Preparation and Evaluation of Sustained Release Venlafaxine HCl Microspheres

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Received: September 05, 2013; Accepted: November 11, 2013; Published (web): June 29, 2014

ABSTRACT: The aim of this study was to formulate and evaluate sustained release microsphere of Venlafaxine HCl (VF-HCl). It has many side effects with a half life around 5 hr. To reduce the adverse actions due to burst effect a sustained release (SR) Eudragit RS-100 microspheres embedded VF-HCl was formulated. The VF-HCl microspheres were prepared by oil in oil (O/O) solvent evaporation method. Drug and Polymer interaction for formulated SR Eudragit RS-100 microsphere embedded on VF-HCl was characterized by FT-IR and X-RD studie. The result showed that there is no interaction between the drug and polymer. Surface morphology of formulation carried out by FE-SEM … showed good spherical geometry and uniformity in size and shape. It can be concluded that the formulated VF-HCl microspheres using widely accepted O/O method and polymer were capable for exhibiting sustained release formulation with decreasing dosing frequency thereby minimizing the occurrence of side effects with improved bioavailability.

Key words: Microspheres, drug loading, venlaflaxin, drug release

INTRODUCTION

Venlaflaxin hydrochloride (VF-HCl, Figire 1) is a new generation antidepressant serotonin/ noradrenalin reuptake inhibitor drug showing effective anti-depressant properties. It has a short bioavailability 12.6% and biological half-life 5 hrs. So, frequent administration of drug is necessary to maintain its therapeutic efficacy. Therefore necessitates of the multiple daily dosing for maintenance of its plasma concentration of the drug within the therapeutic index is necessary, 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.[1]

It is a bicyclic phenyl ethyl amine and chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents and designated as (R/S)-1-[2-dimethyl amino)-1-(4- methoxy phenyl) ethyl] cyclohexanol hydrochloride. This medication is used to treat anxiety.

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VF-HCl is a water soluble drug with a solubility[2] of 572mg/ml. By preparing the sustain release dosage form, the initial burst effect of highly water soluble drugs like VF-HCl can be prevented. It acts by inhibiting selectively the uptake of serotonin and nor-adrenaline but shows no affinity for neurotransmitter receptors.[3] It has many adverse effects like nausea, asthenia, dizziness, insomnia, somnolence, headache, dry mouth, sweating, hypotension, nervousness and abnormal ejaculation. The half life of VF-HCl and its active metabolite O-desmethyl venlafaxine is 5 hr. and 11 hr. respectively.[4] A VF-HCl overdose may be more serious than an overdose with selective serotonin reuptake inhibitors.[5]

The present study was based on preparation of microspheres of VF-HCl by O/O solvent evaporation method using Eudragit RS-100, to overcome from above said life threatening health problems and to achieve better patient compliances.

MATERIALS AND METHODS

VF-HCl was obtained from Alembic Pharmaceutical Ltd. Vadodara was a gift sample. Methanol and sodium hydroxide was purchased from

RFCL Limited New Delhi. Liquid paraffin light and n-Hexane ware purchased from Merck specialities private ltd. Mumbai. Acetone was purchased from Sisco research lab. Pvt. Ltd. Mumbai., and all other chemicals used were of analytical grade.

Eudragit RS-100 embeded SR venlafaxine hydrochloridc (VF-HCl) microsphere were prepared (Table 1) by using O/O solvent evaporation method.[6,8] In this method, required quantity of Eudragit RS-100 was dissolved in 10 ml acetone under magnetic stirring (Remi electrotechnik Limited, Thane, India) VF-HCl 0.5 g and magnesium stearate 50 mg dissolve in 5 ml methanol. This solution was dispersed in above obtained polymer solution. The resulting dispersion solution was added drop by drop with the help of syringe needle (10 ml) into a 250 ml beaker containing a mixture of 100 ml of liquid paraffin light with overhead stirrer (Remi electrotechnik Limited, Thane, India) at constant speed 700 rpm for 4 hr. For complete evaporation of acetone, organic solvent from formulation and harden the microsphere added 15 ml n-hexane. The resulting suspension was filtered using whatman filter paper and collected the microsphere. The microspheres were dried at room temperature for 24 hr. and proceeded for further characterization.

Characterization of microspheres

Determination of process yield. The process yield was determined as the weight percentage of final product after drying with respect to the initial total amount of drug: polymer and other materials used for the preparation of microsphere. [9,10]

$$\text{Process yield (\%)} = \frac{\text{Practical product yield}}{\text{Theoretical product yield}} \times 100$$

Drug loading capacity and drug entrapment efficiency study. For determination of drug loading capacity, known amount of microspheres were added to 25 ml of phosphate buffer (pH 6.8). The resulting mixture was shaken on magnetic stirrer (Remi electrotechnik Limited, Thane, India) for 24 hr. The solution was filtered using whatman filter paper and approximately 1 ml of this solution was diluted to 100 ml using phosphate buffer (pH 6.8) and analyzed it on UV-Visible Spectrophotometer (Hitachi, U-2900) at 224 nm. The drug loading capacity and entrapment efficiency were calculated using the following formula.[11]

$$\text{Drug loading (\%)} = \frac{\text{Actual drug content}}{\text{Weight of powdered microspheres}} \times 100$$

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

***In vitro* drug release studies.** % cumulative drug release from the microsphere formulations were studied using USP dissolution test apparatus Paddle Type 1(HITACHI U-2900, Tokyo, Japan) using 0.1 N. HCl (pH 1.2) and phosphate buffer (pH 6.8) separately for 2 hr. and 12 hr. Respectively.[12,13] Microspheres equivalent to 50 mg of drug was added into the dissolution medium. The dissolution medium was stirred continuously at 100 rpm and temperature was maintained at 37^0 C ± 0.5^0C. The volume of the medium used was 900 ml. Sample were withdrawn at regular time interval and the same volume was replaced with fresh dissolution medium. The samples were measured on UV -Visible Spectrophotometer at 224 nm.

Fourier transform infrared (FTIR) spectroscopy study. IR spectra (FTIR-V 530, Shimadzu) of the Pure VF-HCl, Pure Eudragit RS-100 and Eudragit RS-100 embeded VF-HCl were formulated, examined and study was carried out separately to check the compatibility between the VF-HCl and Eudragit RS-100 used for the preparation of microspheres by the potassium bromide pellet method. For that, sample (1mg) was mixed with potassium bromide (40 mg) and formed into disc in a manual press. Spectra were recorded in the scan range of 4000-500 cm^{-1}.

Field emission scanning electron microscopy (FESEM). Surface morphology was carried out by using FE-SEM (S-4800, Hitachi, Japan.) for formulated microsphere. prior to examination, sample were gold-coated to render them electrically

conductive and examined under the microscope .The SEM was operated at a distance of 8.2mm×400 and accelerating voltage of 10.0KV.

X-ray diffraction (XRD) study. X-RD was carried out for pure VF-HCl, pure Eudragit RS-100 and formulation using X-RD (D-8 Advance, Bruker). Powder X-ray diffractometer was carried out with X-ray diffractometer (Miniflex, Rikagu) using Ni filtered, Cu-kα radiation (λ= 1.5406 A°), a voltage of 40 kV and a current of 40 mA. The scanning rate was 0.06°/min over a 2θ range of 20^0-80^0.

RESULTS

Characterisation - Process yield. As shown in Table 2. Sustained release VF-HCl loaded microspheres were successfully formulated by using O/O solvent evaporation method and result were found to be in the range of 66.66 to 81.83 %.

Drug loading capacity and drug entrapment efficiency. As shown in Table 2, the drug loading capacity of Eudragit RS 100 encapsulated VF-HCl microspheres were in the range 15.22 to 50.85 %. The drug entrapment efficiencies were in the range of 71.20 to 76.00%. The drug loading and drug entrapment efficacy of the microspheres decreased with increased concentration of Eudragit RS-100.

Table 1. Following batches of Eudragit RS-100 encapsulated VF-HCl microsphere.

Ingredients	Batches (v)				
	V1	V2	V3	V4	V5
Venlafaxine HCl (gm)	0.5	0.5	0.5	0.5	0.5
Eudragit RS100 (gm)	0.5	1	1.5	2	2.5
Acetone (ml)	10	10	10	10	10
Methanol (ml)	5	5	5	5	5
n-hexane (ml)	15	15	15	15	15
Liquid parf. light (ml)	100	100	100	100	100
Mg. stearate (mg)	50	50	50	50	50

***In vitro* drug release studies.** The *in vitro* release of drug VF-HCl from the various microspheres formulation (Figures 2 and 3) was carried out by using USP dissolution paddle type 1 in 0.1 N. HCl (pH 1.2) and phosphate buffer (pH 6.8) separately for 2 hr. and 12 hr. respectively. The cumulative percentage release of VF-HCl from the prepared microspheres in pH 1.2 was varied 20.23 ± 0.68% to 25.68 ± 0.32% and in pH 6.8 was varied from 75.29 ± 0.71% to 81.07± 0.73% depends upon the drug polymer ratio.

Table 2. Following process yield, drug loading capacity and drug entrapment efficiency of VF-HCl microspheres.

Batch	Process yield (%)	Drug loading capacity	Drug entrapment efficiency
V1	66.66	50.85 ± 0.17	71.20± 0.87
V2	70.96	32.72 ± 0.86	72.0 ± 0.43
V3	74.24	23.98 ± 0.97	73.00 ± 0.60
V4	79.29	18.39 ± 0.32	74.4 ± 0.31
V5	81.83	15.22± 0.43	76.0 ± 0.65

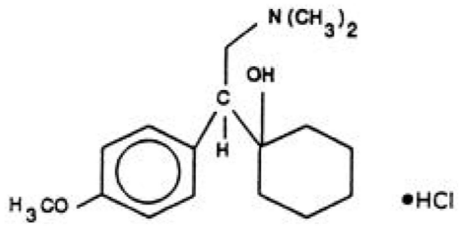

Figure 1. Structure of venlafaxine HCl.

FT-IR study. As shown in Figures 4-6, the characteristic bands of VF-HCl were observed at 3375.54cm^{-1} (OH), 2935.76 cm^{-1} (C-H in CH_2), 2862.46 cm^{-1} (C-H in CH_3) and 1035.81 cm^{-1} (C-O-C). However, the IR spectrum of the VF-HCl–Eudragit RS-100 microspheres showed the respective characteristic bands of VF-HCl at 3350.46, 2941.54, 2864.39, and 1035.81 cm^{-1}. The results confirmed that there was no chemical interaction between VF-HCl and Eudragit RS-100 polymer.

Surface morphology study. The surface morphology of VF-HCl loaded microspheres were analyzed by field emission scanning electron microscopy. The FE-SEM photographs of the surface

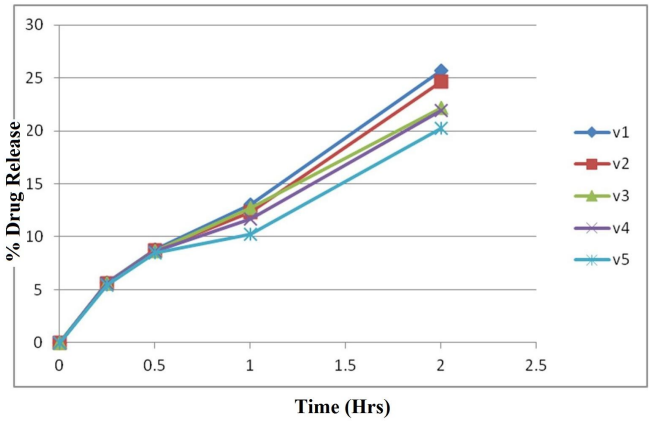

Figure 2. *In vitro* release profile of venlafaxine HCl in pH 1.2 from Eudragit RS 100 microsphere formulation**.**

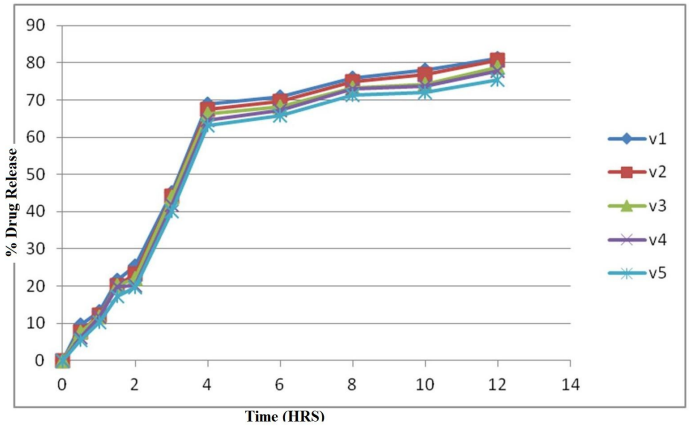

Figure 3. *In vitro* release profile of venlafaxine HCl in pH 6.8 from Eudragit RS 100 microspheres formulation.

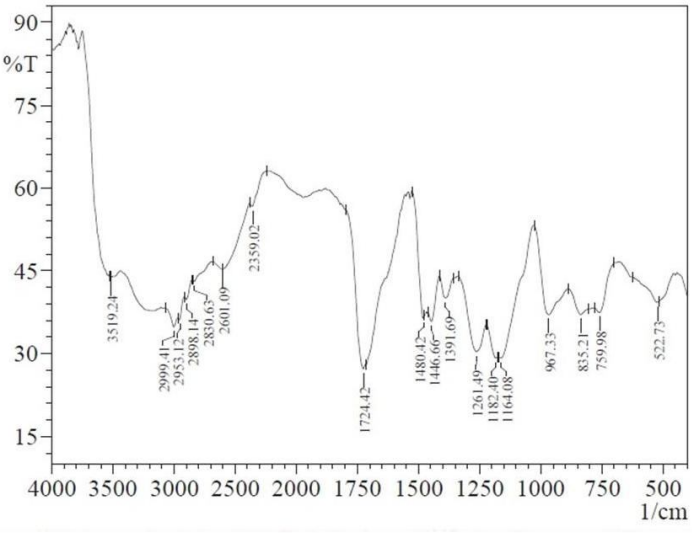

Figure 4. IR spectrum of pure venlafaxine HCl.

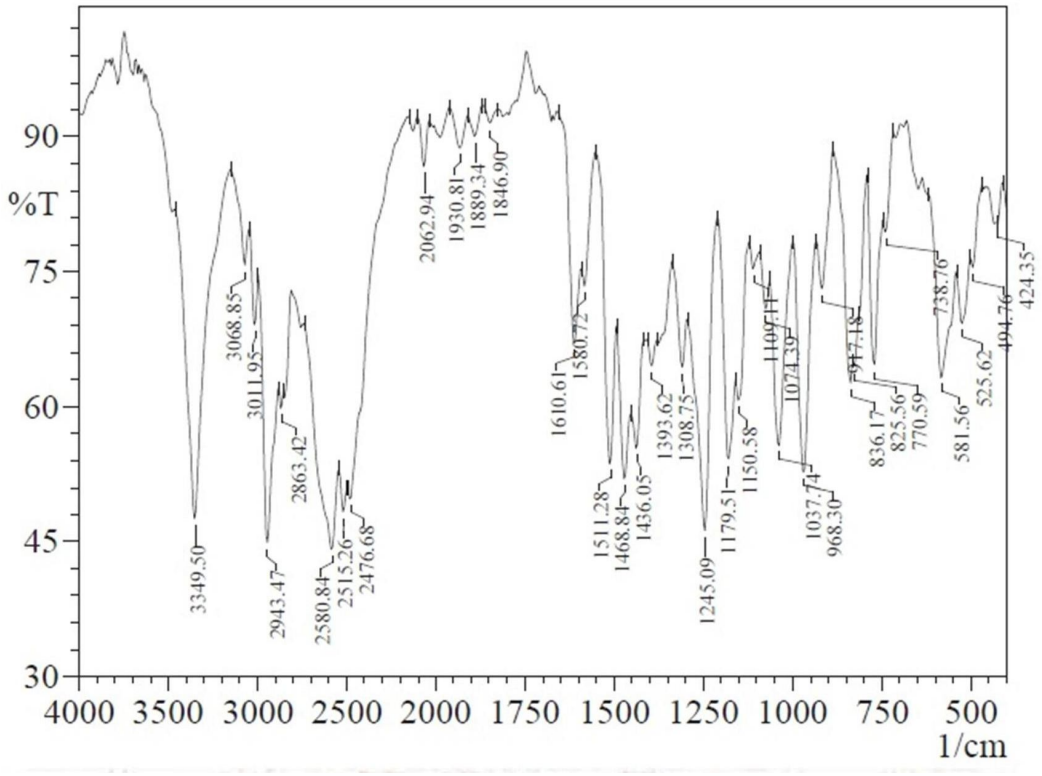

Figure 5. IR spectrum of pure Eudragit RS 100.

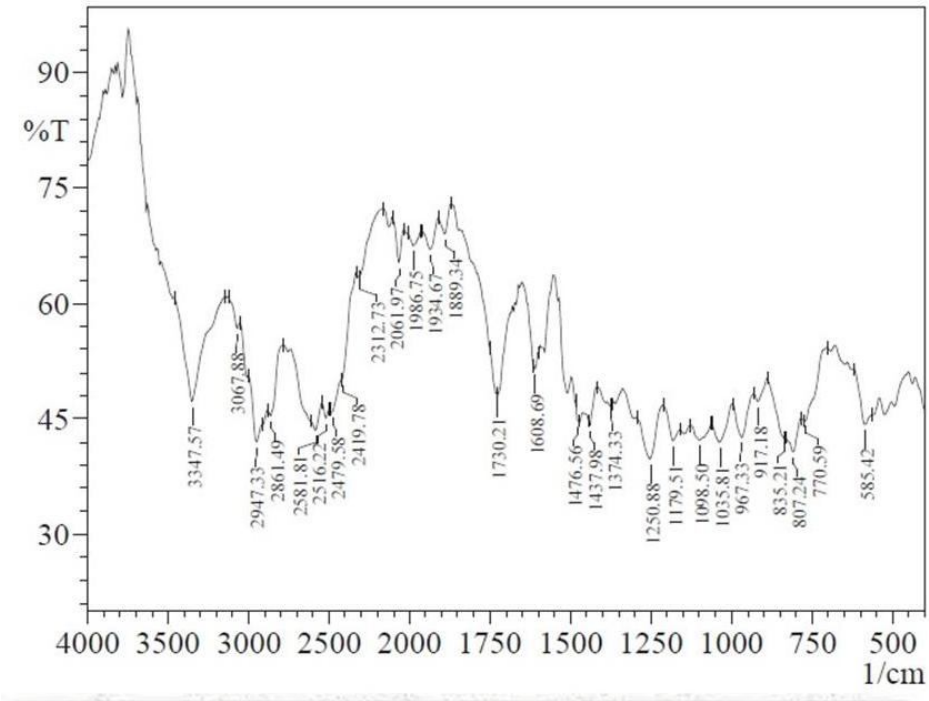

Figure 6. IR spectrum of Eudragit RS-100 loaded venlafaxin HCl microsphere.

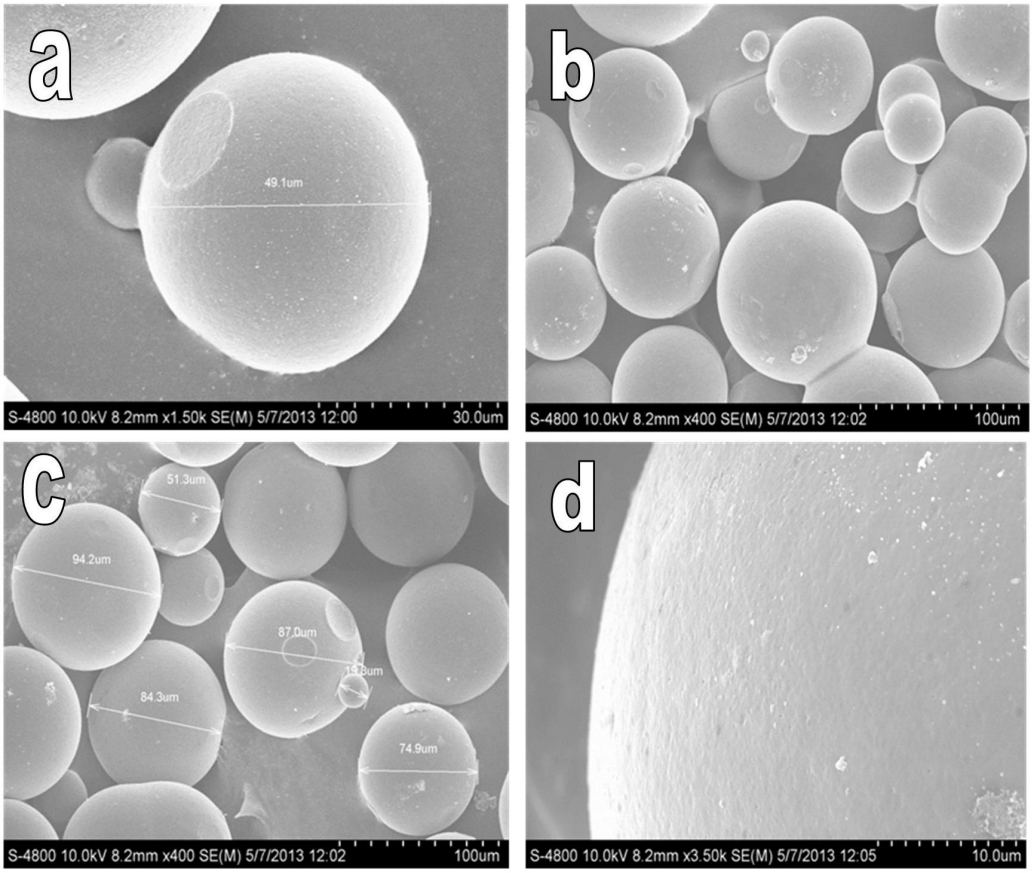

Figure 7. FE-SEM images of Eudragit RS 100 encapsulated venlafaxine HCl microsphere.

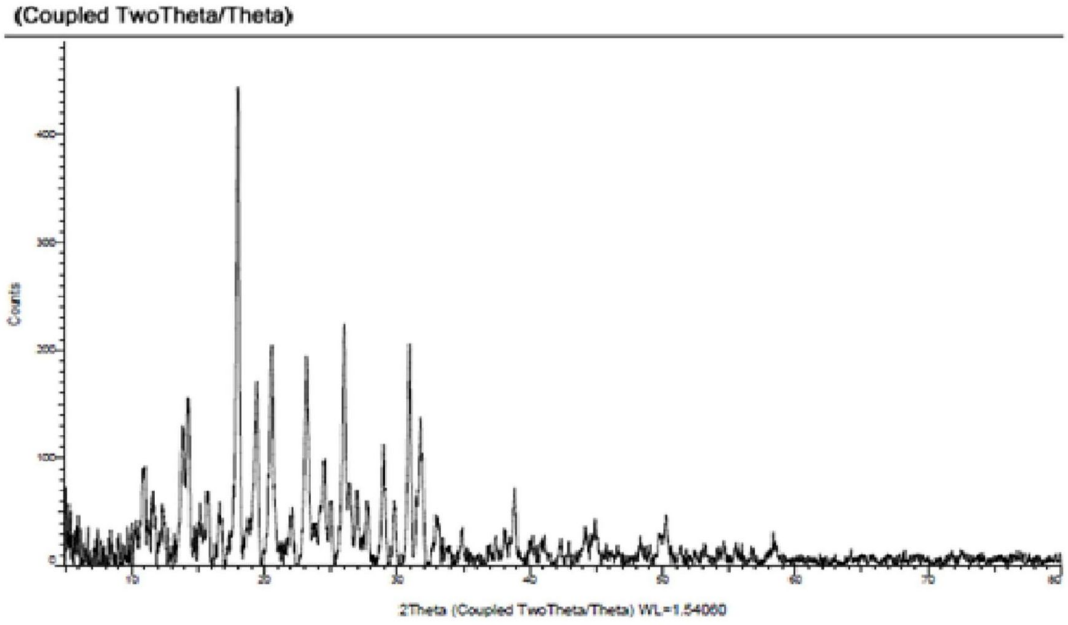

Figure 8. X-RD of pure venlafaxine HCl.

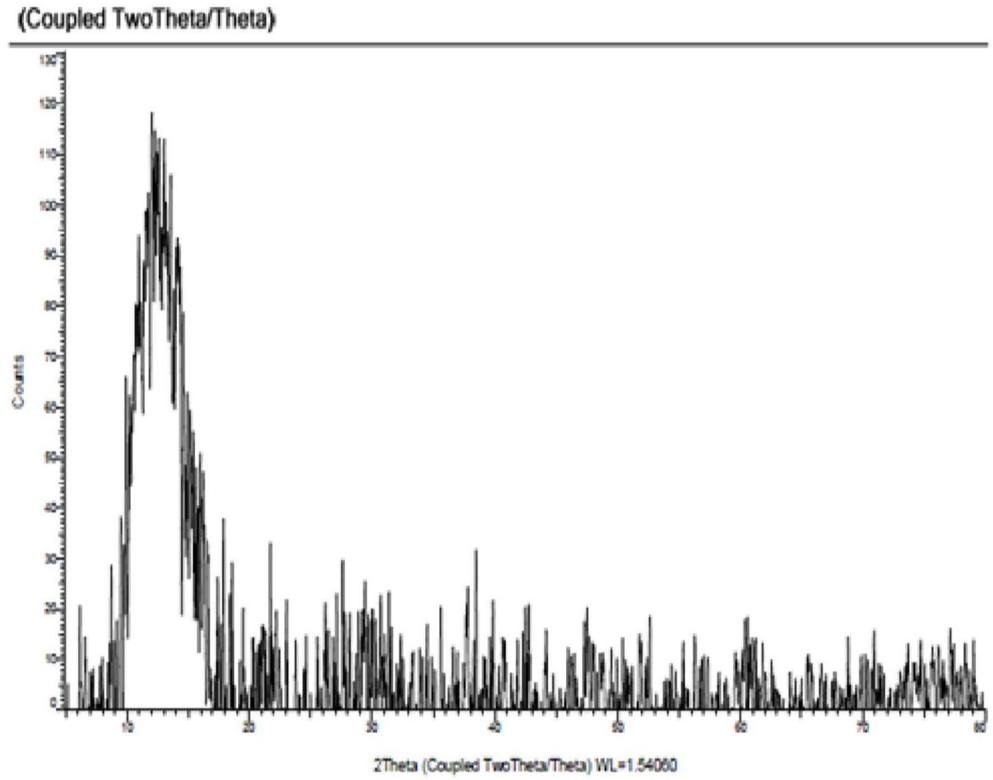

Figure 9. X-RD of pure Eudragit RS-100.

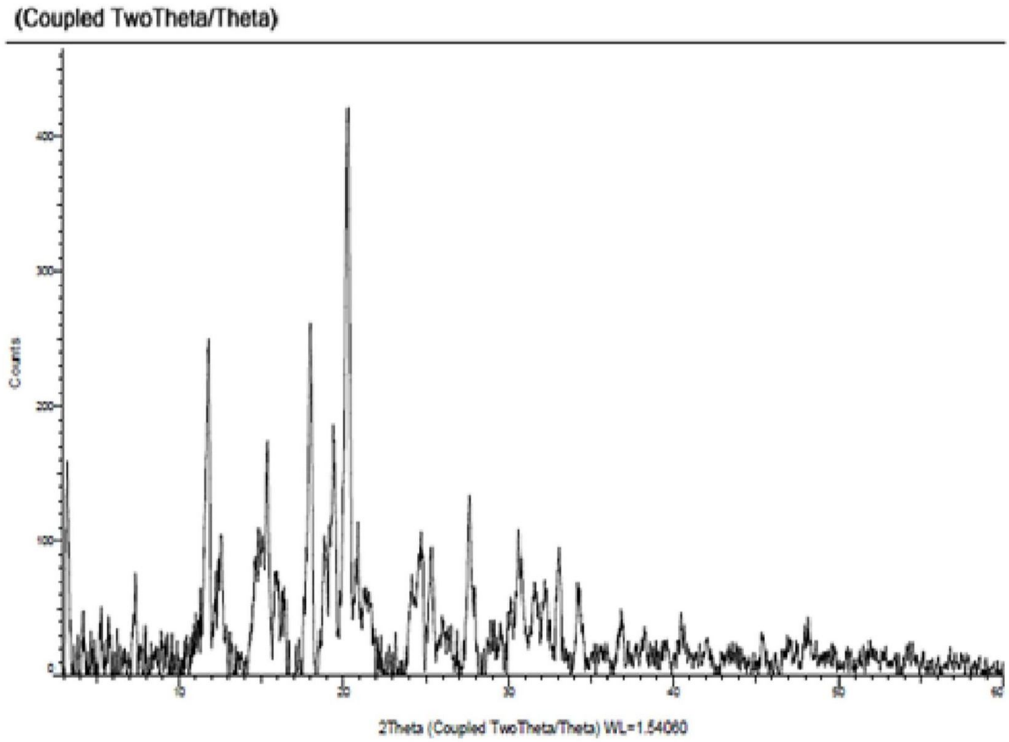

Figure 10. X-RD of Eudragit RS-100 loaded venlafaxine HCl microsphere.

of microspheres are shown in the Fig. 7. The microspheres were discrete and free flowing in nature. The sphericity of the microspheres was good. The particle size of the microspheres was found in the range of 49.1 µ to 94.2µ.it was observed that surfaces of all microspheres were rough and drug crystal were also present on the surface of microspheres. These drug crystal were responsible for the burst release of drug from the microsphere.

X-ray diffraction study. Pure VF-HCl was found to be 96.4% crystalline and 3.6% amorphous in nature, but when VF-HCl was loaded in Eudragit RS-100 microspheres, the crystalline peaks of VF-HCl were decreased and amorphous peak increased. VF-HCl was found to be 64.9% crystalline and 35.1% amorphous in nature when converted into microspheres of Eudragit RS-100 and result found that there were no significant changes in XRD in drug -polymer and shown crystalline in nature. The X-ray differaction studies of various entitites have been shown in Figures 8-10.

DISCUSSION

The present study, Eudragit RS 100 encapsulated VF-HCl microsphere were prepared by O/O solvent evaporation technique with different drug polymer ratio. Liquid paraffin and acetone were used for the preparation of microspheres. Magnesium stearates were used as a droplet stabilizer to prevent droplet coalescence in oil medium and n-hexane were added as a non-solvent to the processing medium to solidify the microspheres. Table 2 represents the summary of the yield of microspheres. Sustained release VF-HCl loaded microspheres were successfully formulated by using O/O solvent evaporation method, and were found to be in the range of 66.66 to 81.83%. The cumulative percentage of drug release from microsphere decreased with increased in concentration of Eudragit RS-100, this was probably due to its higher solubility. Among the different VF-HCl (V1 to V5) microspheres formulations, the formulation V5 was selected as a ideal formulation, after considering its spherical in shape, free flowing, better drug loading capacity and drug entrapment efficiency and also drug release at a sustained manner upto 12 hr. The FT-IR study confirmed that there was no chemical interaction between VF-HCl and Eudragit RS-100 polymer. The FE-SEM photographs of microspheres are shown in the Fig.7. which reviled the surface morphology of formulation. The sphericity of the microspheres was good. The XRD study found that there were no significant changes in drug -polymer and shown crystalline in nature. The procedure used for preparation of microspheres showed good yield, producibility and indicates minimum loss of drug and polymer happened during formulation and recovery.

CONCLUSION

The present study reports the development of sustained release Eudragit RS-100 loaded VF-HCl microspheres by using O/O solvent evaporation method. This method was found ability to produce microsphere in spherical with uniform size, shape and free flowing nature. Based on the observation, it can be concluded that the formulated VF-HCl microspheres using widely accepted O/O method and polymer were capable for exhibiting sustained release formulation with decreasing dosing frequency thereby minimizing the occurrence of side effects with improved bioavailability.

ACKNOWLEDGEMENT

The authors are grateful to Alembic Pharmaceutical Ltd. Vadodara for providing drug as a gift sample for research purpose.

Conflict of interest: Authors do not report any conflict of interest

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