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PREPARATION AND EVALUATION OF MUCOADHESIVE MICROSPHERE OF FLUOXETINE HCl

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Keywords:

Emulsion solvent evaporation, Mucoadhesive microsphere, Gastro retentive delivery, Fluoxetine, Chitosan

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ABSTRACT: The aim of this research was to formulate and evaluate microspheres of Fluoxetine Hydrochloride. It is a selective inhibitor of serotonin reuptake type of drug used in the treatment of depression. It is practically soluble in water belongs to BCS class I with a bioavailability approximately 72%. Fluoxetine HCl mucoadhesive microspheres were prepared by using chitosan polymer and emulsion solvent evaporation method which enhance bioavailability of drug. Microsphere with particle size in the range 192.92µm to 251.18µm was prepared. Fluoxetine HCl microspheres were evaluated for mean particle size, the percentage yield, entrapment efficiencies, *in-vitro* release, *in vitro* mucoadhesive, FTIR, DSC, X-ray diffraction studies and stability study. Formulation F9 microspheres batch was found to be optimized and followed zero-order release kinetic. The optimized formulation was mucoadhesive in nature. Stability studies were carried out for F9 at a temperature of 40±2 °C/RH 75±5% formulation revealed that the drug behaviour was within permissible limits.

INTRODUCTION: Oral route is most suitable and preferable route for drug administration to reach systemic circulation due to its low cost and easy administration. But success of conventional dosage form is limited due to its residence time. Hence mucoadhesive microsphere drug delivery systems are used to prolong the residence time at the site of application, maintain therapeutically effective plasma drug concentration levels for a longer duration, reducing the dosing frequency and minimize fluctuations in the plasma drug concentration at the steady state in controlled and reproducible manner.

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Mucoadhesive microspheres become adhesive on hydration and hence used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolonged period of time. Moreover, it is easy for administration, no patient compliances and flexibility in the formulation. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in gastrointestinal tract (GIT) is to control gastro retentive drug delivery system which will provide important therapeutic options.

Mucoadhesive microspheres delivery system is an attractive due to ability of adherence to the mucosal surface and releases the entrapped drug in a sustained release. Bioadhesion phenomenon is associated with biological surface and mucoadhesion associated with *i.e.* mucin layer of a mucosal tissue. Mucoadhesive microspheres have advantages like efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs and much more intimate contact with

intestinal cells, better patience compliance and targeting to specific absorption site [1- 4].

Fluoxetine hydrochloride a second generation atypical antipsychotic which is selective inhibitor of serotonin reuptake type drug used in treatment of major depression, obsessive compulsive disorder, bulimia nervosa and panic disorder. Fluoxetine is soluble in water belongs to BCS class I having only 72% oral bioavailability, peak plasma concentrations 15 to 55ng/ml and plasma proteins binding (94.5%). Fluoxetine undergoes extensive hepatic metabolism. In this regard our main focus of this research is to prepare sustain microspheres of Fluoxetine which provides slow release in gastrointestinal tract and assures the presence of dosage form at the site of absorption. Fluoxetine has been shown to selectively bind to central dopamine D2 and serotonin (5-HT) receptors and is effective against the negative symptoms of schizophrenia with a lower incidence of extra pyramidal symptoms. Fluoxetine is extensively metabolized in liver (1st pass metabolism) by the cytochrome P_{450} CYP1A2. The drug has a moderate elimination half-life implying that once daily therapy is adequate for treatment of schizophrenic conditions. Hence the objective of the present work was to formulate the mucoadhesive microsphere of Fluoxetine to improve residence of dosage form in GIT, reduced dosing frequency and enhance bioavailability in the treatment of depression [5-10].

MATERIALS AND METHODS:

Materials: Fluoxetine was obtained from Enaltec Lab Private Ltd, Mumbai, India, Chitosan gift sample from Lobachem Mumbai and Span 20 was purchased from S.B. Fine chemicals Ltd, Mumbai.

Preparation of Microsphere: [11]

Emulsion Solvent Evaporation Method: The microspheres were prepared by using emulsion solvent evaporation technique. To the chitosan solution (3-5% w/v) soaked in acetic acid and water. The Fluoxetine (200 mg) was dispersed in the polymeric solution. To this solution, carbapol solution in acetone (3%) was added. The above solution was poured into combination of 300 ml of heavy paraffin and liquid paraffin containing 2% Span 80 sirred for 3 hours at RPM 500 to 1000. After 3 hours the solution was filtered using n-hexane, washed and dried.

Optimization of Microsphere Formulations: The formula optimization was done by 3^2 factorial design using Design expert (Version 9.2; Stat-Ease Inc., Minneapolis, Minnesota, USA) for mathematical modeling and analysis of responses. The optimal levels of variables were determined by 3^2 factorial design. The significant factors selected were concentration of chitosan and RPM examining 9 runs. The dependant variables selected were entrapment efficiency, % mucoadhesion, % drug release.

TABLE 1: FORMULA AND COMPOSITION WITH PROCESS VARIABLES

Ingredient	Formulation Code								
	F1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Fluoxetine HCl	1	1	1	1	1	1	1	1	1
chitosan	1	1	1	3	3	3	5	5	5
Speed	500	1000	500	500	1000	750	750	750	1000
Liquid paraffin	300	300	300	300	300	300	300	300	300

TABLE 2: 3^2 FULL FACTORIAL DESIGN LAYOUT, EXPERIMENTAL RUNS AND THEIR COMBINATIONS

Sr. No	Batch No	X_1	X_2
1	F1	-1	-1
2	F2	-1	0
3	F3	-1	1
4	F4	0	-1
5	F5	0	0
6	F6	0	1
7	F7	1	-1
8	F8	1	0
9	F9	1	1

Particle Size Measurement: [12] The size of the prepared microsphere was measured by optical microscopy method using calibrated stage micrometer. Particle size was calculated by using equation, Xg = 10 x [(ni x log Xi) / N], Where, Xg is geometric mean diameter, ni is number of particle in range, Xi is the midpoint of range and N is the total number of particles.

Factorial Design: [13] A 3^2 full factorial design was constructed using design expert for mathematical modelling and analysis of responses where the

amount of Polymer(X_1) and speed (X_2) were selected as independent factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. A statistical model was used to evaluate the responses which involve polynomial terms.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1 + b_{22}X_2^2$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects ($X_1$and X_2) represent the average result of changing one factor at a time and (X_1X_2) represent interaction factor

Percentage Yield: [14 - 15] The percentage yield of fluoxetine HCl microspheres of various batches were calculated by using the weight of final product after drying with respect to initial total weight of the fluoxetine HCl and polymer used for preparation of fluoxetine mucoadhesive microspheres.

Drug Entrapment Efficiency: [16] To determine the amount of fluoxetine entrapped in microspheres, weighed amount of microspheres (50 mg) was powdered and suspended in 50 ml of 0.1 N HCl followed by 30 min sonication. The solution was kept undisturbed for 24 hours; and filtered. The filtrate recovered was examined spectrophotometrically at 254 nm and entrapment efficiency was calculated by the following formula.

$$\text{Entrapment Efficiency} = \frac{\text{Estimated \% drug content}}{\text{Theorotical \% drug conteny}} \times 100$$

Morphology of Microsphere: [17] The external and internal morphology of the microspheres were studied by using scanning electron microscopy in Pune University (Physics Department). The sample was loaded on copper sample holder and sputter coated with platinum.

***In-vitro* Wash off Test:** [18] The *in-vitro* wash off test was carried out to evaluate the mucoadhesive potential of the microspheres. In brief, a 1cm by 1cm rat mucosa was cut and tied onto glass slide by thread. Around 100 microspheres were spread on the wet mucosa and the prepared slide was hung onto one of the grooves of the USP tablet disintegrating test apparatus filled with 0.1 N HCl giving regular up and down movements for 60 minutes. At the end of 60 min, numbers of microspheres still adhering to the intestinal mucosa were counted.

$$\% \text{ Mucoadhesion} = (Wa-Wl) \times 100 / Wa$$

Where, Wa = weight of microspheres applied;
Wl = weight of microspheres leached out.

***In-vitro* Release Profile of Fluoxetine from Microspheres:** *In- vitro* drug release studies of microspheres were performed in 0.1N hydrochloric acid using USP type I dissolution apparatus. Fluoxetine microspheres (equivalent to 5mg of fluoxetine) were placed in dissolution jar. The dissolution medium was 900ml of 0.1N hydrochloric acid maintained at 37 ºC ± 0.5 ºC. The paddle was rotated at 50.5ml sample was withdrawn after every 5 min and absorbance was taken at 254nm.

Release Kinetic Studies: [19] The rate and the mechanism of release of Fluoxetine from the prepared mucoadhesive microspheres were analyzed by fitting the dissolution data into various zero order, first order, Higuchi's model and coefficient of correlation (r) values were calculated for the linear curves by regression analysis of the above plots.

Fourier Transforms Infrared Spectroscopy (Ftir) Studies: [20] FTIR spectra for pure Fluoxetine and Fluoxetine microspheres were determined to check the interaction between drug and excipient. FTIR spectra of pure drug and microsphere were recorded using KBr disc using FTIR spectrophotometer (Jasco-4100s, Japan).

Differential Scanning Calorimeter (DSC) Studies: [21] The thermal behaviour of pure Fluoxetine and Fluoxetine microspheres were studied using a DSC Perkin Elmer DSC at a heating rate of 10 °C/minutes. Samples were accurately weighed into aluminium pans and then sealed. The measurements were performed at a heating range of 30-250 °C under nitrogen atmospheres**.**

X-Ray Diffraction Study (XRD): [22] X-ray diffractogram of the Fluoxetine and Fluoxetine

loaded microspheres were recorded by a diffractogram (Brucker AXS D8) using Cu line as a source of radiation which was operated at the voltage 40 KV and the current 40 mA. All samples were measured in the 2θ angle range between 5-60°.

Stability Study: [23] Stability studies were carried out for Fluoxetine microsphere as per ICH guidelines. The best mucoadhesive microspheres formulation (F9) was sealed in high-density polyethylene bottles and stored at 25±2 °C/60±5%, 40±2 °C/75±5% relative humidity (RH) for 90 days. The samples (F9) were evaluated for entrapment efficiency and percentage mucoadhesion.

RESULT AND DISCUSSION: The Fluoxetine microspheres were prepared using emulsion solvent evaporation technique. The formula optimization was done by 3^2 factorial design. The significant factors selected were concentration of polymer and speed. The dependant variables selected were entrapment efficiency, % mucoadhesion and % drug release. The model was analysed for fitting into appo. mathematical model and evaluated statistically for ANOVA. The response surface analysis was carried out employing the 3D response surfaces.

Micrometric Studies: The size of the prepared microcapsules was measured by the optical microscopy method using a calibrated stage micrometer. The various batches have the average particle size in the range of 192.92 µm to 251.18 µm. The tapped density value ranged from 0.162-0.638, bulk density in between 0.114-0.662, Carr's index in between 8.29-27.88 % and Hausner ratio within 1.0832-1.996. All formulation showed excellent flow ability as expressed in terms of angle of repose was found within the range of 25°59'-29°01'

Percentage Yield: The percentage yield of microspheres was calculated by using the weight of final product after drying with respect to initial total weight. The maximum percentage yield was found of F9 batch and was noted to be 86.1 % among all the batches. The production yields of microspheres were found to be between 71.5 % an 86.1 % as shown in **Table 3**.

TABLE 3: PHYSICOCHEMICAL PROPERTIES OF FLUOXETINE MUCOADHESIVE MICROSPHERES

Formulation code	Percentage Yield	Particle size
F1	91.31	192.92µm
F2	80.93	198.73µm
F3	90.12	201.49µm
F4	91.13	221.1µm
F5	79.92	221.49µm
F6	87.37	201.72µm
F7	88.12	229.61µm
F8	86.13	231.52µm
F9	81.14	251.18µm

Particle Size: The average particle size of Fluoxetine HCl microspheres were ranged from 192.92µm-251.18µm. The mean particle size was significantly increases with increasing mucoadhesive polymer concentration this may be attributed to high viscosity of mucoadhesive polymer solution.

SEM of Microspheres: The morphology of the mucoadhesive microspheres of best formulation F9 was examined by SEM. SEM photographs revealed that fluoxetine microsphere were discrete and rough surface (**Fig. 1**).

Entrapment Efficiency: The maximum percentage yield was found of F9 batch and was noted to be 92.35 % among all the batches.

Mucoadhesive Test: The study of *in-vitro* wash off test revealed that all the batches of prepared microspheres had good mucoadhesive property ranging from 85% to 93.05%. On increasing the polymer concentration, the bioadhesive property of the microspheres also increased as shown in **Fig. 3**

***In-vitro* Drug Release Studies:** The *in-vitro* drug release data of optimized microspheres were evaluated kinetically using various mathematical models. The drug release from Fluoxetine microsphere was 78 % to 95.23% at the end of 6 h. The *in-vitro* fluoxetine release profile for all batches was shown in **Fig. 4**. Drug release from these mucoadhesive microspheres were slow, controlled release and dependent upon the nature and concentration of mucoadhesive polymers used. It was found that there was decrease in fluoxetine release with increase in mucoadhesive polymer content. Hence it is considered as the best microsphere formulation which seems to be a good candidate for controlled release. The microspheres

were subjected to *in-vitro* drug release rate by dissolution profiles is shown in **Table 4.**

TABLE 4: CHARACTERIZATION OF FLUOXETINE MUCOADHESIVE MICROSPHERES

Formulation code	Percentage mucoadhesion	*In vitro* release
F1	90.1	86
F2	90.8	91
F3	89.93	95
F4	93.05	78
F5	87.34	98.33
F6	87.04	84
F7	90.32	80
F8	85.37	91.66
F9	92.35	86.92

Release Kinetic Study: The *in-vitro* drug release data were fitted into various mathematical models. The model that best fits the release data was evaluated by correlation coefficient (r). The correlation coefficient (r) value was used to choose the best model to describe the drug release from the microsphere. As the regression coefficient (r2) value of the Higuchi model was found to be higher. The r value in various models is given in **Table 6**. All the microsphere formulations (F1-F9) followed Higuchi model with regression values ranging from 0.9472 to 0.9867. The diffusion mechanism of drug release was attributed to the swelling behaviour of chitosan polymer employed in the formulation of microsphere.

TABLE 5: *IN-VITRO* RELEASES KINETICS PARAMETERS FOR FLUOXETINE MICROSPHERES

Formulation code	Zero Order Model R^2	First-Order Model R^2	Higuchi Model R^2
F1	0.9009	0.862	0.9472
F2	0.9273	0.9421	0.9701
F3	0.9879	0.9759	0.9941
F4	0.9362	0.9412	0.9569
F5	0.9461	0.9236	0.9646
F6	0.9783	0.9511	0.9756
F7	0.9565	0.9086	0.9704
F8	0.9454	0.9571	0.9699
F9	0.9629	0.9633	0.9867

TABLE 6: ANOVA OUT PUT OF THE 3^2 DESIGN FOR OPTIMIZATION OF MICROSPHERES

Sr. No.	Outcomes	Entrapment Efficiency (%)	% Mucoadhesion After 1h (%)	Drug Release
1	F value	304.69	13.10	67.43
2	P value	0.0003	0.0299	0.0288
3	R^2 value	0.9976	0.9935	0.9902
4	Adequate Precision	32.66	9.82	72.22

FTIR Studies: FTIR spectrum of pure drug and mucoadhesive microsphere of drug and polymers were studied. It was observed that fluoxetine showed characteristic peak at 3329 cm^{-1} for-NH group whereas chitosan showed -OH group at 3486 cm^{-1} However shift to lower wavelength from 3329cm^{-1} and 3486 cm^{-1} to 3203cm^{-1} for drug loaded microsphere suggested possibility of H-bonding between NH_2 group of drug and -OH group of chitosan.

DSC Studies: The thermal behaviour of prepared fluoxetine microspheres was studied in comparison with thermo grams of pure fluoxetine as shown in (**Fig. 7**). The thermogram of pure fluoxetine showed a sharp endothermic peak at 162.2 °C whereas that of chitosan was observed at 92.99 °C. However DSC of formulation did not show melting point of drug whereas single endothermic peak at 88.5 °C was observed. This could be attributed to solubilization of fluoxetine in molten chitosan polymer.

XRD Study: The X-ray diffractogram of fluoxetine showed multicrystalline pattern while fluoxetine loaded mucoadhesive microspheres showed less intense amorphous nature. This diminished peak suggests conversion of drug into amorphous form.

Stability Studies: Stability studies for the optimized microsphere were carried out at a temperature of 40±2 °C/ RH 75±5% for a period of 90 days. Formulation was evaluated for physical appearance and drug content. There was no any significant change in physical appearance and drug

content during stability studies. Hence, it was concluded that the F9 batch of tablet have good stability during their shelf life.

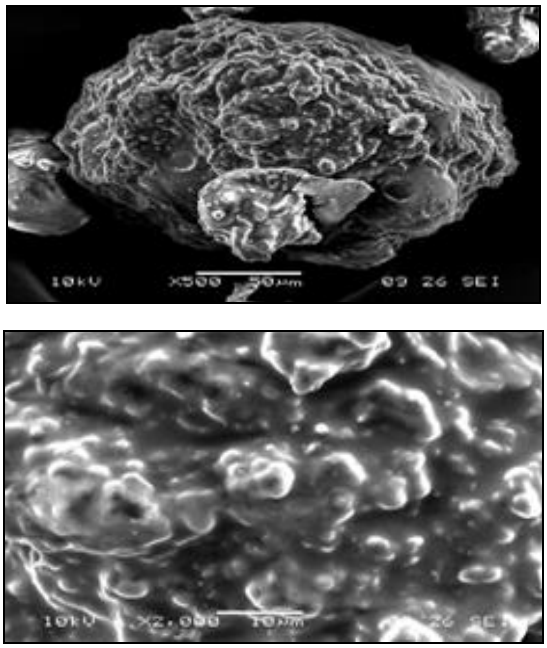

FIG. 1: SEM OF MUCOADHESIVE MICROSPHERES OF OPTIMIZED BATCH: A) × 35 B) × 500

Factorial Equation and Response Surface Plot: A 3^2 full factorial design was constructed using design expert (Version 9.2; Stat-Ease Inc., Minneapolis, Minnesota, USA) for mathematical modelling and analysis of responses where the amounts of Polymer(X_1) and speed (X_2) were selected as the independent factors. The levels of the two factors were selected on the basis of the preliminary studies carried out before implementing the experimental design. The polynomial equations generated are as follow:

% mucoadhesion = + 87.30 + 2.81 X_1 – 0.43X_2 + 0.47X_1X_2 + 0.41X_1^2 +3.02 X_2^2 ---------equation (1)

% Drug content = +87.50 + 0.70 X_1 – 5.10 X_2 +0.053 X_1X_2 –0.44 X_1^2 - 1.45 X_2^2 ------equation (2)

% Drug release = 84.40 + 6.26 X_1 -2.79X_2 + 1.27X_1X_2 +1.24 X_1^2+3.91X_2^2 ----------equation (3)

Where X_1 = conc. of polymer and X_2 = speed.

All the polynomial equations were found to be statistically significant determined using as per provision of design expert software. Equation can draw conclusion after considering magnitude of coeficient and mathematical sign carried.

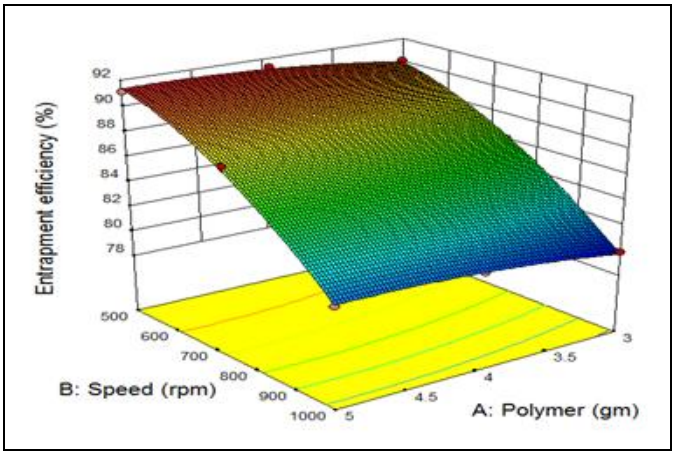

FIG. 2: DRUG CONTENT 3D GRAPH

Entrapment Efficiency = +87.50 +0.70A -5.10B +0.053AB -0.44A^2 -1.45B^2
Where A= Conc. of chitosan and B=RPM

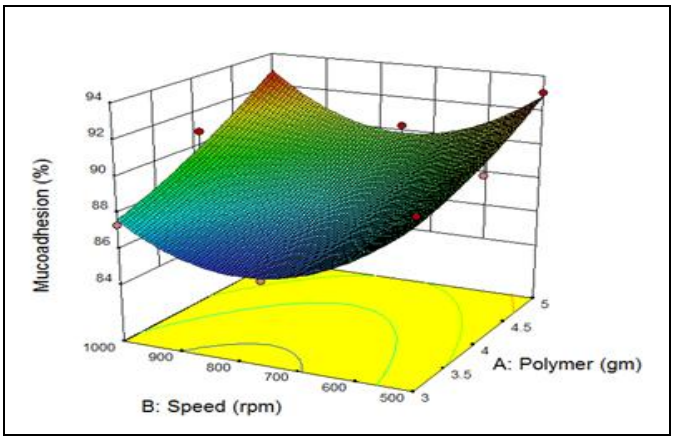

FIG. 3: PERCENT MUCOADHESION 3D GRAPH

Equation: % Mucoadhesion after 1 hour = +87.30 +2.81A -0.43B +0.47AB +0.41 A^2 +3.02B^2
Where A= Conc. Of polymer and B=RPM

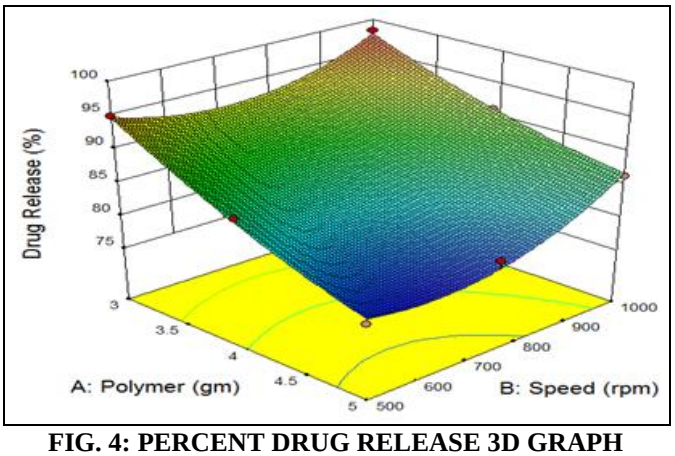

FIG. 4: PERCENT DRUG RELEASE 3D GRAPH

% Drug release = Drug release= 84.40 +6.26A -2.79B +1.27AB +1.24A^2 +3.91B^2
Where A= Conc. Of polymer and B= RPM

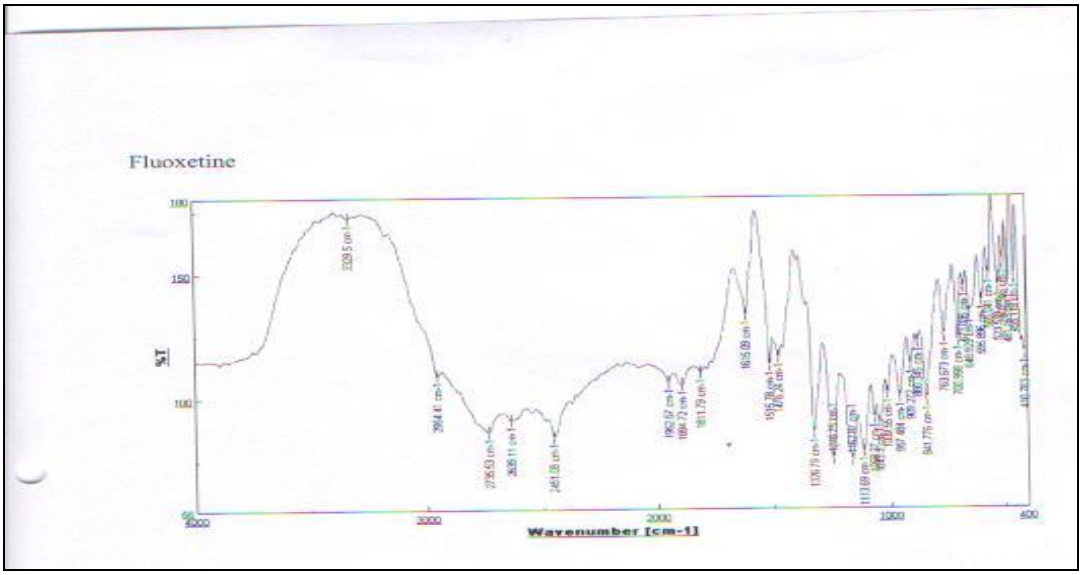

FIG. 5: FTIR OF PURE FLUOXETINE

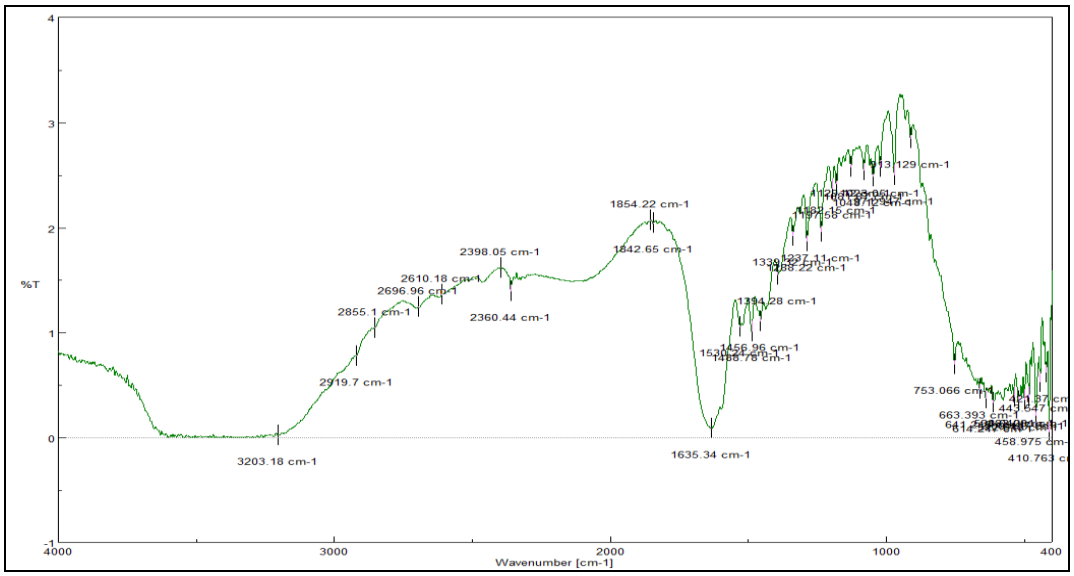

FIG. 6: FTIR OF FLUOXETINE HCl MICROSPHERE CONTAIN CHITOSAN POLYMER

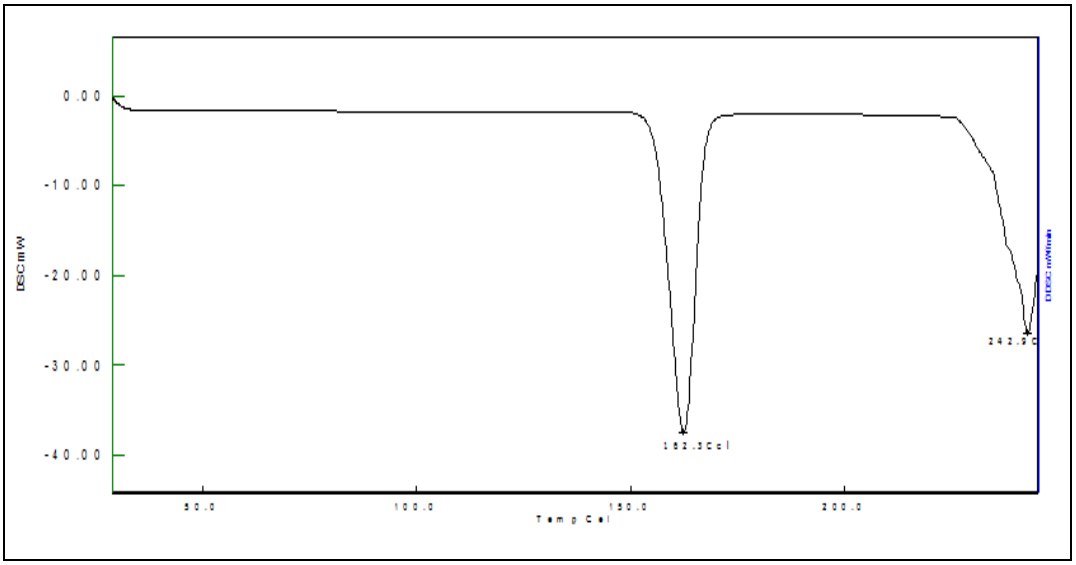

FIG. 7: DSC OF FLUOXETINE HCl

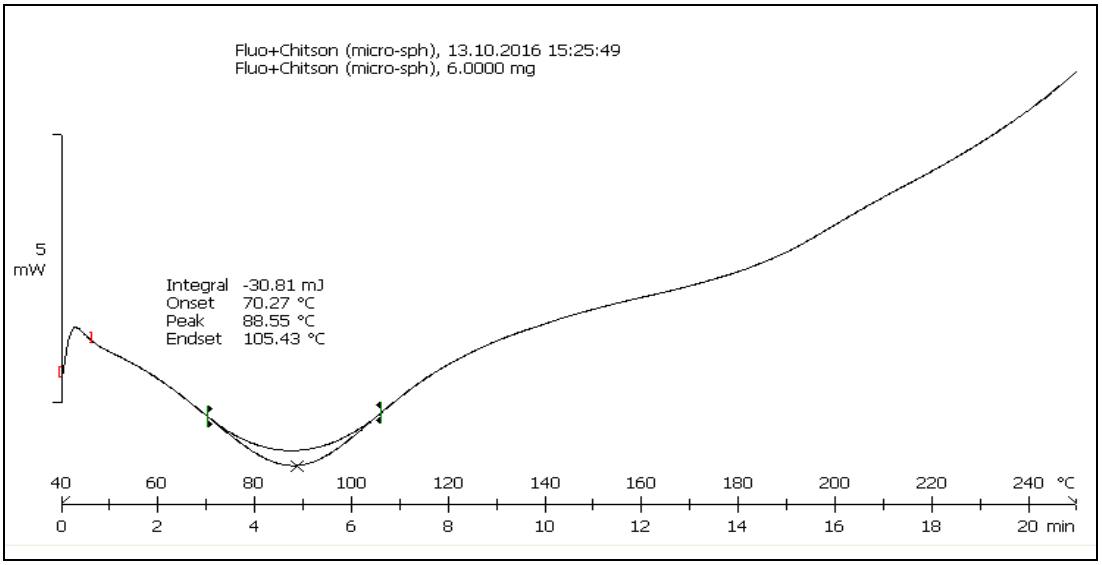

FIG. 8: DSC OF FLUOXETINE MICROSPHERE CONTAINING CHITOSAN POLYMER

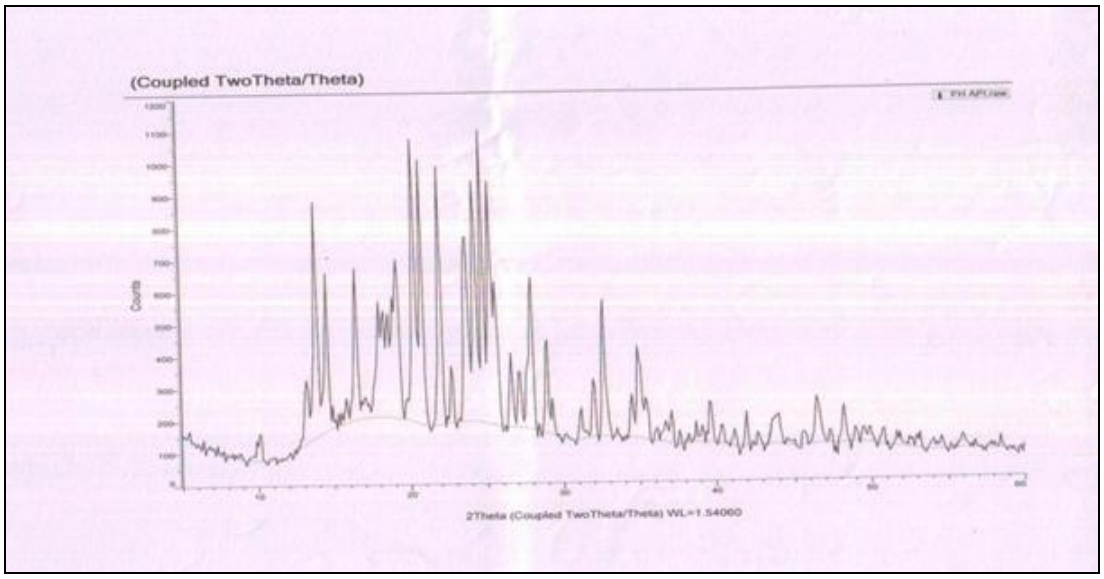

FIG. 9: XRD OF FLUOXETINE API

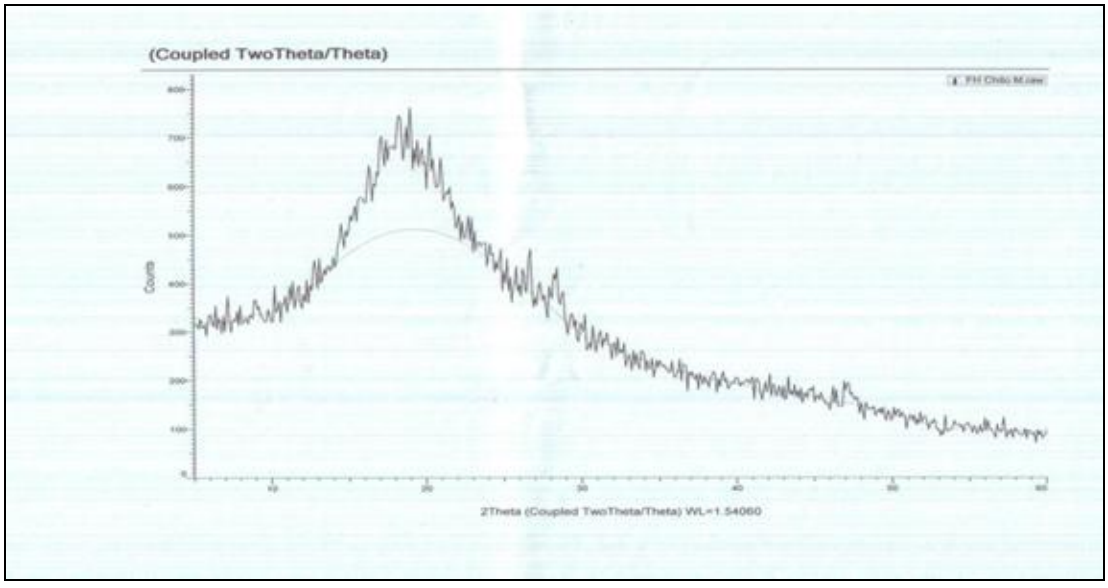

FIG. 10: XRD OF FLUOXETINE MICROSPHERE

TABLE 7: STABILITY STUDIES OF MICROSPHERE

Sr. no	Duration	Drug Content (%)	No. of microsphere adhered to mucous out of 50 (%)	*In vitro* dissolution (%)
1	0	0	0	0
2	1 month	72.1	48	78
3	2 month	68.3	45	77.83
4	3 month	73.01	46	77.12

CONCLUSION: FLU is soluble in water having only 72% oral bioavailability. Fluoxetine undergoes extensive hepatic metabolism. Hence mucoadhesive microspheres were developed to enhance the bioavailability and to prepare sustain microspheres having slow release in gastrointestinal tract. Microsphere formulation of FLU was prepared by using emulsion solvent evaporation method. The significant factors selected were concentration of chitosan and RPM. The dependant variables selected were entrapment efficiency, % mucoadhesion after one hour, % drug release. Factor like polymer conc. and speed showed significant effect on micromeritic properties. The dissolution of FLU of batch F9 was enhanced due to the presence of high quantity of chitosan polymer and high speed. It was found that there was decrease in fluoxetine release with increase in mucoadhesive polymer content and increased bioadhesive property of the microspheres with increasing the polymer concentration.

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CONFLICT OF INTEREST: There is no conflict of interest.

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