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Research Article

Formulation and Development of Particulate Mucoadhesive Drug Delivery System of Venlafaxine Hydrochloride.

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ABSTRACT

The aim of this research was to formulate and evaluate Venlafaxine Hydrochloride mucoadhesive microsphere prepared using Sodium carboxy methylcellulose and sodium alginate combination. Venlafaxine hydrochloride having extensive hepatic first pass metabolism and low bioavailability problem, determined the need for the development of sustained release formulation. Venlafaxine Hydrochloride mucoadhesive microspheres were prepared by ionic gelation method. Mucoadhesive microspheres were prepared by using calcium chloride as cross linking agent. The venlafaxine hydrochloride mucoadhesive microsphere was characterized by particle size measurement, process yield, morphology of microsphere, drug entrapment efficiency, mucoadhesion test, differential scanning calorimetry, powder X-ray diffraction, Fourier transforms infrared (FTIR) study and *in-vitro* drug release. FTIR, XRD and DSC analyses apparently did not indicate any interaction of the drug with the polymers. However, the drug content, drug entrapment efficiency and morphology of the microsphere were found to be influenced by the method of preparation, composition of microsphere as well as exposure to the cross linking agent. The particle size was increase significantly by increasing polymer concentration. In vitro drug release study showed that drug release can be modified by varying drug to polymer ratio. The release rate was found to be decreased in accordance with the increase in the ratio of polymer used. The release profile of drug follows the zero order models indicated that the drug release from these microsphere followed sustain release pattern.

KEYWORDS

Ionic gelation method, Gastro retentive drug delivery, Mucoadhesive microsphere, Sodium carboxy methyl cellulose.

1. INTRODUCTION

The oral route of drug administration is the most largely used and preferred means of drug delivery to the systemic circulation of the body. However the drugs which are administered through oral route in the form of conventional dosage have limitations of their inability to limit and localize the system at gastrointestinal tract. Microencapsulation is one of the approaches to enhance the oral bioavailability. Due to their small size and efficient carrier characteristics, microspheres constitute an important part of particulate novel drug delivery system. The achievement of microspheres is limited due to their short residence time at the site of absorption and it can be subdued by for providing an intimate contact of the drug delivery system with the absorbing membrane.

This can be accomplished by coupling bioadhesion characteristics to microspheres and developing mucoadhesive microspheres.

Mucoadhesive microspheres become adhesive on hydration and hence can be used for localizing the drugs to a particular target site of gastrointestinal tract (GIT) for prolong periods of time. Moreover, it is easy for administration, no patient compliances, and flexibility in the formulation. Mucoadhesive microspheres have advantages such as efficient absorption, enhanced bioavailability of the drugs, maximum utilization of drugs, much more intimate contact with intestinal cells, better patience compliance, and targeting to specific absorption site[1-4]

Venlafaxine Hydrochloride (high solubility and high permeability) was the first marketed anti-depressant in the Serotonin-nor epinephrine reuptake inhibitor (SNRI) class. It has been widely used in treatment of remission in depression, treatment resistant depression and extended- release Venlafaxine Hydrochloride for generalized anxiety disorder. It is freely soluble in water and has relatively short elimination half-life (5hrs.). The bioavailability is very limited (45%) due to the hepatic first pass effect. In this regards our main focus to prepare sustain microspheres which provides slow release in GIT and also assures the presence of dosage form at the site of absorption. The objective of this work was to formulate the mucoadhesive microsphere of Venlafaxine hydrochloride to improve residence of dosage form in GIT, reduced dosing frequency and enhance bioavailability in the treatment of depression.

2. MATERIALS AND METHODS

2.1. Materials

Venlafaxine hydrochloride was obtained from Lupin research park, Aurangabad. Sodium alginate and Sodium CMC is gift sample from Loba chemicals, Mumbai, Calcium chloride was purchased from S.B. Fine chemical, Ltd, Mumbai.

2.2. Formulation of mucoadhesive microspheres[5]

Sodium alginate and sodium carboxy methyl cellulose were dissolved in distilled water (20 ml) to form a homogeneous polymer solution. The active core material Venlafaxine hydrochloride was added to the polymer solution and mixed thoroughly with a stirrer to form a smooth viscous dispersion. The resulting dispersion was then added drop wise into calcium chloride (5% w/v) solution (40 ml) through a syringe with a needle of size No: 20. The added droplets were retained in the calcium chloride solution for 30 min to complete the curing reaction and to produce

spherical rigid microspheres. The microspheres were collected by decantation and the product, thus separated was washed repeatedly with water and dried at 60°C for 1 hr.

2.3. Experimental design for optimization[6,7]

In order to obtain "best" or an "optimized product" nine different formulations were generated using 3^2 factorial designs. The amount of sodium alginate (X1) and amount of sodium carboxy methyl cellulose (X2) were taken as independent formulation variables while % drug content (Y1), % entrapment efficiency (Y2) and % drug release at 12 h (Y3) were considered as dependent or response variables. A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. Design Expert (Version 7.0.0) software was used for the generation and evaluation of the statistical experimental design. The effects of independent variables were modeled using a quadratic mathematical equation generated by a 3^2 factorial design such as

$$\mathbf{Y= b_0 +b_1X_1 +b_2X_2 +b_{12}X_1X_2 +b_{11}X_1^2+b_{22}X_2^2} \quad \text{----------} \quad \mathbf{(1)}$$

Where Y is the response; b_0 is the intercept, and b_1, b_2, b_{12}, b_{11}, b_{22} are regression coefficients. X_1 and X_2 is individual effects; X_{12} and X_{22} are quadratic effects; X_1, X_2 is the interaction effect. One-way ANOVA was applied to estimate the significance of models ($p < 0.05$). Individual response parameters were evaluated using the F test. The surface response plots were analyzed to reveal the effect of independent factors (amount of SCMC and sodium alginate) on the measured responses (% DC, % DEE and % DR). The details of the design are shown in Table 2.

Table 1. Selection of levels of independent variables.

Coded value	Sodium Alginate (mg)	Sodium Carboxy Methyl Cellulose (mg)
-1	100	100
0	200	200
1	300	300

Table 2. Design Layout of 3^2 factorial batches.

Batch code	Coded value		Actual value		Drug (mg)
	SA	Na CMC	SA (mg)	Na CMC (mg)	
F1	-1	-1	100	100	400
F2	-1	0	100	200	400
F3	-1	+1	100	300	400
F4	0	-1	200	100	400
F5	0	0	200	200	400
F6	0	+1	200	300	400
F7	+1	-1	300	100	400

F8	+1	0	300	200	400
F9	+1	+1	300	300	400

2.4. Characterization of Microspheres

2.4.1. Drug content estimation[8]

Drug loaded microsphere (100 mg) were powdered and suspended in 100 ml 0.1N HCl solution and kept for 24hr. It was stirred for 5 minutes and filtered by whatman filter paper. Venlafaxine hydrochloride content in the filtrate was determined using spectrophotometer at 225.37 nm.

% Drug content = Actual drug content / total wt. of microsphere taken× 100. ----------(2)

2.4.2. Drug entrapment efficiency[9]

Microspheres equivalent to 5 mg of Venlafaxine hydrochloride were crushed using a glass mortar and pestle and the powdered microspheres were suspended in 25 ml of 0.1N HCl. After 24 hrs, the solution was filtered, 1 ml of the filtrate was pipette out and diluted to 10 ml and analyzed for the drug content by using UV Visible Spectrophotometer at 225.37 nm.

The drug entrapment efficiency was calculated using the following formula.

Entrapment efficiency = (Actual drug content/theoretical drug content) ×100. ------(3)

2.4.3. Mucoadhesive Test [10,11]

The mucoadhesive property of microspheres was evaluated by an in vitro adhesion testing method known as wash-off method. Freshly excised pieces of goat intestinal mucosa were mounted onto glass slides with cotton thread. About 20 microspheres were spread on to each prepared glass slide and immediately thereafter the slides were hanged to USP II tablet disintegration test. When the test apparatus was operated, the sample was subjected to slow up and down movement in the test fluid at 37 ^{0}C contained in a 1-liter vessel of the apparatus. At an interval of 1hours up to 8 hours the machine was stopped and number of microspheres still adhering to mucosal surface was counted. The test was performed in 0.1 N HCl. The adhesion number was determined by the following equation:

$Na=N/N_0\times100$ ----------(4)

Where Na is adhesion number, N_0 is total number of particles in a particular area, and N is number of particles attached to the mucosa after washing.

2.4.4. Particle Size Analysis[10]

The sample of prepared microspheres was randomly selected and their size was determined using an electronic microscope with the help of eye piece and stage micro meter. In all measurements at least 50 beads in five different fields were examined. Each experiment was carried out in triplicate.

2.4.5. In vitro drug release study[12]

The in vitro release of Venlafaxine hydrochloride from mucoadhesive microspheres was measured using basket type dissolution test apparatus. Venlafaxine hydrochloride microsphere equivalent to 50 mg were placed in the basket. The volume of dissolution medium was 900 ml and maintained at 37±0.5^{0}C at 100 rpm. An aliquot of 5ml of the solution was withdrawn at predetermined time intervals and replaced by 5ml of fresh dissolution medium immediately. The samples were assayed via UV-Vis spectrophotometer (lab India) at 225.37 nm after filtration through a 0.45µm membrane filter. The dissolution medium was used as a reference while UV scanning of the samples. All dissolution tests were performed in triplicate.

2.4.6. Fourier transforms infrared spectroscopy[12,13]

Fourier transform infrared spectra were obtained using Shimadzu FTIR-8400S spectrometer, Japan. Samples of Venlafaxine hydrochloride, physical mixtures and optimized formulation of microsphere were taken for the study. The scanning range was 500 to 4000 cm^{-1}and the resolution was 4 cm^{-1}.

2.4.7. Powder X-ray diffraction (PXRD)[14,15]

X-ray diffractogram of the drug and drug-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° and 60°

2.4.8. Differential scanning calorimetric (DSC)[16,17]

DSC analysis of the samples was carried out on a Perkin-Elmer DSC7, USA. Samples (6.5-10 mg) were heated under nitrogen atmosphere on an aluminum pan at a heating rate of 10 °C/min over the temperature range of 5 and 300 °C. DSC analysis was carried out under nitrogen gas flow of 20 lb/in^2.

2.4.8. Scanning Electron Microscopy and Morphology Characterization (SEM)[7]

Surface morphology was determined by the method SEM. In this microcapsule were mounted directly on the SEM sample slab with the help of double sided sticking tape and coated with gold film under reduced pressure.

2.4.9. Release kinetic studies[8]

The rate and the mechanism of release of venlafaxine hydrochloride from the prepared mucoadhesive microspheres were analyzed by fitting the dissolution data into various kinetic models such as 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.

2.4.10. Stability study[18]

Stability studies were carried out for venlafaxine hydrochloride 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.

3. RESULTS AND DISCUSSION

3.1. Drug content[1]

Orifice-Ionic gelation method is a convenient method for the preparation of mucoadhesive microspheres with good drug content. In these method drug is uniformly distributed in the

polymer solution so drug can be loaded easily in the polymer. Drug content of all nine batches based on sodium alginate and sodium carboxy methyl cellulose concentration in 0.1 N HCl was ranging from 29.49% to 42.83% (Table 3).

Table 3 Drug content, Entrapment efficiency and particle size of all batches of venlafaxine hydrochloride microsphere.

Batch No.	**Variable levels in coded form**		**Drug content (0.1N HCl)**	**Entrapment efficiency (0.1N HCl)**	**Particle size (nm)**
	X1	X2			
F1	-1	-1	29.49%	37.65%	330 ±0.33
F2	-1	0	32.78%	40.45%	438 ±0.88
F3	-1	+1	36.31%	44.61%	440 ±0.66
F4	0	-1	33.43%	41.69%	462 ±0.66
F5	0	0	37.42%	45.30%	478 ±1.52
F6	0	+1	39.99%	48.76%	526 ±1.20
F7	+1	-1	37.10%	45.59%	554 ± 0.33
F8	+1	0	40.56%	49.63%	578 ±2.66
F9	+1	+1	42.83%	52.88%	602 ±0.88

3.2. Entrapment efficiency[9,11]

The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into polymer solution. Effect of polymer content on encapsulation efficiency was studied. The encapsulation efficiency in 0.1 N HCl ranging from 37.65% to 52.88% respectively (table 3), it is evident that with the increase in polymer concentration encapsulation efficiency also increased. This may be due to the increase in viscosity of the polymer solutions to the increasing amount of polymer addition. This might have been prevented drug discharge from the prepared microsphere to the cross-linking solution.

All the formulations were spherical in particle shape with smooth surface. The mean particle size of microspheres ranged from 330 to 602μm (table 3), which indicate narrower particle size distribution. It was also noted that increasing the drug to polymer ratio particle size increased the particle size and lower drug to polymer ratio decreased the particle size. The increase in drug to polymer ratio increases particle size due to increased viscosity of feed solution which influence the interaction between disperse phase and dispersion medium that affects the size distribution of particle.

3.3. Mucoadhesive Test[8,19]

The in-vitro wash off test using goat intestinal mucosa for assessing mucoadhesivity of microsphere containing Venlafaxine hydrochloride was performed in gastric pH (0.1N HCl, pH1.2) for 8 h. In 0.1N HCl, the percentage of microsphere adhering to the goat intestinal mucosal tissue varied from 10% to 20 % over 8 h (table 4). In 0.1N HCl less mucoadhesion of microsphere containing Venlafaxine hydrochloride may be due to the reason that at lower concentration the polymer structure is more loose and the polymer chain have more space to extend within the mucus, as the number of polymer chains penetrating in mucus is increased a

strong bond, either chemical, mechanical or the both is formed between the mucus and the polymer. The rapid in-vitro wash off test in observed may be due to ionization of carboxyl and other functional groups in polymers at this pH, which increases their solubility and reduces adhesive strength. Amongst all nine batches in these F9 batch gives highest mucoadhesive property.

Table 4 Mucoadhesion test in pH 0.1N HCl

Formulation	% of microsphere adhere to mucosa (hr)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
F1	60	50	40	30	25	20	10	-
F2	70	60	50	40	30	25	15	10
F3	85	80	65	60	40	30	20	10
F4	60	40	35	30	20	15	10	10
F5	90	80	65	50	40	35	30	20
F6	85	70	60	50	45	35	25	-
F7	60	40	35	25	15	10	-	-
F8	65	50	40	20	10	10	-	-
F9	80	65	55	45	30	15	5	-

Table 5 In-vitro drug release study of venlafaxine hydrochloride microsphere.

Time	% Drug released								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	4.58 ±0.017	8.59 ±0.012	9.73 ±0.041	5.76 ±0.035	8.02 ±0.063	5.19 ±0.049	6.66 ±0.030	4.62 ±0.046	7.17 ±0.052
1	11.99 ±0.230	10.86 ±0.012	13.69 ±0.026	8.59 ±0.056	9.73 ±0.023	9.16 ±0.075	9.16 ±0.080	9.44 ±0.038	10.01 ±0.033
2	15.11 ±0.072	15.96 ±0.136	17.1 ±0.12	14.26 ±0.048	13.13 ±0.15	13.13 ±0.10	10.86 ±0.11	12.28 ±0.034	15.11 ±0.027
3	18.8 ±0.284	19.36 ±0.038	20.22 ±0.031	17.66 ±0.023	17.38 ±0.14	16.81 ±0.129	16.81 ±0.015	15.96 ±0.11	16.53 ±0.0317
4	25.04 ±0.146	24.75 ±0.012	25.09 ±0.029	23.05 ±0.046	21.63 ±0.033	22.2 ±0.28	20.5 ±0.16	19.08 ±0.081	24.27 ±0.044
5	31.27 ±0.080	31.84 ±0.011	32.12 ±0.075	26.17 ±0.074	30.14 ±0.048	25.6 ±0.26	28.44 ±0.063	27.3 ±0.22	27.3 ±0.129
6	36.3 ±0.127	35.81 ±0.049	37.23 ±0.068	31.56 ±0.029	37.51 ±0.040	30.14 ±0.11	36.09 ±0.073	34.66 ±0.075	32.12 ±0.0458
7	43.75 ±0.153	42.61 ±0.143	44.6 ±0.20	34.39 ±0.049	43.75 ±0.055	35.24 ±0.24	44.32 ±0.057	45.45 ±0.061	36.38 ±0.0416
8	49.7 ±0.367	48.88 ±0.029	50.55 ±0.095	42.61 ±0.014	53.67 ±0.049	41.76 ±0.043	56.79 ±0.055	57.92 ±0.063	44.88 ±0.057
9	55.94 ±0.211	54.81 ±0.023	56.22 ±0.030	46.87 ±0.120	60.76 ±0.030	50.55 ±0.15	63.88 ±0.076	62.46 ±0.054	62.46 ±0.023
10	62.46 ±0.135	64.73 ±0.031	66.71 ±0.060	58.49 ±0.026	66.71 ±0.061	60.76 ±0.058	68.98 ±0.052	67 ±0.161	72.67 ±0.055
11	68.41	70.4	71.25	65.3	70.97	72.1	73.5	72.67	80.61

Venlafaxine hydrochloride release from the microspheres was studied in gastric buffer 0.1N HCl for 12 hours. In case of microsphere containing higher polymer contents, the more hydrophilic property of the polymers could probably bind better with water to form a viscous gel structure, which might blockade the pores on the surface of microsphere and could delayed the drug release from these formulated microspheres. The another reasonable explanation of the delayed drug release can be attributed to increasing coating efficiency of the drug particles with the increasing polymer content employed in the formulation. Among all the fabricated formulation, F9 was chosen as an ideal formulation showing an extended drug release over a period of 12h (88.55%) with acceptable mucoadhesive property.

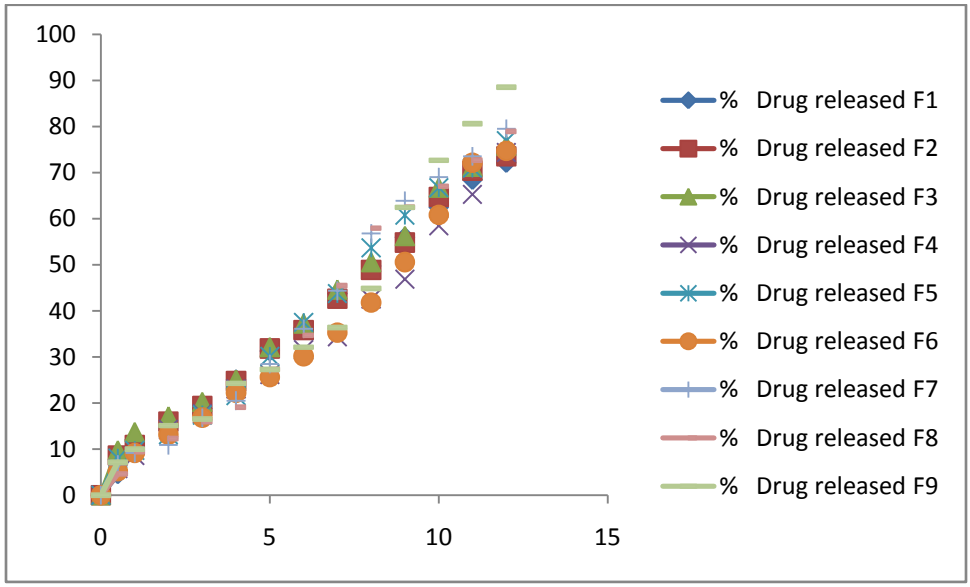
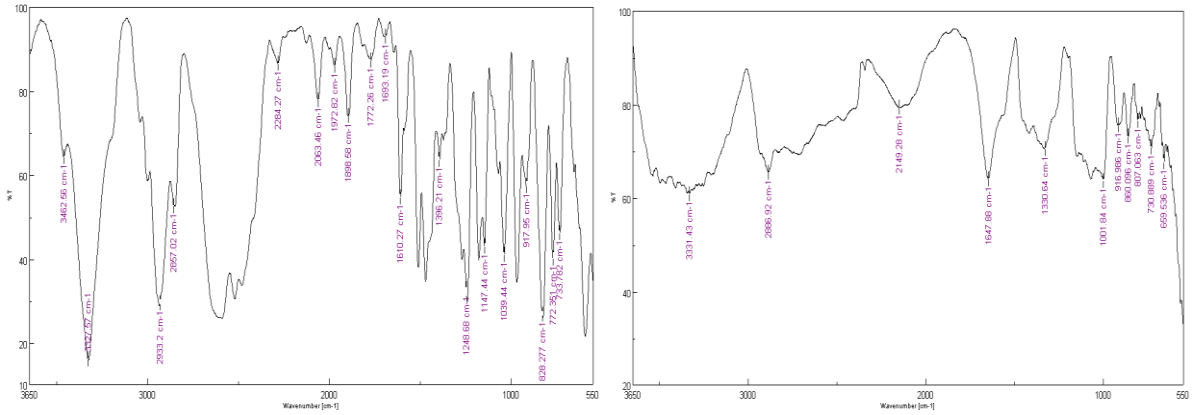


Fig. 1. Invitro drug release of all batches.



(A) **(B)**

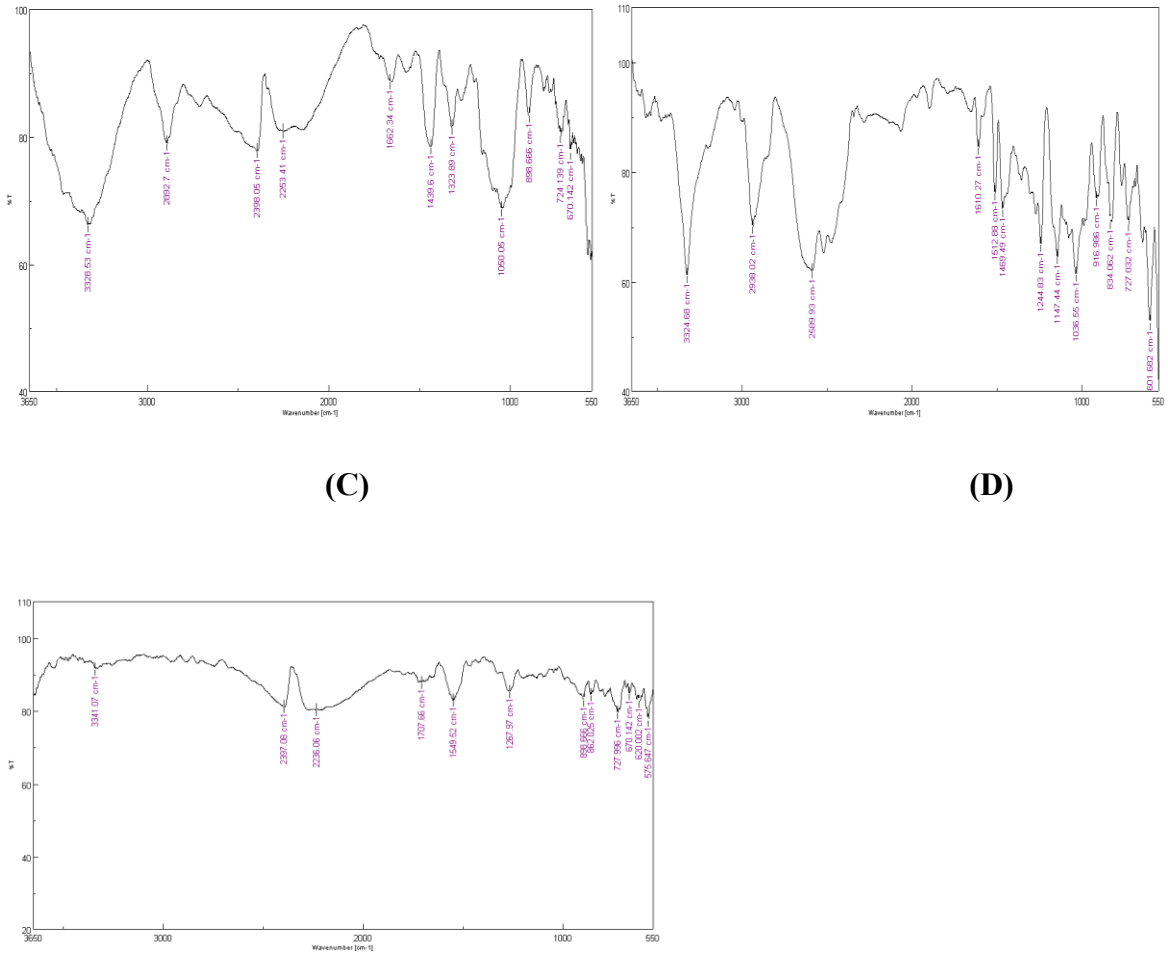


Fig. 2. FTIR of (A) Venlafaxine hydrochloride (B) Sodium alginate (C) Sodium CMC (D) Physical mixture (E) Formulation F9.

IR spectra of Venlafaxine hydrochloride and its combination with excipients are shown in figure 13. An IR spectrum of pure Venlafaxine hydrochloride showed characteristic peaks at 34.62.54 cm^{-1}(N-H stretching vibration peaks), 2857.02.40cm^{-1}(C-H Aldehydic), 828.277 cm^{-1}(C-Cl) and 1610.27cm^{-1}(Aromatic). These peaks can be considered as characteristic peaks of Venlafaxine hydrochloride and were not affected and prominently observed in IR spectra of Venlafaxine hydrochloride along with excipients as shown in the (Fig. 2) indicated no interaction between Venlafaxine hydrochloride and excipients. The IR spectrum of the formulation showed that there is no significant evidence for interaction between drug and the polymer. Peaks of both drug as well as formulation were observed and interpreted. So this clearly suggests that drug,

polymers and excipients used for the current study were compatible. There is no significant or any shift in the positions of the characteristic absorption bands of drug in the formulations.

3.4. DSC[11]

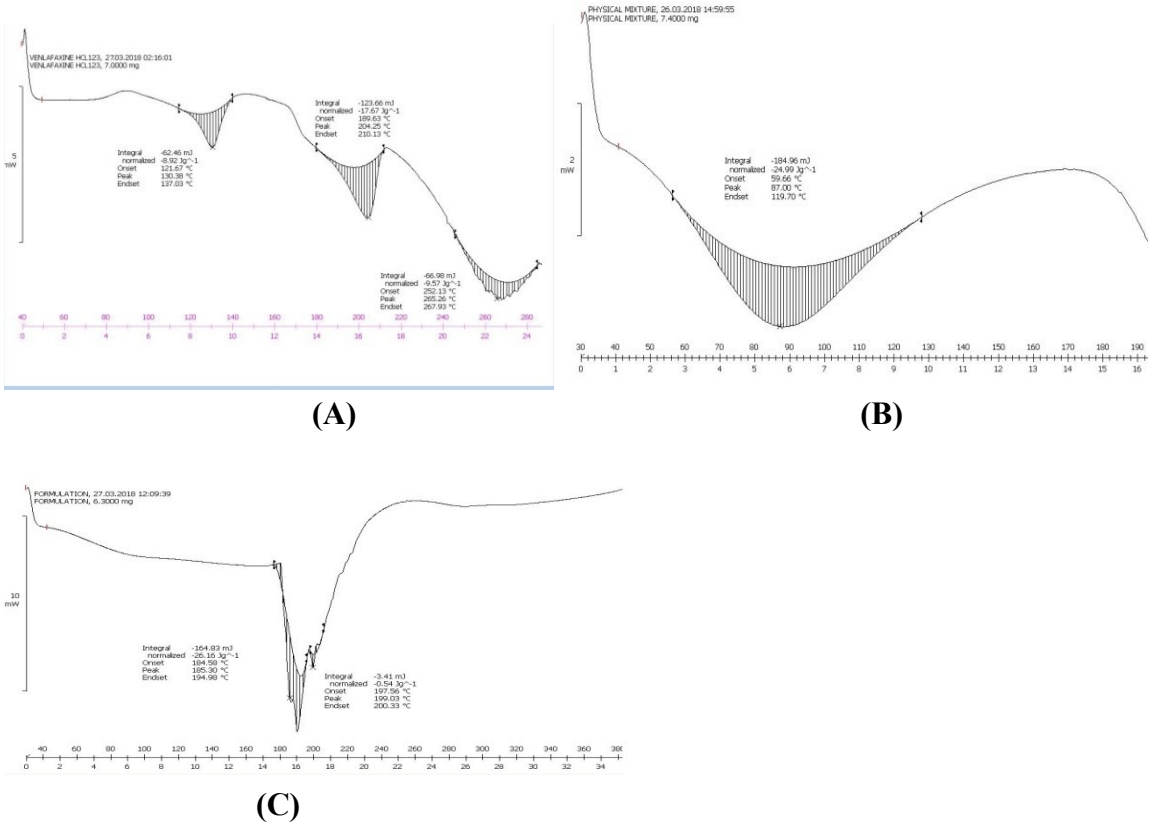


Fig. 3. (A) Pure Venlafaxine hydrochloride (B) Venlafaxine hydrochloride + SCMC+ NA. Alginate (C) Formulation F9

The result of DSC study is shown in Fig. 3. DSC thermogram showed an endothermic peak of Venlafaxine hydrochloride at 215^0 C, which corresponds to its melting point. DSC is a fast and reliable method for understanding polymorphic transition when screening drugs and excipients for compatibility, obtaining information about possible interactions. The presence of detectable peaks of Venlafaxine hydrochloride in physical mixture is indication of uniform mixing of excipients. The absence of peaks of Venlafaxine hydrochloride loaded microsphere in formulation F9 clearly indicates that Venlafaxine hydrochloride was dispersed completely in formulation, thus modifying the microsphere to an amorphous, disordered crystalline phase. The additional peak due to loss of moisture (hydrate form) and degradation peak. The absence of detectable crystalline domains of Venlafaxine hydrochloride in drug loaded microsphere clearly indicates that Venlafaxine hydrochloride encapsulated in microsphere is in the amorphous crystalline phase or in the solid state solublized form in the polymer matrix.

4. CONCLUSION

From the present study it was concluded that mucoadhesive microsphere of Venlafaxine hydrochloride can be prepared using the ionotropic gelation method. The preparation process was simple, reliable, and inexpensive. 3^2 full factorial designs were used to study the effect of process variables on formulation characteristics by applying statistical analysis. From the study, we successfully developed micro particulate drug delivery system of Venlafaxine hydrochloride by using mucoadhesive polymer like Na CMC and rate retardant sodium alginate polymer. Further, in vivo investigation is required to establish efficiency and IVIVC of this formulation.

5. ACKNOWLEDGMENT

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