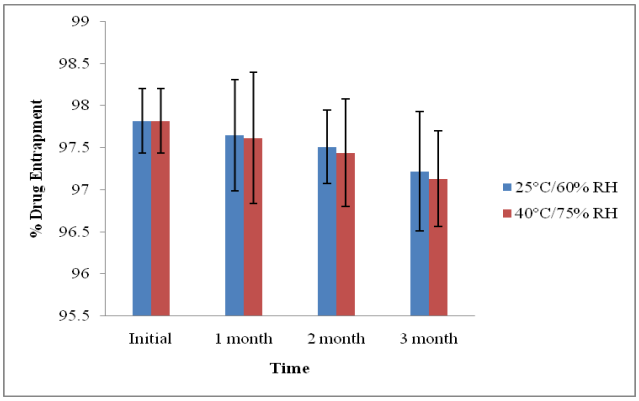

Figure 7: Comparative %drug entrapment of formulation F9 during stability study

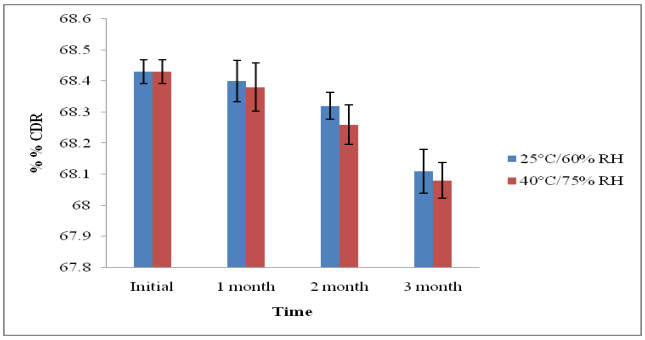

Figure 8: Comparative *in-vitro* drug release from formulation F9 during stability study

olmesartan was either molecularly dispersed or disseminated in an amorphous state.

In-vitro drug release studies

Initially, for the first 2 hours, buffer pH 6.8 was used as dissolving media. Figure 6 demonstrates statistics for various formulations. At the conclusion, the cumulative %DR ranged from 68.43 to 96.78%. The %DR from the produced microsphere was larger during the first four hours, then rapidly declined. This could be due to the fact that microspheres eventually begin to inflate, which regulates medication release from microsphere formulations. Because the medicine may have caused an initial burst release be present on the surface of particles. Following that, the medication was steadily released. The cumulative medication release is determined by the polymer mix utilized. After 12 hours, formulation F9 demonstrated nearly 96.78% drug release, whereas formulations F5 and F9 containing eudragit L100: chitosan in 7:1 and 1:7 ratios showed 85.12 and 83.29% drug release, respectively. Results show an enhanced diffusional path length. Which has the potential to reduce total medication release from the polymer matrix. Eudragit L100, a pH-independent and hydrophobic polymer, hindered dissolution medium penetration into the microspheres. Furthermore, at this ratio, smaller microspheres are generated with a higher surface area available to the dissolving media, resulting in quicker drug release.

Table 7: Mean size of microspheres

Batches	*Mean size (µm) ± SD*
F1	187.44 ± 4.35
F2	198.38 ± 6.11
F3	228.56 ± 5.42
F4	249.07 ± 4.14
F5	290.97 ± 4.73
F6	213.40 ± 3.82
F7	285.36 ± 3.93
F8	323.68 ± 2.24
F9	358.75 ± 5.45

Table 8: Drug loading, drug entrapment and percentage yield of microspheres

Formulation	*%Drug loading*	*%Drug entrapment*	*% yield*
F1	48.54 ± 0.13	68.30 ± 0.25	78.14 ± 0.58
F2	57.78 ± 0.46	82.48 ± 0.27	80.91 ± 0.33
F3	65.81 ± 0.20	86.40 ± 0.28	83.73 ± 0.62
F4	83.73 ± 0.25	90.12 ± 0.36	85.98 ± 0.28
F5	87.88 ± 0.44	94.62 ± 0.38	79.20 ± 0.35
F6	82.86 ± 0.22	84.44 ± 0.12	81.88 ± 0.27
F7	88.78 ± 0.47	89.90 ± 0.84	85.53 ± 0.45
F8	91.08 ± 0.61	91.90 ± 0.28	89.38 ± 0.18
F9	98.78 ± 0.41	97.82 ± 0.82	93.28 ± 0.34

Table 9: Various kinetic models for optimized batch

Batches	*Zero-order*	*First-order*	*Higuchi's-plots*	*Korsmeyer - Peppas plot*	*Best fit model*
	r^2				
F9	0.8341	0.9518	0.9953	0.9988	Korsmeyer-peppas plot

Drug release kinetics

To examine, various kinetic models were used in order to better understand the drug release behaviour. Table 9 shows the correlation coefficient (r^2) values of the optimized batch for the fit of several kinetic models.

Stability study

Depending on the results, formulation F9 was chosen for short-term accelerated stability experiments. The selected formulation was stored for a stiputed period and condition, respectively. The sample was then examined after the completion of time periods for its appearance, *in-vitro* drug release and entrapment efficiency. Results are as indicated in Table 10, Figures 7, and 8.

The stability analyses revealed that the appearance of the F9 did not vary significantly (p >0.05). As a result, the produced formulation remained physicochemically stable throughout the study period.[19,20]

Table 10: Stability studies for microsphere formulation F9

Duration in months	*To-25°C/60% RH*		*To-40°C/75% RH*	
	%Drug entrapment	*%CDR*	*%Drug entrapment*	*%CDR*
Initial	97.82 ± 0.82	68.43 ± 0.81	97.82 ± 0.82	68.43 ± 0.81
1	97.65 ± 0.65	68.40 ± 0.64	97.62 ± 0.95	68.38 ± 0.76
2	97.51 ± 0.33	68.32 ± 0.77	97.44 ± 0.73	68.26 ± 0.44
3	97.22 ± 0.94	68.11 ± 0.92	97.13 ± 0.44	68.08 ± 0.78
p-value	>0.05			

CONCLUSION

The solvent evaporation method was used to successfully manufacture olmesartan microspheres in this investigation. Micromeritic investigations revealed that the produced microspheres had an optimum particle size. SEM examination resulted in a good appearance and somewhat aggregated units. The polymer employed determined the best drug entrapment as well as practical yields. The percentage of drug entrapment and drug concentration rose as polymer concentration increased. After 12 hours of *in-vitro* drug release, formulation F4 with a 7:1 chitosan:eudragit L100 ratio and formulation F9 with a 1:7 chitosan:eudragit L100 ratio demonstrated regulated drug release behavior. Within several mathematical models, the curve fitting was observed. The formulation F9 fit the Higuchi type and DR. Formulation F9 was chosen for three months of short-term accelerated stability experiments according to the findings of %DR studies. Overall, the produced formulation remained stable till the stipulated period. Conclusively, the constructed olmesartan medoxomil-loaded microspheres were found good candidates for oral controlled drug delivery systems to extend drug retaining in the stomach and enhance drug bioavailability for effective management of hypertension.

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