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Der Pharmacia Lettre, 2011, 3(3): 202-211
(http://scholarsresearchlibrary.com/archive.html)

Scholars Research Library
ISSN 0975-5071
USA CODEN: DPLEB4

Design and optimization of mucoadhesive microspheres of Venlaflaxine HCl using 2^3 full factorial designs

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ABSTRACT

The objective of the present study is to design a prolonged release dosage form to be used for targeted and controlled release drug delivery. Preparation of mucoadhesive microspheres containing venlafaxine HCl helps in releasing small quantities of drug, advantage for treating of depressive disorders. Slowly dissolving polymers for sustaining the release may be suitable for long term therapy in controlled alleviation of clinical manifestation. Ethyl cellulose and Eudragit RS100 provide a potentially useful means of delivering drugs because they are stable, both physically and chemically amenable to preparation in large batches. However the present work is aimed to design and evaluate the mucoadhesive microspheres of Venlafaxine HCl. In this present work the mucoadhesive microspheres of venlafaxine HCl were prepared by employing 2^3factorial design by using Ethyl cellulose along with Eudragit RS100 and Hydroxy Propyl Methyl cellulose K4M. In this experimental model, our goal is to determine how the $t_{80\%}$ of drug release and mucoadhesive characters can be affected by adjusting three parameters, concentration of polymers Ethyl cellulose, Eudragit RS100 & HPMC K4M. For each of these parameters, the levels will define for use in this 2-level experiment. In formulations, the low and high levels of Ethyl cellulose, EUDRAGIT RS100 and HPMC K4M were 750 mg and 1000 mg, 100 mg, 200 mg and 200 mg, 300 mg respectively were used. The drug polymer compatibility studies were carried out using FTIR. The stability studies were conducted for the optimized formulation. The optimized formulation exhibited high drug entrapment efficiency and the drug release was also sustained for more than 24 hours.

Keywords: Venlafaxine HCl, Microspheres, Ethyl cellulose, Hydroxy Propyl methyl cellulose.

INTRODUCTION

A primary object of using mucoadhesive formulations orally would be to achieve a substantial increase in length of stay of the drug in the GI tract. Stability problem in the intestinal fluid can be overcome. Therapeutic effect of drugs insoluble in the intestinal fluids can be improved[5]. Mucoadhesive microsphere carrier systems are made from the biodegradable polymers in sustained drug delivery. Recently, dosage forms that can precisely control the release rates and target drugs to a specific body site have made an enormous impact in the formulation and development of

novel drug delivery systems[1-4]. Microspheres form an important part of such novel drug delivery systems. They have carried applications and are prepared using assorted polymers[1]. However, the success of these microspheres is limited owing to their short residence time at the site of absorption. It would therefore be advantageous to have means for providing an intimate contact of the drug delivery system with the absorbing membranes[6-9]. This can be achieved by coupling bioadhesion characteristics to microspheres and developing bioadhesive microspheres. Bioadhesive microspheres have advantages such as efficient absorption and enhanced bioavailability of drugs owing to a high surface-to-volume ratio a much more intimate contact with the mucus layer and specific targeting of drugs to the absorption site[10-13].

Venlafaxine HCl is a new generation anti depressant serotonin / noradrenalin reuptake inhibitor drug showing effective anti-depressant properties. It has a short bioavailability 12.6% and biological half-life of 5 hours. So, frequent administration is necessary to maintain its therapeutic concentration. This necessitates multiple daily dosing for maintenance of its plasma concentration of the drug within the therapeutic index hence, there is an impetus for developing sustained release dosage form that maintains improved bioavailability and therapeutic plasma drug concentration for long period compared to conventional dosage forms[14].

In this present work the mucoadhesive microspheres of venlafaxine HCl were prepared employing 2^3factorial design by using Ethyl cellulose along with Eudragit RS100 and HPMC K4M. In this experimental model, our goal is to determine how the $t_{80\%}$ of drug release and mucoadhesive characters can be affected by adjusting three parameters, concentration of polymers EC, Eudragit RS100 & HPMC K4M of the mucoadhesive microspheres. For each of these parameters, the levels will define for use in this 2-level experiment. In formulations, the low and high levels of EC, EUDRAGIT RS100 and HPMC K4M were 750 mg and 1000 mg, 100 mg, 200 mg and 200 mg, 300 mg respectively. The drug polymer compatibility studies were carried out using FTIR. The stability studies were conducted for the optimized formulation.

MATERIALS AND METHODS

Venlaflaxine HCl was obtained as gift sample from ORCHID Pharma Ltd, Kanchipuram. Ethyl Cellulose (30-50 cps) from Himedia Laboratories Ltd. Mumbai, Hydroxy Propyl Methyl Cellulose K4M and Eudragit RS100 was obtained from Micro Labs, Hosur, Span 80 and Liquid paraffin was obtained from Loba Chemical Pvt.Ltd.Mumbai, Acetone AR from Research labs fine chemicals, Mumbai, Con. HCl, Potassium dihydrogen Phosphate , Sodium Hydroxide from Nice Chemicals Pvt. Ltd, Chennai, Petroleum ether from Chempure, Chennai.

UV Spectrophotometer, Scanning Electron Microscopy, USP XXIV Basket Apparatus (Dissolution), Image analyzer, Optical Microscope, Propeller stirrer, USP Tablet disintegration apparatus.

Preparation of Microspheres by Solvent Evaporation Technique

Accurately weighed quantity of the polymer (Ethyl Cellulose & Eudragit RS100) was dissolved in 20 ml of acetone. Weighed quantity of Venlafaxine HCl and Polymer HPMC K4M (previously passed through the sieve # 150) were then dispersed in the above polymer phase and stirred for 2 hours. Then it was emulsified with the 100 ml of liquid paraffin containing 1% w/v of Span 80 with continuous stirring at 800 rpm under a magnetic stirrer. The stirring was continued for 2 hours to ensure complete evaporation of acetone. The microspheres were then separated from liquid paraffin by filtration through Whatmann filter paper No. 44, washed three times with 50 ml of petroleum ether, and air dried for 12 hours.

Evaluation of microspheres

Percentage Yield

Thoroughly dried microspheres were collected and weighed accurately[17]. The percentage yield was then calculated using formula given below.

$$\% \text{ yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer}} \text{ x } 100$$

Microsphere Size Analysis

Microsphere size determination was done by optical microscopy method. Size distribution plays a very important role in determining the release characteristics of the microspheres[18].

Shape and Surface Characterization

The shape and surface characterization of microspheres were observed under a Scanning Electron Microscope (SEM) [18, 26].

Angle of Repose

Angle of repose was calculated by static method using funnel[19]. The angle of repose (θ) is calculated by the following formula,

$\theta = \tan^{-1} (h/r)$

Where, h = pile height of microspheres, r = radius of the circular are formed by the microspheres on the ground.

Bulk Density

The bulk density was determined by 3-tap method. Weighed quantities of prepared microspheres were filled in 10 ml of graduated cylinder the initial volume was noted. After tapping for three times the final volume was noted[20]. The bulk density was calculated as per following formula:

$$\rho = \frac{W_o}{V_o}$$

Where,

ρ= Bulk density, Wo =Weight of sample in gm, Vo= Final volume after tapping

Drug Content

Accurately weighed 100 mg microspheres, crushed in glass mortar and pestle and the powdered microspheres were suspended in 100 ml of 0.1N HCl. After 12 hours the solution was filtered and the filtrate was analyzed for the drug content using UV –Visible spectrophotometer at 224nm[21].

Encapsulation Efficiency

Encapsulation efficiency was calculated using the following formula;

$$\text{Encapsulation efficiency} = \left(\frac{\text{Estimated drug content \%}}{\text{Theoretical drug content \%}} \text{x} 100 \right)$$

Where, Wo = initial weight of the dry microspheres, We = weight of the swollen microspheres at equilibrium swelling in the media[22].

In Vivo Wash-Off Test

The mucoadhesive property of microspheres was evaluated by an In vitro adhesion testing method known as wash-off method**.** Freshly excised piece of intestinal mucosa (2 x 2 cm) from goat were mounted on to glass slides (3 x 1 inch) with cyanoacrylate glue. Two glass slides were connected with a suitable support, about 25 microspheres were spread on to each wet rinsed tissue specimen and immediately thereafter the support was hung on to the arm of a USP tablet disintegrating test machine. When the disintegrating test machine was operated, the tissue specimen was given slow, regular up-and-down moment in the test fluid (900 ml of 0.1N HCl/phosphate buffer pH 6.8 at 37 ± 0.5°C). At the end of one hour, and at the hourly intervals up to 5 hours, the machine was stopped and number of microspheres still adhering to tissue was calculated. The studies were carried out in triplicate[23].

In-Vivo Dissolution Studies

Dissolution studies were carried out for all the formulations, employing USP XXIII apparatus (Basket method) at 37 $\pm$ 0.5°C rotated at constant speed of 50 rpm using 0.1N HCl as the dissolution medium for first 2 hrs and remaining in phosphate buffer pH 6.8. A sample of microspheres equivalent weight to 75 mg of venlafaxine HCl was used in each test. An aliquot of the sample was periodically with drawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The sample was analyzed spectrophotometrically at 224nm[24].

Release kinetics and mechanism

To know the release mechanism and kinetics of venlafaxine HCl, optimized formulation was attempted to fit in to mathematical models and n, r^2 values for zero order, First order, Higuchi and Peppas models.The peppas model is widely used, when the release mechanism is not well known or more than one type of release could be involved. The semi-empirical equation.

$$Mt/M\infty = ktn$$

Where, $Mt/M\infty$ is fraction of drug released at time't', k represents a constant, and n is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-fickian release, the value of n falls between 0.5 and 1.0; while in case of fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1. Observation of all the r^2 values indicated that the highest r^2 (0.9756) value was found for Zero order release. According to 'n' value it is one, so it follows non-fickian diffusion with zero order release (case II transport) [25, 27-28].

2^3 Factorial Designs

The optimization phase was designed statistically using 2^3 factorial design in which three variables namely concentrations of polymers such as EC, Eudragit RS100 and HPMC K4M were kept at two levels. Except the optimization phase whose purpose was validated by extra design check point and main interactive influences were tested using statistical methods. The eight formulations of optimization phase were categorized in to four groups for ease of analysis and comparison as follows

Group I : All variables at low level (F_1)
Group II : Any one of three variables at high level (F_2, F_3, F_5)
Group III : Any two of three variables at high level (F_4, F_6, F_7)

Fourier Transform Infrared Spectrophotometer (FTIR).

Compatibility study of drug with the excipients was determined by FTIR Spectroscopy. The pellets were prepared at high compaction pressure by using KBr and the ratio of sample to KBr is 1:100. The pellets thus prepare were examined and the spectra of drug and other ingredients in the formulations were compared with that of the original spectra[15-16].

RESULTS AND DISCUSSION

Mucoadhesive Microspheres of Venlafaxine HCl were prepared by Solvent Evaporation Technique employing 2^3factorial design by using Ethyl cellulose along with Eudragit RS100 and HPMC K4M shown in Table No I & II. The FTIR spectral analysis showed that there was no appearance or disappearance of any characteristic peaks of pure drug Venlafaxine HCl and the physical mixture of drug and polymer, which confirms the absence of chemical interaction between drug and polymers shown in Fig No II & III.

The percentage yield of microspheres of all formulations was in the range of 43.68% to 91.82%. The microsphere prepared by this method was found to be discreet, spherical, free flowing and it was observed by Scanning Electron Microscopy (SEM) Fig No IV. The microspheres were uniform in size with a size range of 65.66µm to 105.30µm. The angle of repose revealed that the microspheres of all the batches had good flow characteristics and flow rates. The bulk density was in the range of 0.50 to 0.62 were shown in Table No III.The drug content determination showed that even if the polymer composition was changed the process was highly efficient to give microspheres having maximum drug loading. The entrapment efficiency was in the range of 68.38% to 93.08%. Microspheres of Venlafaxine HCl exhibited good mucoadhesive properties in the invitro wash of test were shown in the Table No III. The F5 formulation has more adhesive strength than others. The optimization phase was designed statistically using 2^3 factorial design in which three variables namely concentrations of polymers such as EC, Eudragit RS100 and HPMC K4M were kept at two levels shown in Table No II.

Although all formulation were analyzed for uniformity of release pattern, amount of drug release at the end of 24 hours and mechanism of drug release were shown in Table No IV & V and all of these parameters were considered for selection of best formulation in the optimization phase, only release rate and t_{80}% values were used for comparative analysis as they characterize the entire kinetic profile.

Compare to base line response of Group-I formulation the $t_{80\%}$ values of all formulations in Group-II were relatively high. It indicates that every polymer has the ability to sustain and retard the release at high concentration, though the magnitude of their impact was chiefly indicated by their extent of solubility and swellability. The formulation F_2, F_3 and F_5 contains higher proportion of EC, Eudragit RS100 and HPMC K4M respectively shown in Table No 1. Based on the $t_{80\%}$ value of the above formulations, the degree of retardency is in the order of EC > HPMC K4M >Eudragit RS100.The formulation F_4, F_6 and F_7 containing any two of three polymer in higher concentration namely Eudragit RS100 & EC, HPMC K4M & EC and Eudragit RS100& HPMC K4M. The observed $t_{80\%}$ value demonstrated the influence in retarding the release as follows HPMC K4M & EC > Eudragit RS100 & EC > Eudragit RS100 & HPMC K4M. The formulation F_8 containing three polymers in high concentration showed the $t_{80\%}$ value of 23.88 hours. The drug release was retarded by increasing the polymer concentration due to increased viscosity and strength of gel matrix formed due to EUDRAGIT RS100 and HPMC K4M and low water permeability of EC. This swelling of EUDRAGIT RS100 is independent on medium pH, which

forms hydrogen bonds with imbibing water and also holds water inside the gel matrix. Increasing the amount of HPMC K4M also forms a gel network and there the drug diffusion is controlled by penetration of liquid through the gelled network and thereby increasing the $t_{80\%}$ value. Since the design was optimized statistically using 2^3 factorial designs it is possible to authenticate the design by selecting an extra design check point residing within the influential matrix space and verifying the proximity of predicted response to the observed one. This was done by constructive polynomial equation of linear interactive model type using pertinent statistical calculations listed in following pages.In order to understand the complex mechanism of drug release from the mucoadhesive microspheres, the *in vitro* Venlafaxine Hcl release data were fitted to korsmeyer-peppa's release model and interpretation of release exponent values (n) enlightens in understanding the release mechanism from the dosage form. The release exponent values thus obtained were ranged from 0.5763 to 0.6692are shown in Table No IV. All the formulations exhibited anomalous (non-fickian transport) diffusion mechanism. The drug release was diffusion controlled as the plot of Higuchi's model was found to be linear ($r > 0.983$).

Table No I. Composition of Formulations of Mucoadhesive Microspheres of Venlafaxine Hcl

Formulation Code	Venlafaxine Hcl (mg)	EC (mg)	Eudragit RS100 (mg)	HPMC K4M (mg)
F_1	500	750	100	200
F_2	500	1000	100	200
F_3	500	750	200	200
F_4	500	1000	200	200
F_5	500	750	100	300
F_6	500	1000	100	300
F_7	500	750	200	300
F_8	500	1000	200	300

Table No II. Signs to Calculate Effects in a 2^3 Factorial Designs

Factor	Low level	High level	Average	1/2 of difference of two values
EC	750	1000	875	125
EUDRAGIT RS100	100	200	150	50
HPMC K4M	200	300	250	50

Table No III. Evaluation of Prepared Mucoadhesive Microspheres of Venlafaxine Hcl

Batch Code	% yield	% drug content	% Mucoadhesion After1h	Drug Entrapment Efficiency (%)	Average Particle Size	Angle of repose	Bulk density	t_{80} (hours)	In vitro drug release after 24 hours
F1	47.10	22.74	46	70.49	65.66	26° 21'	243	19.80	87.80
F2	80.00	24.71	40	88.94	71.13	24° 22'	236	22.05	85.72
F3	76.91	24.65	38	81.34	72.17	25° 20'	223	21.05	83.47
F4	43.68	18.00	64	68.38	78.59	24° 10'	211	23.27	82.81
F5	91.82	28.20	62	93.08	81.92	22° 53'	232	20.86	82.58
F6	48.32	19.47	58	73.97	83.76	23° 25'	241	22.82	80.74
F7	62.06	25.67	52	89.86	100.04	22° 12'	478	21.75	82.83
F8	87.00	73.53	48	73.51	105.30	25° 11'	448	23.88	80.40

Table No IV. InVitro Release Kinetic Data for Venlafaxine Hcl Mucoadhesive Microspheres

Formula code	$t_{80\%}$	Zero order		First order		Higuchi's	Korsmeyer-Peppas	
		K_0	r	K_1	r	r	n	R
F_1	19.8	3.0111	0.92517	-0.0328	-0.9867	0.9833	0.6153	0.9627
F_2	22.05	3.0114	0.9413	-0.0307	-0.9899	0.9888	0.6593	0.9656
F_3	21.23	2.9960	0.9413	-0.3054	-0.9944	0.9910	0.6193	0.9726
F_4	23.27	2.9550	0.9521	-0.0275	-0.9909	0.9913	0.6692	0.9751
F_5	20.86	2.9422	0.9491	-0.0285	-0.9913	0.9910	0.6408	0.9698
F_6	22.82	2.9382	0.9520	-0.0267	-0.9927	0.9933	0.6576	0.9828
F_7	21.75	2.8704	0.9474	-0.0280	-0.9913	0.9919	0.5972	0.9714
F_8	23.88	2.9423	0.9503	-0.0270	-0.9967	0.9969	0.6333	0.9901

*K_0 – Zero order rate constant, K_1 – First order rate constant, **r**- Coefficient of Correlation, **n**- Diffusion exponent*

Table No V. Comparative Cumulative Percentage Drug Release Profile of F1-F8

Time in hrs	Mean Cumulative % drug release F1	Mean Cumulative % drug release of F2	Mean Cumulative % drug release of F3	Mean Cumulative % drug release of F4	Mean Cumulative % drug release of F5	Mean Cumulative % drug release of F6	Mean Cumulative % drug release of F7	Mean Cumulative % drug release of F8
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	9.73	8.01	9.44	8.87	9.44	9.44	10.59	9.73
2	16.62	14.61	16.62	11.75	12.61	12.33	14.62	14.62
3	30.35	26.66	30.35	26.33	28.87	26.62	31.43	26.67
4	38.51	38.07	39.77	31.04	35.59	29.39	37.50	31.71
5	44.44	41.87	41.36	34.81	38.20	30.33	39.65	33.46
6	51.23	46.98	44.50	39.90	43.02	35.70	43.63	35.46
7	55.79	50.69	47.92	43.89	47.29	43.03	49.30	39.71
8	59.96	52.74	52.76	48.73	51.01	46.19	51.33	44.25
9	61.02	55.34	55.92	53.01	54.18	51.02	53.38	47.96
10	62.52	59.36	58.53	56.47	55.67	53.07	54.86	50.84
11	64.58	60.85	60.86	57.97	57.73	54.84	56.91	53.16
12	66.93	63.08	63.20	59.19	60.07	56.90	58.97	55.20
13	68.44	63.86	66.95	60.13	61.58	58.40	60.47	56.97
14	70.51	65.37	68.74	61.64	63.65	59.62	62.81	61.55
15	71.19	67.44	70.54	63.43	64.32	60.84	66.28	63.34
16	72.60	70.20	72.05	65.79	65.27	62.63	67.23	64.84
17	73.67	71.32	73.58	67.59	66.79	64.70	69.03	66.07
18	75.20	73.41	74.82	69.95	71.11	68.15	71.67	67.87
19	77.29	75.22	76.63	72.04	73.20	69.70	73.19	69.67
20	80.78	77.03	78.16	73.85	75.01	72.07	75.28	72.03
21	81.76	78.29	79.14	75.10	77.67	73.32	76.26	73.83
22	82.74	79.83	80.11	76.08	79.49	75.13	77.79	76.20
23	85.41	83.61	81.93	77.06	80.48	78.91	80.45	78.58
24	87.80	85.72	83.47	82.81	82.58	80.74	82.83	80.40

Fig No I. comparative plot of invitro drug release of formulation F1-F8

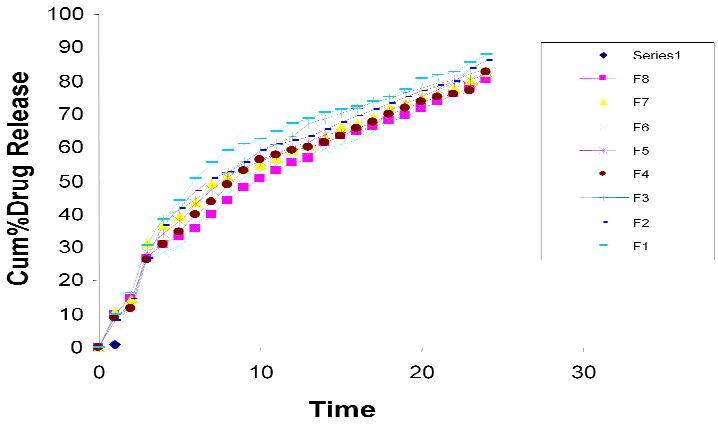
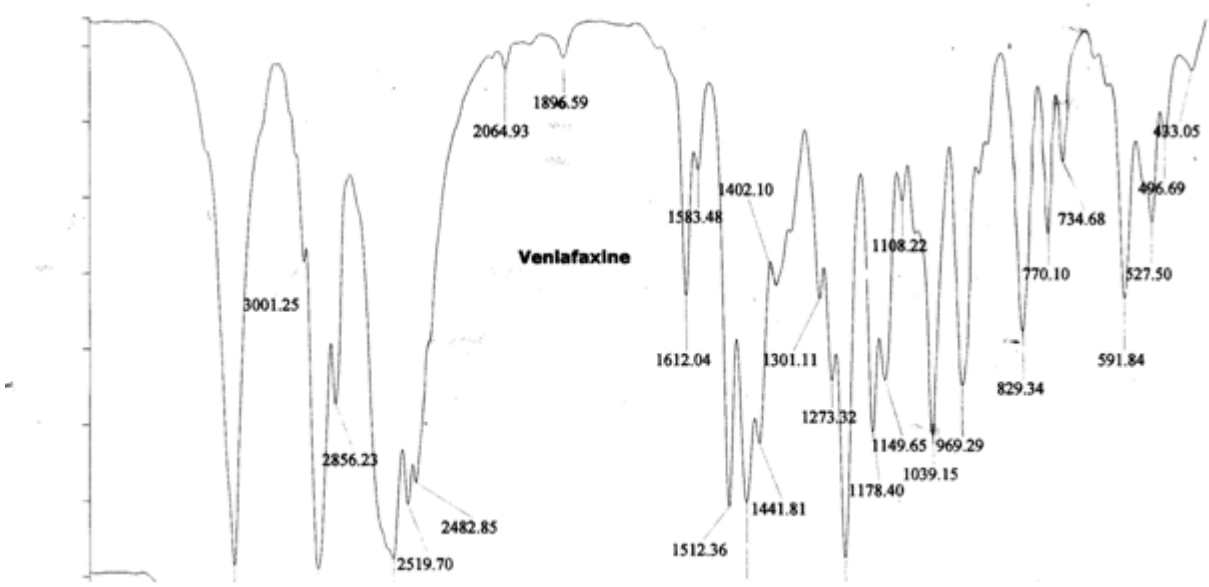


Fig No II.FTIR Spectra of Drug Venlafaxine



These formulations are also showed as highest ‘r’ values of zero order kinetics indicating the Venlafaxine HCl were shown in Table No IV. Releases from these mucoadhesive microspheres were by both diffusion and erosion. The entrapment efficiency was in the range of 68.38%.to 93.08%. Microspheres of Venlafaxine HCl exhibited good mucoadhessive properties in the in vitro wash off test. The F5 formulation has more adhesive strength than others. The result of the dissolution studies indicates that the polymer concentration is having a substantial effect on the drug release after 24 hours was found to be 80.74 to 87.89%.

Fig No III.FTIR Spectra of Physical mixtures of Venlafaxine,EC,HPMC K4M and Eudragit RS100

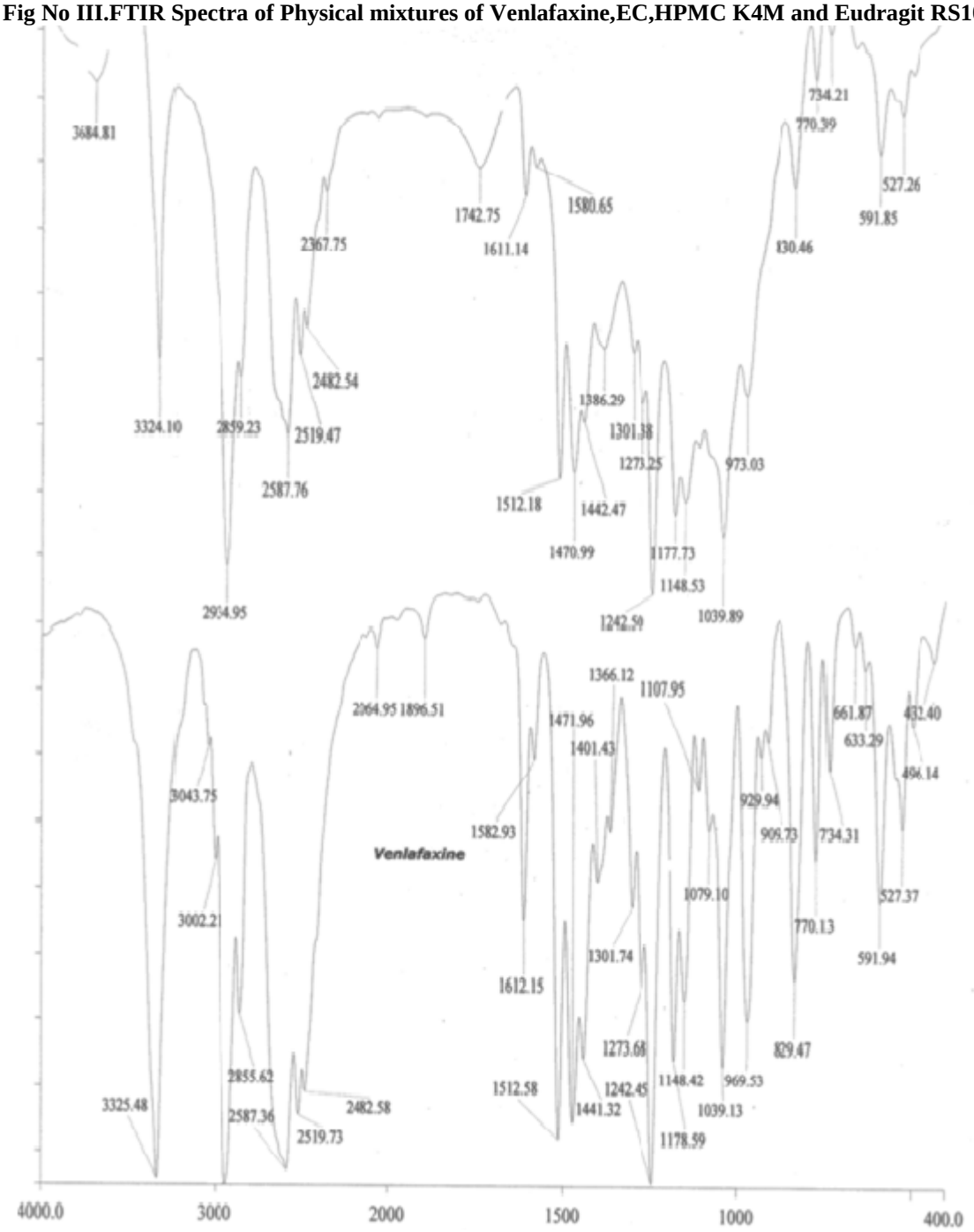


Fig No IV. Scanning Electron Microphotograph of Venlafaxine Hcl Mucoadhesive Microspheres

CONCLUSION

In the present work efforts have been made to design and evaluate mucoadhesive microspheres of venlafaxine HCl and the results obtained in the study have been summarized below.A 2^3 full factorial design was performed to study the effect of formulation variables (concentration of polymers) on the release properties by applying optimization technique. The polymer concentration is a major factor affecting the release and mucoadhesion strength of the prepared microspheres. The observed response ($t_{80\%}$) is close agreement with the predicted $t_{80\%}$ value there by demonstrating the feasibility of the optimization procedure in developing mucoadhesive microspheres containing Venlafaxine HCl. All the formulations exhibited anomalous (non-fickian transport) diffusion mechanism and follow first order kinetic. The formulation F_5 was selected as optimized formulation with 82.58% of drug release at 24^{th} hours.

REFERENCES

[1] Woo BH, Jiang G. Jo YW. Deluca PP., *Pharm Res*. **2001**; 18: 1600-1606.
[2] Capan Y, Jiang G, Giovagnoli S, Deluca PP. *AAPS Pharm Sci Tech*. **2003**; 4:E28.
[3] Gohel MC, Amin AF. *J Control Release* **1998**; 51:115-122.
[4] Vasir JK, Tambwekar K, Garg S, *Int J Pharm*. **2003**; 225:13-32.
[5] Jaya Krishnan and M.S Latha, Biodegradable polymeric microspheres as drug carriers control and novel drug delivery system by N.K Jain.
[6] Ikeda K. Murata K, Kobayashi M, Noda K. *Chem Pharm Bull* (Tokyo). **1992**; 40: 2155-2158.
[7] Nagai T, Nishimoto Y, Nambu N, Suzuki Y, Sekine K, *J. Control Release*. **1984**; 1:15-22.
[8] Llium L, Farraj NF, Critchley H, Davis SS. *Int J Pharm*. **1988**; 46:261-265.
[9] Schaefer MJ, Singh J. *AAPS Pharm Sci Tech*. **2000**; 1:E32.
[10] Rao SB, Sharma CP, *Bio med Mater Res.* **1997**; 34:21-28.
[11] Lehr CM, Bouwstra JA. Schacht EH, Junginger HE. *Int J Pharm*. **1992**; 78:43-48.
[12] Henriksen I, Green KL, Smart JD, Smistad G, Karlsen J. *Int J Pharm*. **1996**; 145:231-240.
[13] Chowdary KPR, Rao YS. Design and in vitro and in vivo evaluation of mucoadhesive Venlafaxine HCl descriptions, pharmacology, side effect, over dose by www.rxlist.com Skoog, Holler," *Principles Of Instrumental Analysis*" fifth edition, pg. No: 380-426.
[14] Applications of Absorption Spectroscopy of Organic compounds by John.R.Dyer, Indian edition pg no: 33-38.
[15] *Indian Pharmacopoeia*, Published by Government of India, Ministry of Health& Family welfare, **1996**, vol. II, A 1011.
[16] Subramanyam CVS; *Physical Pharmaceutics*, 2^{nd} Edition, pp 192.
[17] Alferd Martin, *Physical Pharmacy*, 4^{th} Edition, pp 427-429
[18] CVS Subramanyam; *Physical Pharmaceutics*, 2^{nd} Edition, pp 217.
[19] Liebermann, lachmann:" Theory and Practice of Industrial Pharmacy" pg.no:425-436
[20] Arul B, Kothai R, Sangameswaran B, Jayakar B, *Ind.J.Pharm.Sci.*, **2003**, 65 (6): 640-642
[21] Controlled Drug Delivery concepts and advances by S.P. Vyas and Roop.K. Khar first edition (**2002**) pg no: 285-287.
[22] Paulo Costa, Jose Manuel Sousa Lobo, *Eur.J.Pharm.*, **2001**; 13: 123-133.
[23] Lehr CM, Bowstra JA, Tukker JJ, Junginer HE. *J.Control.Rel.* **1990**; 13: 51-62.
[24] Skoog, Holler," *Principles Of Instrumental Analysis*" fifth edition, pg. No: 550- 552
[25] Korsmeyer R. W; Gurny R. Peppas. Mechanism of Solute Release From Porous Hydrophilic Polymers. *J Pharm*., **1983**, 25-35.
[26] Higuchi T. *J Pharm.Sci*., **1963**, 1145-1149.