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FORMULATION AND EVALUATION OF VENLAFAXINE HYDROCHLORIDE MICROSPHERES

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ABSTRACT

Microspheres have been widely accepted as a mean to achieve oral and parenteral controlled release. A number of different substances both biodegradable as well as non-biodegradable have been investigated for the preparation of microspheres 1,2,3. Venlafaxine hydrochloride is an effective widely used novel antidepressant drug. It has a short biological half-life of 5±2 hrs and is rapidly eliminated. Therefore attempts have been made to develop sustained release microspheres of venlafaxine hydrochloride. So, in this present study an attempt was made to incorporate venlafaxine hydrochloride into ethyl cellulose microspheres by using emulsification and organic solvent evaporation technique and its release profile was evaluated through the in-vitro release pattern study of drug from ethyl cellulose microspheres containing Venlafaxine hydrochloride, Stability studies of ethyl cellulose microspheres containing Venlafaxine hydrochloride and Evaluation of the optimized formulation by Scanning Electron Microscope (SEM).

KEYWORDS: Microspheres, Venlafaxine hydrochloride, ethyl cellulose, short half-life.

INTRODUCTION

Microspheres are multiparticulate drug delivery systems which have free flowing powder characteristics, consisting of synthetic polymers and proteins. They are prepared to obtain prolonged or controlled drug delivery to improve bioavailability, stability and to target the drug to specific site at a predetermined rate. These are biodegradable in nature having particle size less than 200um. The range of techniques for the preparation of microspheres provides multiple options to control as drug administration aspects and to enhance the therapeutic efficacy of a given the drug. They have various advantages over the other dosage forms, which include improved efficacy, reduced toxicity, improved patient compliance and convenience. Microspheres are having wide range of applications because of controlled and sustained release. In microspheres, the drug is located centrally within the particle where it is encased within the unique polymeric membrane. Most important application is that it is used for targeting tumours using anticancer drugs. It is important carrier for safe and effective in-vivo drug delivery.

The micro particulate delivery system are considered and accepted as a reliable means to deliver the drug to the target site with specificity, if modified, and to maintain the desired concentration at the site of interest without untowards effects. For many drugs, a well-designed drug delivery system is as important as pharmacological activities of drug and it can accurately deliver the drug to the site of action at desired rate and minimize its side effects by reducing exposure of drug to the other tissues.

MATERIALS AND METHOD

Venlafaxine Hydrochloride - Hetero drugs Private Limited, Andhrapradesh, **Ethyl cellulose-** Himedia Laboratories Ltd. Mumbai 400086, **FT-IR-** Schimadzu, **Scanning Electron Microscope**- Hitachi S-450, **UV-Visible spectrophotometer Double beam-** Schimadzu Pharmaspec 1700, **Dissolution apparatus -** USP XXIII-Electro lab, Mumbai.

PREPARATION OF MICROSPHERES

Ethyl cellulose microspheres containing Venlafaxine hydrochloride were prepared in six different drug to polymer ratios (1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1:4.5, 1:5) by emulsification and organic solvent evaporation technique 11. Dissolve specific amount of ethyl cellulose in 20ml of dichloromethane and add slowly 100mg of venlafaxine hydrochloride to form uniform solution. Add gradually ethyl cellulose solution containing the drug to beaker containing distilled water and 50ml of 0.5% gelatin solution. The beaker is heated in a water bath at 40^{o}C. The dispersed phase was then added and stirred with using stainless steel mechanical propeller at 2000rpm. Continue mixing (45 min to 60 min) so that all the dichloromethane evaporates. Separate microspheres by filtration using whatman filter paper and

the microspheres thus obtained can be washed four times with 20ml of distilled water and dry in a desiccator. Average particle was determined by using a calibrated stage micrometer and the surface characters were analyzed by Scanning Electron Microscope (SEM).

EVALUATION OF MICROSPHERES

1. Determination of % yield of microspheres

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

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

2. Determination of % encapsulation efficiency

Encapsulation efficiency was calculated by using the following formula.

$$\text{Encapsulation efficiency} = \frac{\text{Estimated drug content}}{\text{Theoretical drug content}} \times 100$$

3. Particle size determination

Optical microscope was used to determine the size of the particle that lies within a range from 0.2 µm to 100 equal divisions and hence, each division is equal to 10 µm and the particles are measured along an arbitrarily chosen fixed line across the centre of the particle. The particle size is a factor to be considered important in formulation of microspheres.

4. Scanning electron microscope study

The microspheres were observed under a scanning electron microscope. The instrument used for this study was Hitachi S-450 scanning electron microscope. The microspheres were mounted directly on to the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

5. FTIR spectra Analysis

FTIR spectroscopy can be used to investigate and predict any physicochemical interactions between different components, in a formulation and therefore it can be applied to the selection of suitable chemically compatible excipients. While selecting the vehicle ingredients, we would choose those, which are stable, compatible, cosmetically & therapeutically acceptable. The aim of the present study was to test, whether there is any interaction between the polymer and the drug and also compatibility between the drug and polymer. 10 mg of the sample and 30 mg of KBr were taken in a mortar and triturated. A small amount of triturated sample was taken into a pellet maker and was compressed at 10 Kg/cm^2 using a hydraulic press. The pellet was kept on to the sample holder and scanned from 4000cm to 400cm in Schimadzu FT-IR spectrophotometer.

6. Tapped Density

A required quantity of microspheres from each formula was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 sec intervals. The tapping was continued until no further change in volume was noted. Tapped density were calculated using the following formula, Tapped density = W / V_f

where, W = weight of the powder, V_o = initial volume, V_f = final volume

7. Angle of repose

Angle of repose was determined by using funnel method, the accurately weighed spheres were taken in funnel. The height of funnel was adjusted in such as way that the tip of funnel just touches the apex of heap of blends. The blends were allowed to flow through funnel freely on to surface. The diameter of powder cone was measured, angle of repose was calculated by using following equation, $\text{Tan } \theta = h/r$

where, h – height of pile, θ – angle of repose, r – radius of base pile

8. Compressibility index %

It is one of method for determining flow properties and also called as Carrs's index of compressibility. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is simple, fast and popular method of predicting powder flow characteristics. It was calculated by using following equation, $CI = 100 (V_o – V_f) / V_o$

9. Stability studies of Microspheres

All the formulations were studied for stability profile for 1 month at different environmental conditions such as 4^oC, 25^oC and 45^oC. The microspheres were placed in screw capped glass containers and stored at ambient temperatures by keeping the microspheres in refrigerator to produce 4^oC environment, 45^oC environment was produced by keeping the microspheres in hot air oven. From the above samples every week upto one-month period suitable representative samples were taken and it is analyzed for drug content. Change in average drug content was noted.

10. In-vitro release study

The drug release study was performed using USP type XXIII dissolution test apparatus, paddle model and at 100rpm using 900ml of phosphate buffer saline 7.4pH as a dissolution medium. The medium temperature was maintained at 37 ± 0.5^oC. Periodically 1 ml of the samples were withdrawn and diluted to 10 ml by using phosphate buffer pH 7.4. After each withdrawal the same quantity of the fresh medium was replaced immediately. Then the samples were assayed spectrophotometrically by Schimadzu Pharmaspec 1700 UV spectrophotometer at 496 nm using medium as blank.

RESULTS AND DISCUSSION

The sustained release microspheres of Venlafaxine Hydrochloride were prepared by using ethyl cellulose and evaluated with an aim to prevent side effects and increase bioavailability. It also leads to reduction in frequency of dosing which in turn improves patient

compliance and reduce fluctuation in drug levels. Prepared venlafaxine hydrochloride microspheres were subjected to various evaluation parameters such as FTIR characterization, size determination by microscopic method, shape and surface determination by digital photography, micromeritics properties like bulk density, tapped density, flow property by angle of repose, encapsulation efficiency determination and in-vitro dissolution studies.

Percentage of Entrapment

It is essential to know the quantity of the drug entrapped in the microspheres before going to study the behaviours of this drug in physical or biological system. The percentage of entrapment was determined for all the batches. The encapsulation efficiency was in the range of 68.03-74.08% with various batches. Drug content of the microspheres was found to be nearly same in all the nine batches.

Size and Shape of Microspheres

The microspheres were found to be discrete, spherical and free flowing. The nature of the method indicates that the microspheres were multi-nucleated, monolithic type. The mean particle size of the obtained microspheres containing venlafaxine hydrochloride was determined by the optical microscopy under 45X magnification. The particle size range increased as the polymer ratio was increased. The sizes could be separated and a more uniform size range of microspheres could readily be obtained. The mean size of the microspheres was increased as the proportion of coat in the microspheres was increased. The mean size of the microspheres were found to be 58.9±5.3, 66.6±4.7, 71.1±8.4, 75.2±7.6, 80.6±4.7, 96.1±8.4, 116.2±7.6, 153.7±6.7 and 205.1±10.9 µm, respectively in the batches of microspheres prepared employing core:coat ratio of 1:1, 1:1.5, 1:2, 1:2.5, 1:3, 1:3.5, 1:4, 1.4.5, and 1:5.

Table 1: Theoretical Drug Content, Estimated Drug Content and Percentage Entrapment of Microspheres of Venlafaxine hydrochloride.

S.NO	Formulation Code	Theoretical Drug Content In (Mg)	Estimated Drug Content In (Mg)	Encapsulation Efficiency %
1	FE1	40.0	27.3	68.3
2	FE2	50.4	57.4	69.7
3	FE3	63.7	59.7	70.1
4	FE4	87.5	62.5	70.5
5	FE5	93.6	65.2	71.0
6	FE6	95.6	68.2	71.3
7	FE7	94.8	68.7	72.5
8	FE8	96.5	71.3	73.9
9	FE9	97.3	72.8	74.8

Table 2: Percentage yield of microspheres.

S.No.	Formulation Code	Percentage Yield
1	FE1	90.0
2	FE2	91.8
3	FE3	92.4
4	FE4	93.0
5	FE5	93.6
6	FE6	95.6
7	FE7	94.8
8	FE8	96.0
9	FE9	97.3

Table 3: The Stability of Microsphere Formulations at Various Temperatures.

Fc	Refrigeration Temp. (4^0 C)				Room Temp (25^0 C)				High Temp. (45^0 C)			
	DAYS				DAYS				DAYS			
	7	14	21	28	7	14	21	28	7	14	21	28
FE1	100	98.1	96.2	96.1	96.2	95.1	92	90.6	85	82	81.2	80
FE2	100	98.2	96.3	96.2	96.4	95.3	93.3	91.1	85.3	82.3	81.5	80.4
FE3	100	98.3	96.7	96.3	96.8	95.7	93.5	91.3	85.5	82.7	82.7	82.1
FE4	100	98.4	97.1	96.5	97.1	96	93.8	91.5	85.7	83.1	83.6	82.7
FE5	100	98.5	97.2	96.7	97.4	96.1	94.1	92	85.8	83.7	83.9	83
FE6	100	98.6	97.5	97	97.8	96.3	94.2	92.3	86.2	83.9	84.2	83.5
FE7	100	99.1	98.7	97.1	98.3	97.1	95.4	93.6	86.6	84	83.6	82.7
FE8	100	99.4	98.59	98.1	98.5	97	95.1	94.2	87.1	85	83.9	83
FE9	100	99.7	98.8	98.2	100	99.3	98.1	96.4	88.5	86.3	84.2	83.5

Fc – Formulation Code

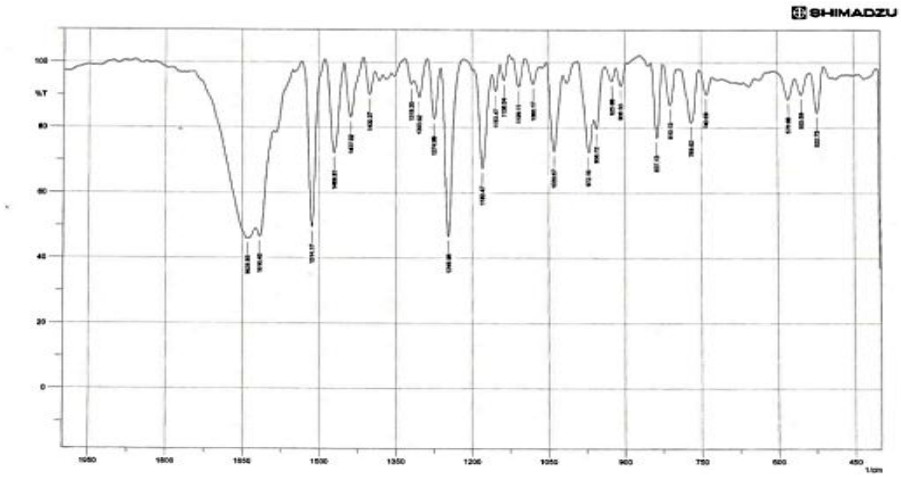

Figure 1: FTIR spectrum of Venlafaxine hydrochloride.

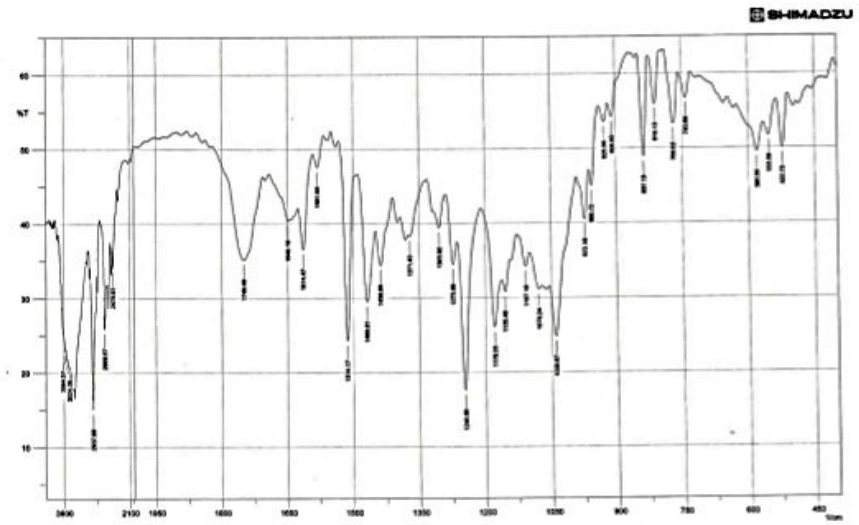

Figure 2: FTIR spectrum of physical mixture of Venlafaxine hydrochloride and ethyl cellulose.

Hydrochloride Microspheres (FE9)

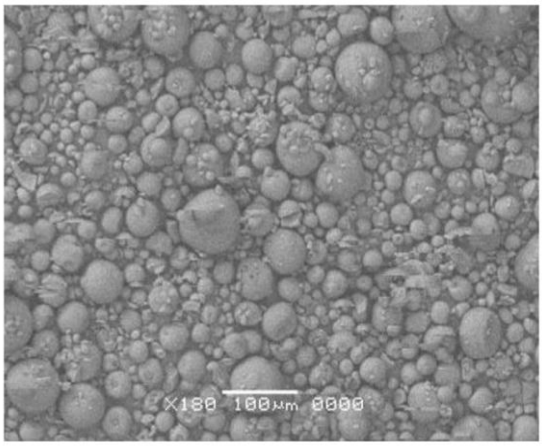

Figure 3: SEM Photographs of Venlafaxine

Hydrochloride Microspheres (FE9)

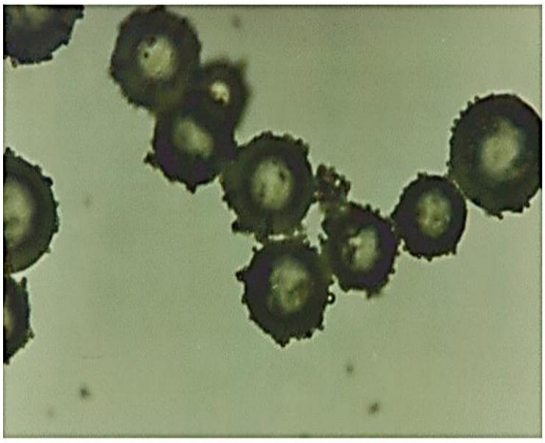

Figure. 4: Optical microscopic view of Venlafaxine

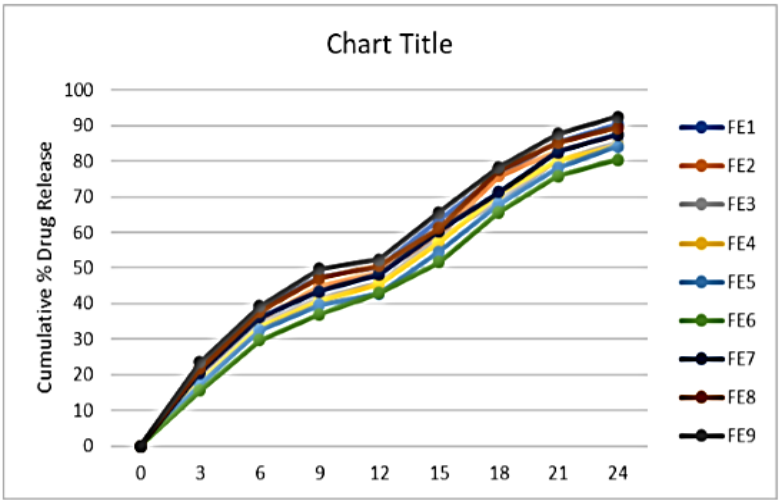

Figure 5: In-vitro release profile of Venlafaxine hydrochloride Microspheres (FE1 – FE9)

SUMMARY AND CONCLUSION

The present study was made to develop a new sustained drug delivery for Venlafaxine hydrochloride microspheres by using ethyl cellulose to improve patient compliance and safety. The Venlafaxine hydrochloride microspheres were prepared by Emulsification and Organic Solvent Evaporation Method and characterized by using Scanning Electron Microscope for prolonged activity with increased stability without losing its therapeutic activity. The compatibility studies were done by FTIR spectroscopy. The in-vitro release profiles of microspheres in phosphate buffer pH 7.4 at 37^{o}C confirmed the sustained release of microspheres which results in decreased release rate with the increase in the concentration of the polymer. The Formulation FE9 was found to be the optimized formulation out of nine formulations potentially due to high concentration of the polymer Ethyl Cellulose. The drug release of FE9 in 24 hours is found to be 97.3% which was the highest among the formulations carried out which results in enhancing the sustained delivery of the drug.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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