International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-2, 2012

Preparation and Evaluation of Venlafaxine HCl Microspheres

Jobanputra UM[1*], Patel KS[1], Patel PD[1], Makwana ST[1], Oza PJ[1], Ravat MK[1]

[1]*Department of Pharmaceutics, K.B.Raval College of Pharmacy, Shertha, Gandhinagar, Gujarat, India*

Manuscript No: IJPRS/V1/I2/00115, Received On: 10/06/2012, Accepted On: 14/06/2012

ABSTRACT

Venlafaxine HCl is a new generation serotonin reuptake inhibitor drug having antidepressant activity with half-life of 4-5 hours. The aim of this study was to formulate and evaluate microspheres of a highly water soluble drug, venlafaxine HCl by non-aqueous solvent evaporation method. Ethylcellulose(EC) (100 cps) and Eudragit RS-100 were selected as drug release retardant polymers and heavy liquid paraffin as a continuous phase. The prepared batches were evaluated for mean particle size, % encapsulation efficiency, % yield, % cumulative drug release and surface morphology. As concentration of polymer increased, In vitro drug release was decreased but % encapsulation efficiency and mean particle size of microspheres was increased. Microspheres prepared from EC showed higher particle size and sustained drug release as compared to microspheres prepared from Eudragit RS-100. From the release profile it was observed that all the formulations followed Higuchi model indicated that drug release was through diffusion from homogenous matrix.

KEYWORDS

Venlafaxine HCl, Ethylcellulose, Eudragit RS-100, Microspheres, Higuchi model.

INTRODUCTION

The efficacy of a drug in a specific application requires the maintenance of appropriate drug blood level concentration during a prolonged period of time. However the conventional administration of drugs, gives a poor control of the concentration of these substances in plasma because of variations in the concentration of the bioactive product, once a specific dose has been administered[1]. The conventional dosage systems can give rise to alternative periods of inefficacy or toxicity. These difficulties have been called for the development of new administration techniques for bioactive compounds, directed towards attaining the steady state plasma concentration[2]. In the recent years, considerable attention has been focused on the development of Novel Drug Delivery Systems (NDDS).

***Address for Correspondence:**
Jobanputra Urvish
Department of Pharmaceutics,
K.B.Raval College of Pharmacy,
Shertha, Gandhinagar, Gujarat, India
E-Mail Id: urvish_pharma@yahoo.com

The reason for this paradigm shift is due to the low development cost and time required for developing a NDDS for the existing drugs rather developing a new drug molecule[3]. In the form of NDDS, existing drug molecule can get a new life, thereby increasing the market value and product patent life. Controlled release, prolonged action, sustained release, extended release, depot dosage forms are terms used to identify these drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. Number of advances took place in the field of Controlled drug delivery systems in the last few decades. During the preliminary stages of research on controlled drug delivery, major accent was focused on the development of zero-order devices[4]. The primary objective of zero-order release is to up-hold constant drug concentration in blood for a prolonged period of time. Microspheres have played a vital role in the development of controlled/sustained release

drug delivery systems[5]. Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained and controlled drug release. Controlled drug delivery using biodegradable polymeric carries has gained increasing interest in last two decades. In a majority of studies the homo and copolymer have been used for drug delivery application because they can be fabricated into a variety of morphologies, including films, rods, and micro particles by compression molding, solvent casting, solvent evaporation technique and phase separation technique[6]. After the employment in the body, biodegradable polymers of natural and synthetic origin like Eudragit, ethyl cellulose and egg albumin have a unique advantage that after performing their function they degrade into non toxic monomers. Administration of drugs in the form of microspheres, usually improves the treatment by providing the localization of the active substance at the site of action and by prolonging release of drug[7].

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 4-5 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[8].

There are different methods to use microencapsulation. The choice of the method that will give rise to an efficient drug encapsulation depends on the hydrophilicity or the hydrophobicity of drug. For insoluble or poorly water-soluble drugs, the oil-in-water (o/w) method is frequently used. For highly water soluble drugs, the oil-in-oil (o/o) non-aqueous method is used[9]. The present study was based on preparation of microspheres of Venlafaxine HCl by solvent evaporation method using EC and Eudragit RS-100 in various ratios of 1:1, 1:2, 1:3 and 1:4.

MATERIALS AND METHODS

MATERIALS

Venlafaxine HCl, Ethyl cellulose (100 CPs) and Eudragit RS 100 were obtained as gift sample from Amneal Pharmaceuticals, Gujarat. All other chemicals used of analytical grade were purchased from RFCL Ltd, New Delhi.

METHOD

Method of Preparation

Microspheres were prepared by non aqueous solvent evaporation method. In this method EC or Eudragit RS 100 in different proportion was solubilized in 30 ml mixture of solvent system methanol: acetone (1:9). Then 500 mg Venlafaxine HCl and 25 mg Magnesium stearate were added into polymer solution.

Then solution was cooled at ≤ 10 ºC and slowly introduced into previously cooled (≤ 10 ºC) 100 ml of heavy liquid paraffin containing 10 ml of n-hexane, which was continuously stirred at 1000 rpm using mechanical stirrer equipped with three bladed propellers at room temperature. Stirring was applied continuously until complete evaporation of solvent took place. The prepared microspheres were filtered by using vacuum filter. The microspheres obtained were washed repeatedly with n-hexane until free from oil. The collected microspheres were dried at room temperature.[9]

EVALUATION OF MICROSPHERES

Percentage Yield[9]

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

$$\text{Percentage yield} = \frac{\text{Weight of microsphere recovered}}{\text{Weight (drug + polymer)}} * 100$$

Table 1: Composition of all batches prepared non-aqueous solvent evaporation method

Batches	Venlafaxine HCl (mg)	Ethyl cellulose (mg)	Eudragit RS-100 (mg)	Methanol + Acetone (ml)	Heavy liquid paraffin (ml)	n-hexane (ml)
F1	500	500	-	30	100	10
F2	500	1000	-	30	100	10
F3	500	1500	-	30	100	10
F4	500	2000	-	30	100	10
F5	500	-	500	30	100	10
F6	500	-	1000	30	100	10
F7	500	-	1500	30	100	10
F8	500	-	2000	30	100	10

%Entrapment Efficiency[10]

% Entrapment efficiency was calculated using the following formula,

$$EE = (Pc / Tc) * 100$$

Where - Pc is practical drug content,

Tc is the theoretical drug content.

In-Vitro Dissolution Studies[11]

Dissolution studies were carried out for all the formulations, employing USP Type-I apparatus (Basket method) at 37 ± 0.5°C rotated at constant speed of 100 rpm using distilled water as the dissolution medium. 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 274nm.

In Vitro Drug Release Kinetics[12]

In order to study the exact mechanism of drug release from the microspheres, drug release data was analyzed according to Zero order, First order, Higuchi square root and Peppas models as shown in table 3. The criteria for selecting the most appropriate model were chosen on the basis of goodness of fit test.

Surface Morphology [13]

Morphological characterization of the microcapsules was carried out by using scanning electron microscopy (JEOL JSM - 5200) under higher and lower resolution. The dried samples were coated with gold palladium of 200A° thickness under argon atmosphere of gold coating prior to microscopy evaluation.

RESULTS AND DISCUSSION

Microspheres of venlafaxine HCl were prepared by non-aqueous solvent evaporation method using EC and Eudragit RS-100 as polymers with various proportions. The parameters which were evaluated for microspheres are given in the Table 2.

%Yield

To observe the effect of polymer concentration on the % yield of the resulting microspheres, formulations were prepared at varying concentrations of EC and Eudragit RS-100. The percentage yield of microspheres varied from 72.5% to 91.4% for EC and 70.53% - 86.88% for Eudragit RS-100. From Table 2 it was observed that % yield of the resulting microspheres increased with increasing Drug: Polymer ratio (Figure 1).

Table 2: Characterizations of Prepared Microspheres

Batch no.	Yield (%)	EE (%)	Mean Particle Size (µm)
F1	72.5	94.21±0.38	98.3
F2	78.8	93.64±1.73	120.7
F3	88.3	95.19±2.01	168.4
F4	91.4	91.57±1.24	210.5
F5	70.53	93.17±0.98	71.6
F6	75.74	95.84±1.32	90.4
F7	79.2	90.1±1.47	135.1
F8	86.88	94.28±0.82	176.7

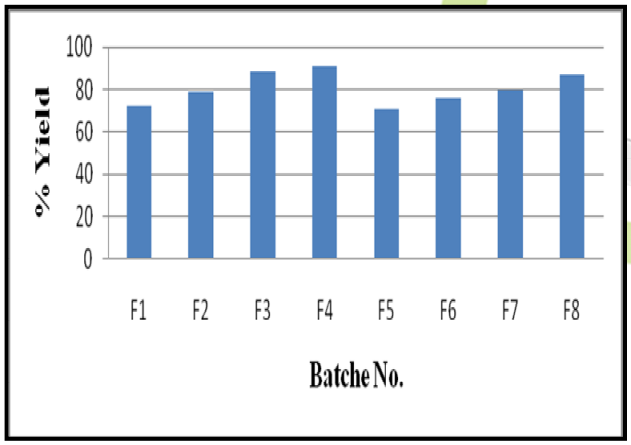


Figure 1: % Yield of batches F1-F8

% Entrapment Efficiency

In the following method there was no loss of drug because dug was insoluble in heavy liquid paraffin, so theoretically 100% drug entrapment was achieved. So if we increase polymer concentration then it is insignificant. From Table 2 it was observed that Drug polymer ratio had no effect on % entrapment efficiency (Figure 2).

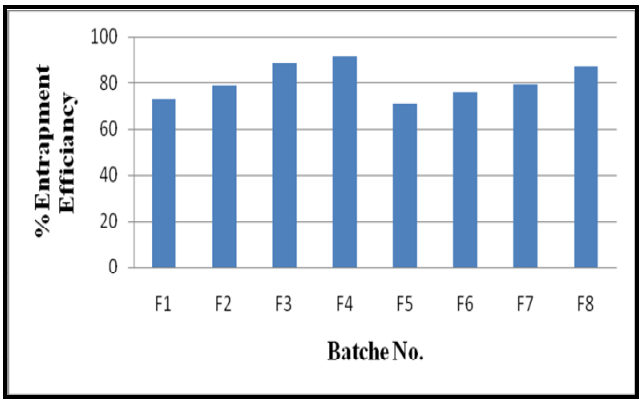


Figure 2: % Entrapment Efficiency of batches F1-F8

Mean Particle Size

The effect of polymer concentration on the particle size of the microspheres was determined and it showed that particle size of the microspheres was increased with the increasing polymer concentration. Mean particle size of Microspheres was in the range of 98.3 - 210.5µm for EC and 71.6 -176.7µm for Eudragit RS-100 (Table 2, Figure 3). As the concentration of polymer increased, the viscosity of the dispersed phase was also increased. When the dispersed phase with higher viscosity was poured into the dispersion medium, bigger droplets were formed and mean particle size of microspheres was increased. Viscosity of the dispersed phase of EC was high as compared to the Eudragit RS-100 so microspheres prepared from EC had higher particle size compared to the Eudragit RS-100 microspheres.

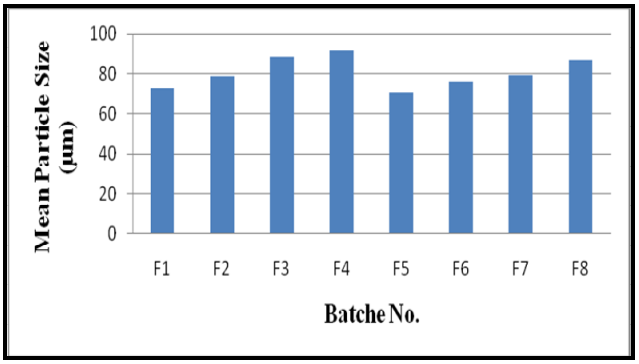


Figure 3: Mean particle size of batches F1-F8

In Vitro Dissolution Studies

In vitro dissolution studies of Venlafaxine HCl microspheres were performed in distilled water for 20 hours using USP I (basket type) dissolution test apparatus. Microspheres having weight equivalent to 75 mg of drug was used to carry out dissolution. All these results showed that drug dissolution rate could be decreased with increased polymer amount. As increased in polymer concentration the matrix wall of microspheres became thicker. Due to formation of a thicker matrix wall dissolution rate of drug became slower. From figure 4 it was observed that as the concentration of polymer increased, the % cumulative release of Venlafaxine HCl was decreased.

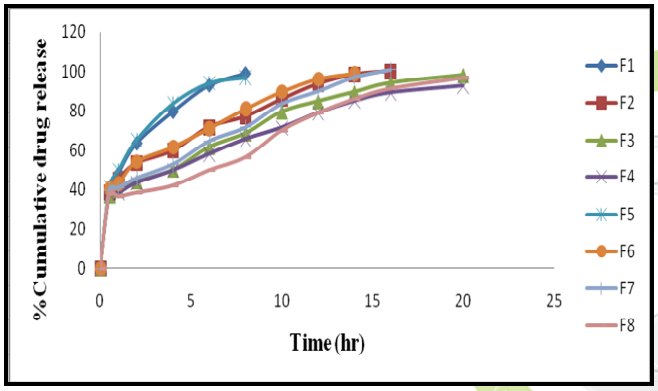


Figure 4: % Cumulative drug releases of batches F1-F8

In vitro drug release study of marketed product (VENLOR- XR 75) was performed and drug release pattern was shown in figure 5.

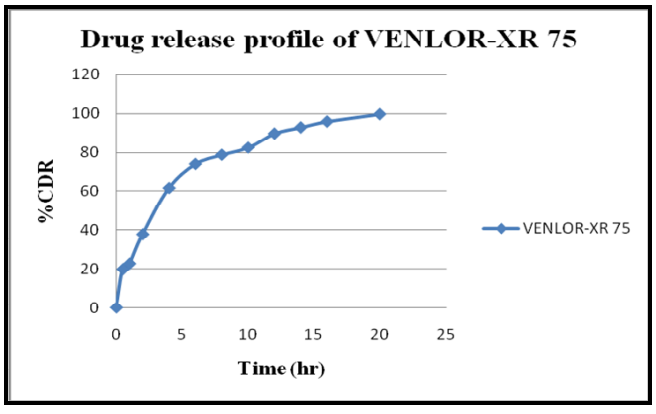


Figure 5: Drug release profile of VENLOR-XR 75

Drug release profiles of all batches were compared with the drug release profile of VENLOR-XR 75 by f1 and f2. For the calculation of f1 and f2 five time points 2hr, 4hr, 8hr, 12hr, and 20hr of dissolution profile were compared[7]. Table-3 shows that for EC F2 batch, and for Eudragit RS-100 F7 batch was found more similar to the marketed product. These batches showed acceptable result for % yield, % entrapment efficiency, and mean particle size.

Table 3: Comparison of drug release profile with marketed product

Batches	f1	f2
F1	20	38
F2	5	60
F3	7	57
F4	12	50
F5	21	37
F6	7	57
F7	6	62
F8	15	43

Mechanism of Release

The in vitro release data obtained were fitted in to various kinetic equations. Correlation coefficients of individual batch with applied equation were given in Table 4. All batches showed higher correlation with Higuchi plot than zero order and first order etc. so predominant drug release mechanism was found to be diffusion controlled mechanism.

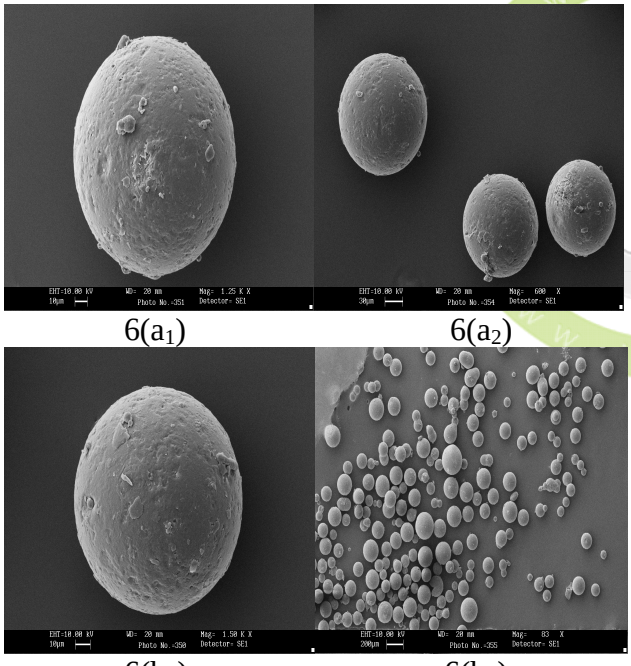
Surface Morphology

In the preparation of microspheres temperature of dispersion medium was < 10 ^{0}C, so the evaporation rate of dispersed phase was very slow. Thus droplets have sufficient time to stabilize and achieved completely spherical shape. From figure 6 it was observed that surfaces of all microspheres were rough and

drug crystals were also present on the surface of microspheres. These drug crystals were responsible for the burst release of drug from the microsphere.

Table 4: Drug release kinetic studies of all batches

Batch code	Regression Values (R^2)			
	Zero order	First order	Higuchi	Korsemeyer-Peppas
F1	0.944	0.884	0.992	0.987
F2	0.969	0.917	0.993	0.98
F3	0.962	0.92	0.981	0.943
F4	0.973	0.936	0.982	0.938
F5	0.911	0.855	0.976	0.951
F6	0.975	0.931	0.992	0.972
F7	0.971	0.968	0.979	0.924
F8	0.973	0.945	0.983	0.811



6(a_1) 6(a_2)

6(b_1) 6(b_2)

Figure 6: Scanning electron micrographs of microspheres of F2 batch (a_1, a_2) and F7 batch (b_1, b_2)

CONCLUSION

Microspheres of Venlafaxine HCl were prepared by a non-aqueous solvent evaporation method. The nature of polymer influenced the physical characteristics as well as in vitro drug release behavior of the microspheres. The drug release was sufficiently sustained and non-Fickian transport of the drug from microspheres was confirmed. Microspheres prepared from EC showed higher particle size and sustained drug release as compared to microspheres prepared from Eudragit RS-100. Microspheres of Venlafaxine HCl prepared with EC and EudragitRS-100 may provide a convenient dosage form for achieving patient compliance and once daily sustained release dosage form.

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