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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE MICROSPHERES OF SERTRALINE FOR IMPROVING BIOAVAILABILITY

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ABSTRACT

The objective of the current investigation was to optimize and formulate mucoadhesive microspheres loaded with sertraline utilizing guar gum as the mucoadhesive polymer and stabilizing the particles with magnesium stearate so that the formulation could control the release of the drug thereby reducing its dosing frequency and improving the bioavailability. The microspheres were prepared using emulsion coacervation method and the micromeritic features were evaluated. The angle of repose was measured using the fixed funnel method and was found to be ranging from 21.57 ± 0.121 to 28.14 ± 0.620. This indicates that good flow property of powder blend. The bulk and tapped density of the formulations ranged from 0.379 ± 0.009 to 0.608 ± 0.002 g/cm3 and 0.408 ± 0.003 to 0.735 ± 0.006 g/cm3 respectively. The values of Hausner's ratio ranged from 1.04 to 1.25 whereas the Carr's Index ranged from 3.92 to 19.94. The yield of all the batches of microspheres was found to be reasonably good ranging from 50.69 % to 73.84 %. The drug loading was found to be 68.35 ± 0.221 to 72.63 ± 0.535 % while the size of microspheres ranged from 13.64 ± 0.055 µm to 17.90 ± 0.121 µm. Swelling study was performed on all the formulation for 24 h and swelling index ranged from 2.69 to 4.72. The optimization was done and the optimized formulation was studied for particle size, mucoadhesion time and in vitro release. The particles size of the optimized formulation was found to be 13.92 µm with polydispersity index of 0.301. The mucoadhesion time of the formulation was obtained to be 6 h 08 min. The in vitro release of sertraline was studied for 12 h and it was found that the microsphere formulation was able to sustain the release of the drug for more than 12 h with 73.5 % drug released at the end of the 12th hour.

Key words: Sertraline, microspheres, bioavailability, mucoahesion, release.

INTRODUCTION

Sertraline is a popular antidepressant medication commonly known as a selective serotonin reuptake inhibitor (SSRI). Sertraline is indicated for the management of major depressive disorder (MDD), post-traumatic stress disorder (PTSD), obsessive-compulsive disorder (OCD), panic disorder (PD), premenstrual dysphoric disorder (PMDD), and social anxiety disorder (SAD).[1] Slightly soluble in water and isopropyl alcohol, sparingly soluble in ethanol. Following once-daily administration the mean peak plasma concentrations (Cmax) of sertraline occurred between 4.5 to 8.4 hours after administration. Bioavailability has been estimated to be above 44%. Sertraline is approximately 98-99% bound to human plasma proteins. Sertraline is heavily metabolized in the liver and has one major active metabolite. It undergoes N-demethylation to form N-desmethylsertraline, which is much less potent in its pharmacological activity than sertraline. The half -life of sertraline is 22-36 hours.[2] Since sertraline is extensively metabolized, excretion of unchanged drug in the urine is a minor route of elimination, with 12-14% of unchanged sertraline excreted in the feces. The bioavailability of sertraline low and its protein binding is very high. This makes it a good candidate for mucoadhesive delivery for improving bioavailability[3-5]. The objective of this work was the development and investigation of mucoadhesive microspheres of sertraline in order to enhance its bioavailability and reduce the dose. Treatment of disease requires maintenance of uniform concentration of drug in blood for a long period of time. Factorial design is an

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optimization approach widely used to optimize the excipient concentration/ratios for development of delivery systems with desired properties.

Material and Methods

Calibration curve of sertraline[6]

A stock solution of sertraline (1mg/ml) was prepared in 50% aqueous methanol. Diluted sertraline solution (100µg/ml) in methanol was prepared from the stock solution. Then, serial dilutions were prepared from that diluted into sertraline solution in ethanol to obtain different concentrations ranging from 5 to 25 µg/ml. The absorbance of these serial dilutions was determined spectrophotometrically at λmax 273 nm, using methanol as a reference. Each sample was analyzed in triplicate and the results are presented as mean ± SD. The measured absorbance was plotted against the corresponding concentrations to obtain the standard calibration curve.

Formulation of mucoadhesive microspheres[7]

Sertraline microspheres were prepared according to the oil-in-oil emulsification-coacervation method using guar gum as the polymer. Guar gum was dissolved in 15.0 mL of acetone in a 250 mL beaker with stirring at room temperature. Guar gum (110 mg) and magnesium stearate (0.1 g) were dispersed in the polymer solution. The resulting milky white dispersion was added drop-wise into a beaker containing a mixture of liquid paraffin (50 mL) and span 60 (0.5 g) and homogenized using a paddle stirrer at 500 rpm for 2 h. The formed microspheres were separated by filtration and washed many times with n-hexane to make them completely free from oil. The microspheres were dried at room temperature and stored at 4°C until used. Eight batches of the microspheres were prepared for optimization of the process variables by varying the ratio of drug to polymer, stirring speed and amount of droplet stabilizer utilizing a 23 full factorial approach, as shown below in Table 1. The particles size (minimum size) and mucoadhesive ability (maximum) were taken as the desired responses for optimization.

Table 1 Batch Formula for formulation of mucoadhesive microspheres

Formulation Code	Sertraline (mg)	Guar gum (mg)	Magnesium stearate (g)	Stirring Speed (rpm)
F1	50	200	0.1	500
F2	50	200	0.2	500
F3	50	100	0.2	500
F4	50	100	0.1	500
F5	50	100	0.2	250
F6	50	200	0.1	250
F7	50	100	0.1	250
F8	50	200	0.2	250

Evaluation of micromeritic characteristics

Angle of repose, Carr's Index, Bulk density, Tapped density and Hausner's ration were determined to assess the flow ability of the prepared granules.

Yield

The formed microspheres were weighed accurately and the yield of the microspheres was determined by comparing the weight of the microspheres against the combined weight of the copolymer and drug using the equation:

Drug content

The sertraline content of the microspheres was determined using UV spectrophotometery. 10 mg of microspheres were dispersed in 10 mL of simulated intestinal fluid (SIF, pH 7.2). The dispersion was allowed to stand for 2 h, vortexed for 5 min and then centrifuged at 4,000 rpm for 10 min. The amount of sertraline contained in each batch of the formulations was determined by the UV at 273 nm. The drug-loading efficiency was then determined by the equation:

Particles Size

The average particle size was calculated using calibrated optical micrometer by dispersing the prepared formulation in distilled water and counting the size of individual particles under an optical microscope.

In-vitro release

The USP type II paddle apparatus with a paddle speed of 50 rpm was used for studying the release of the drug from the microspheres. The dissolution media used consisted of 900 mL of phosphate buffered saline (pH 6.8) and maintained 37±0.5°C. 5 mL of samples were collected at time points of every hour until 12 h and the media was replenished with the same volume of fresh media. The free sertraline concentration was estimated using a UV spectrophotometer at a wavelength of 273 nm. The release kinetic was studied by various kinetic models like zero order, first order, Higuchi plot and Korsemeyer-Peppas model. The best fit model was confirmed by the value of correlation coefficient.

Swelling Index

100 mg microspheres were allowed to swell for 24 h in 6.8 pH phosphate buffer. After 24 hr excess liquid were removed by blotting paper and microspheres were weighed. The degree of swelling was then calculated by the following formula

Degree of Swelling= ((M0-Mt))/(M0)*100)

In-vitro mucoadhesion wash-off test[8]

Mucoadhesive property of microspheres was determined by in-vitro adhesion test. Eggshell membrane was used for this purpose. A 2x1 cm piece of eggshell membrane were taken and fixed on a glass slide (kept at an angle of 45°C). About 100 mg microspheres were spread on rinsed, tissue specimen and hung onto one of the groves of a USP tablet disintegrating test apparatus containing 6.8 pH phosphate buffer. The disintegrating test apparatus was started, the tissue specimen showed regular up and down movements in a beaker. The time required for detaching of microspheres from mucosal surface membrane was recorded by visual inspection.

Results and Discussion

Calibration Curve of sertraline

The standard calibration curve of sertraline was constructed in 50% aqueous methanol to obtain different concentrations ranging from 5 to 25 µg/ml, for which the absorbance readings were determined spectrophotometrically at λmax 273 nm (Figure 1). The standard calibration curve was linear over the concentration range studied and obeys Beer-Lambert's law with a correlation coefficient (R2) 0.9972.

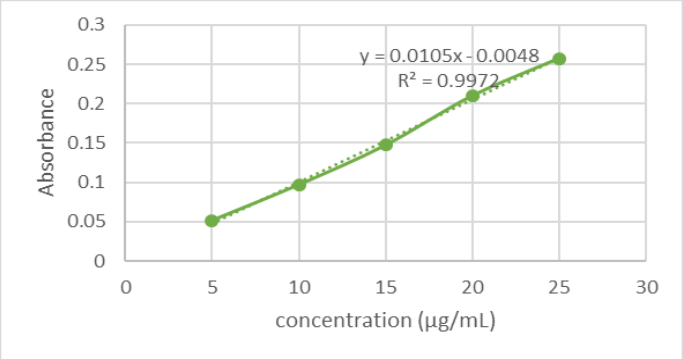

Figure.1 Calibration curve of sertraline

Characterization of Formulation Blends

The bulk and tapped density of the formulations ranged from 0.379 ± 0.009 to 0.608 ± 0.002 g/cm3 and 0.408 ± 0.003 to 0.735 ± 0.006 g/cm3 respectively. The bulk and tapped density play a vital role in pharmaceuticals as it reflects processing ability of the blend. It also reflects flow ability of the blend using various calculative ratios. The angle of repose was measured using the fixed funnel method and was found to be ranging from 21.57 ± 0.121 to 28.14 ± 0.620. Angle of repose of less than 30° is considered to be good for the flow of the powder. The Hausner's ratio and Carr's Index were calculated using the data obtained from bulk and tapped density. The values of Hausner's ratio ranged from 1.04 to 1.25 whereas the Carr's Index ranged from 3.92 to 19.94 (Table 2).

Table 2 Characteristics of the formulation blends

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Angle of Repose (°)	Carr's Index	Hausner's Ratio
F1	0.379 ±0.009	0.443 ±0.002	21.57 ±0.121	14.45	1.17
F2	0.448 ±0.005	0.521 ±0.004	22.15 ±0.060	14.01	1.16
F3	0.554 ±0.006	0.692 ±0.005	23.31 ±0.146	19.94	1.25
F4	0.608 ±0.002	0.735 ±0.006	23.62 ±0.297	17.28	1.21
F5	0.392 ±0.004	0.408 ±0.003	25.44 ±0.234	3.92	1.04
F6	0.390 ±0.003	0.412 ±0.005	26.54 ±0.075	5.34	1.06
F7	0.405 ±0.003	0.423 ±0.003	26.74 ±0.055	4.26	1.04
F8	0.386 ±0.004	0.429 ±0.005	28.14 ±0.620	10.02	1.11

Results are represented as mean ± standard deviation; n =3

All the results of powder characterization indicate that the formulation blends exhibited good to fair ability to flow and compress in to tablets.

Yield

The yield of all the batches of microspheres was found to be reasonably good ranging from 50.69 % to 73.84 % (Table 3). The highest yield was exhibited by the formulation F7. The good yield of the microspheres indicates that the formulation process and variables employed in preparing the microspheres are efficient.

Drug loading

As such the drug loading percentage was almost similar for all the formulations indicating that the concentration of guar gum did not had much effect on drug loading. The highest loading was however found in F3 (Table 3). The high drug loading efficiency in all the formulations was also suggestive of the high efficiency of the process parameters used for microsphere formulation.

Particle Size

The particle size was calculated using calibrated eye piece (n=30). The average particles size of the microspheres ranged from 13.64 ± 0.055 µm to 17.90 ± 0.121 µm.

Swelling index and mucoadhesive property of microspheres

For the evaluation of mucoadhesion eggshell membranes were utilized as the substitute of animal mucosa. The swelling index ranged from 2.69 to 4.72 whereas the time of mucoadhesion was from 2h 15min to 6h 21min (Table 3). The mucoadhesion increased with the higher concentrations of guar gum in the formulations.

Table 3 Yield, drug loading and size of microspheres

Formulation Batch	Yield (%)	Drug loading (%)*	Size (µm)**	Swelling Index	Mucoadhesion time (h)
F1	50.69	71.75 ± 0.630	13.64 ± 0.055	2.69	5.49
F2	64.15	71.58 ± 0.615	14.49 ± 0.248	3.17	6.21
F3	71.92	72.63 ± 0.535	16.48 ± 0.230	3.37	3.75
F4	72.31	72.55 ± 0.408	17.65 ± 0.133	4.72	2.34
F5	67.84	68.35 ± 0.221	17.90 ± 0.121	2.59	3.57
F6	70.76	69.69 ± 0.363	17.17 ± 0.058	3.21	5.34
F7	73.84	70.28 ± 1.756	16.61 7 0.292	3.62	2.15
F8	72.69	68.94 ± 0.843	16.85 ± 0.721	3.03	6.10

Results are represented as mean ± standard deviation; *n =3; **n=30

Optimization of the process variables

The optimization of process variables for formulation with maximum mucoadhesion and minimum particle size was done using the trial version of Design Expert version 7.0.0. A 23 full factorial approach with 8 runs was utilized to obtain the solutions for optimized formulation. The standard error of design was studied and the graphical representation is presented in Figure 2.

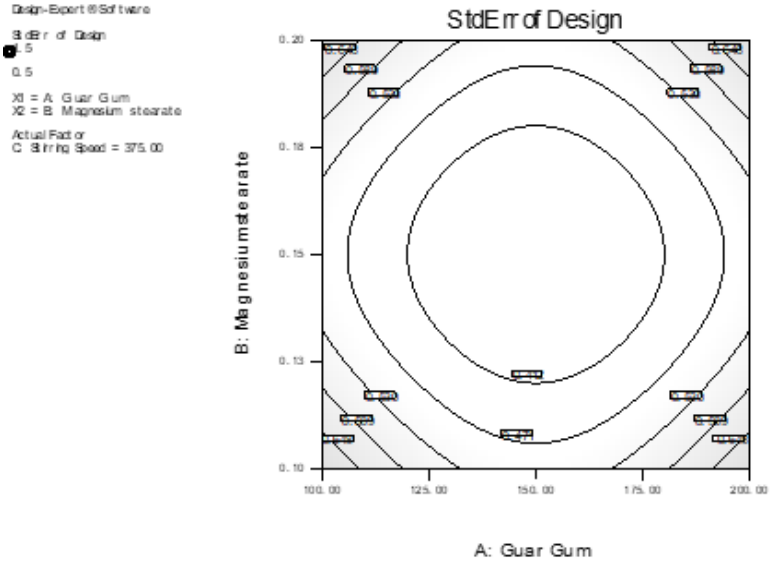

Figure 2 Contour plot for standard error of design

The particle size and mucoadhesion were statistically analyzed by ANOVA and the equations defining the effect of variables is presented in equation 1 and 2 respectively.

Particle Size = 16.59 + 0.71*A + 0.17*B - 0.76*C ------ Eq (1)

The standard deviation, and R-squared for Eq 1 were 1.12 and 0.7023 respectively suggesting that the process variables did not significantly contribute to particle size as such.

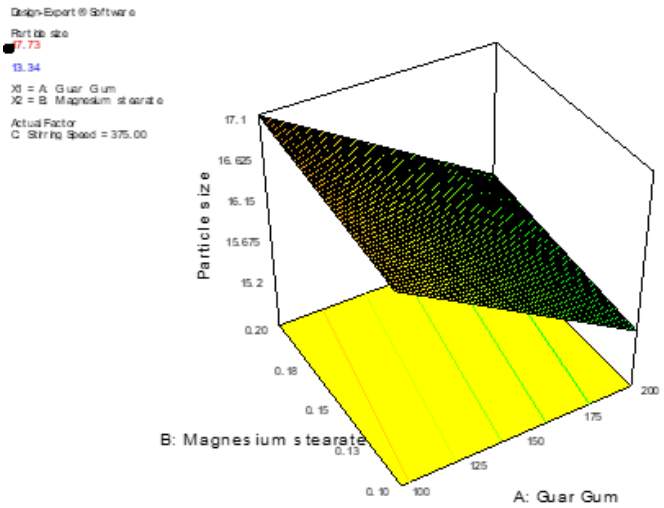

Figure 3 3D surface plot depicting effect of process variables on particle size

Mucoadhesion Time = 4.17 + 1.69*A + 0.28*B +0.068*C ------- Eq (2)

The standard deviation, and R-squared for Eq 1 were 0.13 and 0.9936 respectively, suggesting a highly significant correlation of the process variables with mucoadhesion time. The Eq 2 was able to predict the mucoadhesion of the formulation with minimum residuals.

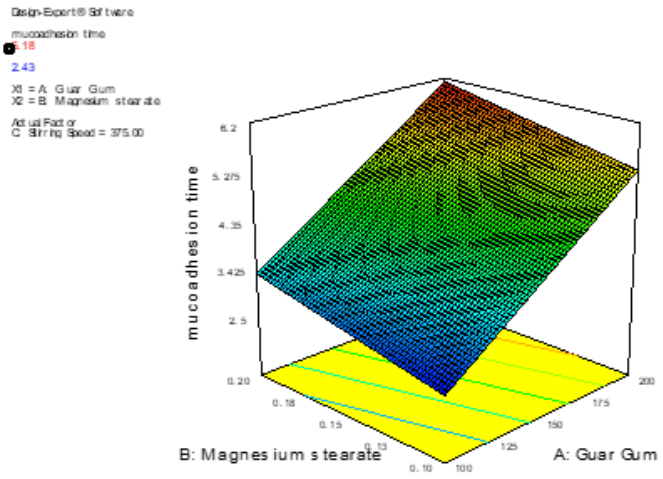

Figure 4 3D surface plot for effect of process variables on mucoadhesion

A total of 25 solutions were obtained by the above equations for achieving maximum mucoadhesion time and minimum particle size. The highest desirability was found with 196.4 mg guar gum, 0.17 g magnesium stearate and a stirring speed of 500 rpm. The solution predicted a particle size of 13.2695 µm and mucoadhesion time of 6.1733 h.

Evaluation of the optimized formulation

A formulation with the optimized process variables was prepared as per the reported procedure and was tested for particle size, mucoadhesion and in vitro release. The particles size of the formulation was found to be 13.92 µm with polydispersity index of 0.301. The mucoadhesion time of the formulation was obtained to be 6 h 08 min.

The in vitro release of sertraline was studied for 12 h and it was found that the microsphere formulation was able to sustain the release of the drug for more than 12 h with less than 80% drug released at the end of the 12th hour. The data obtained was fitted to various mathematical models to determine the release kinetics of sertraline from the microspheres (Figure 5-8).

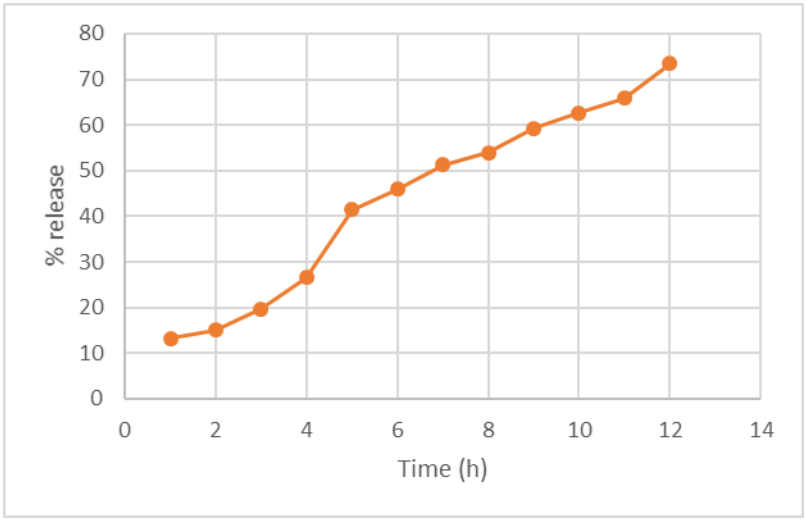

Figure 5 Zero order plot for drug release from microspheres

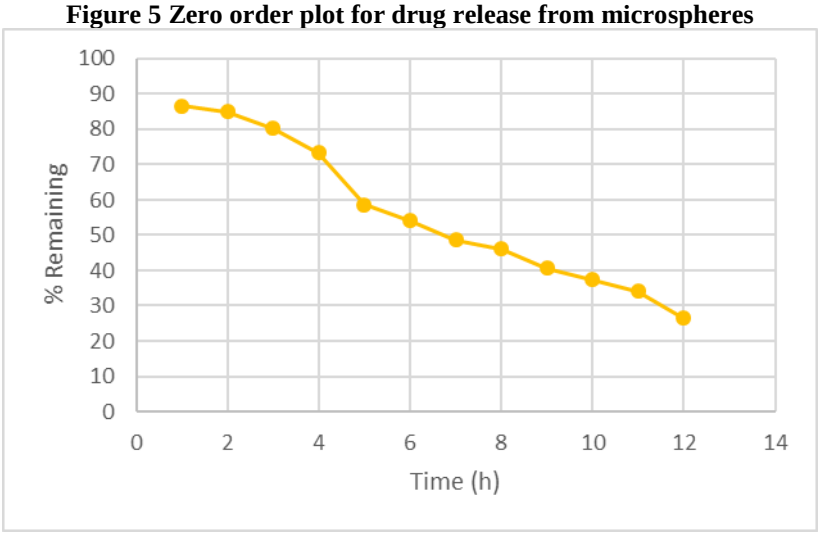

Figure 6 First order plot for drug release from microspheres

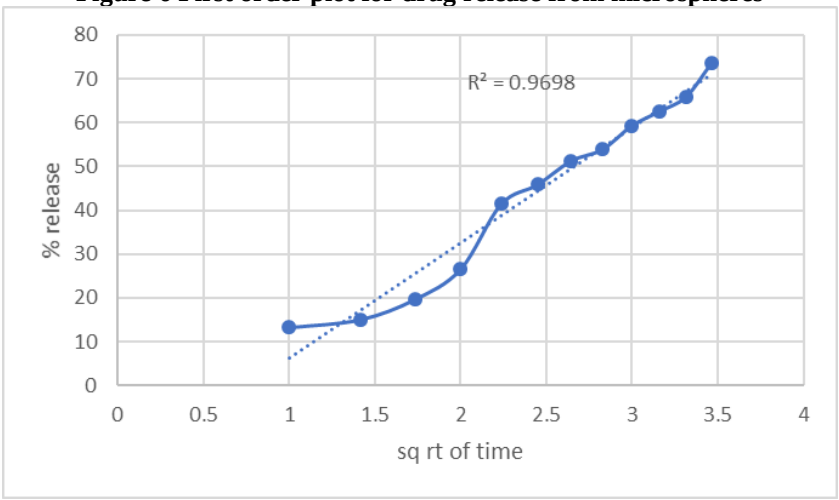

Figure 7 Higuchi plot for drug release from microspheres

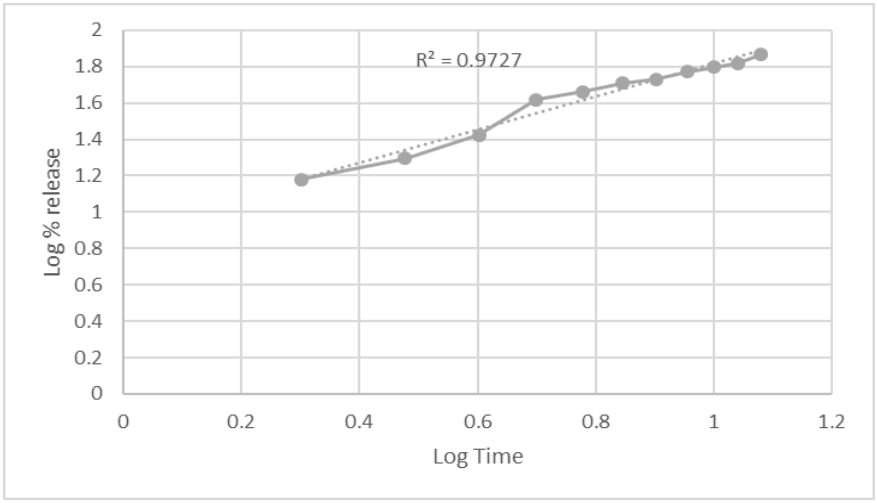

Figure 8 Korsemeyer-Peppas plot for drug release from microspheres

The correlation coefficient for each formulation was obtained from the statistical software (Excel) and the best fit was determined by the closeness of the correlation value to one. The best fit model was found to be Korsemeyer-Peppas model suggesting that the sustained release of the drug from the microspheres was due to the degradation of the matrix over time. The regression coefficient of the kinetic models suggest that the release of sertraline from the mucoadhesive microspheres followed zero and first order kinetics suggesting a release dependent on the concentration of drug in the solution.

CONCLUSION

The results obtained from the study indicate that use of guar gum as the mucoadhesive polymer could help in achieving sustained release over a longer duration and help in reducing the dose as well as frequency of administration of the medicaments. Further in vivo release studies are needed to support for the conclusion of thesimv present investigation.

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