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FORMULATION AND IN-VITRO CHARACTERIZATION OF FLOATING MICROCARRIERS OF VENLAFAXINE HYDROCHLORIDE

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ABSTRACT

The objective of the present study was to develop multiparticulate gastro retentive drug delivery system of Venlafaxine hydrochloride by Emulsion gelation method using sodium alginate as a polymer and liquid paraffin. Floating microcarriers of the Venlafaxine hydrochloride was developed to prolong the gastric residence time, increase therapeutic efficiency, reduce frequency of administration and improve patient compliance. The prepared microcarriers were evaluated for micrometric properties, particle size, % drug entrapment efficiency, buoyancy percentage, in vitro-drug release studies. The prepared microcarriers were free flowing and discrete. The %drug entrapment was found in the range of 46.93 to 71.88. F1 formulation showed highest entrapment efficiency (71.88). There was no lag time was observed, the microcarriers immediately floated and remained floating for more than 10 hours. The particle size of the floating microcarriers was in the range of 0.54-1.26 mm. the drug release was studied up to 7 hours and results indicates that F6 formulation was found to be best suitable one.

Keywords: Venlafaxine hydrochloride, Floating microcarriers, Emulsion gelation, Sodium alginate, Liquid paraffin.

INTRODUCTION

Despite tremendous advancement in the drug delivery system, oral route remains the preferred route for the administration of therapeutic agents because of low cost therapy and ease of administration leads to higher levels of patient compliance. The design of oral controlled drug delivery system should be primarily aimed to achieve more predictable and increased bioavailability. An incomplete release of the drug and shorter residence time of the dosage forms in the upper GIT, which is a prominent site for the absorption of many drugs, leads to decreased bioavailability [1, 2].

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time. After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) [3].

Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs. Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach [4], low density (floating) systems that causes buoyancy in gastric fluid [5,6,7], mucoadhesive systems that causes bioadhesion to stomach mucosa [8], unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach [9,10], superporous hydrogel systems [11], magnetic systems [12] etc.

The main objective of the present study was to prolong the half-life of the Venlafaxine hydrochloride (2.9-4.5 hours) by retaining the drug in the stomach. Venlafaxine hydrochloride was having good absorption in the upper part

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of the GI tract. The floating microcarriers of Venlafaxine hydrochloride were prepared by using emulsion gelation method.

MATERIALS AND METHODS

Sodium alginate was purchased from Sigma-Aldrich Chemicals (India), Venlafaxine hydrochloride was received as gift sample from Strides Arco Labs, Bangalore, Liquid paraffin was purchased from SD Fine Chemicals Ltd., Mumbai and all other chemicals used were of analytical grade.

Preparation of oil-entrapped microcarriers

1. *Ionotropic gelation method*

Formulation AF1 was prepared without using mineral oil by conventional ionotropic gelation method, which was previously described.

2. *Emulsion gelation method*

Formulations AF2-AF6 was prepared by emulsion gelation method. Sodium Alginate (4%) was dissolved in distilled demineralized water with agitation. Venlafaxine hydrochloride and different concentrations of mineral oil were added to the solution. This solution (2.5g) containing Venlafaxine hydrochloride (500 mg) and oil (0-40 % (w/w)) was dropped through 24 G needle in to 2% calcium chloride. The resultant microcarriers were washed twice with distilled water and kept for drying at room temperature up to 12 hours.

EVALUATION OF FLOATING MICROCARRIERS

FTIR Studies

IR spectroscopic studies were carried out for prepared beads, by using Shimadzu FT IR 8700 model to determine the integrity of the drug in the formulation.

Particle size

The mean diameter of 100 dried beads was determined by optical microscopy. The optical microscope was fitted with a stage micrometer by which the size of microcarriers could be determined [13].

Micromeritic properties

The floating microcarriers were characterized by their micrometric properties such as bulk density, angle of repose, Carr's index, Hausner's ratio [14].

Drug loading (%) and entrapment efficiency (%)

50mg of floating microcarriers were weighed and ground to fine powder in a pastel mortar and fine powder was dissolved in 25ml of 0.1 N HCl. Volume of this solution was made up to 50ml with washings of mortar. The solution was kept for 24hrs. Then it was filtered. The filtrate was assayed by spectrophotometrically at 266nm [15]. The drug loading (%) and entrapment efficiency (%) was calculated according to following relationship.

$$\%\ \text{Drug loading} = \frac{\text{Actual drug content}}{\text{Weight of powered microcarriers}} X100$$

$$\text{Drug entrapment efficiency} = \frac{\text{Actual drug content}}{\text{theoreticaldrugcontent}} X100$$

Floating behaviour

300 mg of the dried microcarriers were spread over the surface of USP XXIV dissolution apparatus type II. Simulated gastric fluid without enzyme of pH 1.2 was used as medium (900 ml) and the temperature of the medium was maintained at $37^oC \pm 0.5^o$ C for 10 hrs. The paddle speed was controlled at 100 rpm. The floating and the settled portion of beads were recovered separately. After drying, each fraction of the microspheres was weighed and their buoyancy was calculated by the following equation [16]

Buoyancy (%) = Qf / (Qf + Qs) ×100

In-vitro drug release study

In vitro release rate studies were carried out using XXIV apparatus type II. Simulated gastric fluid without enzymes of pH 1.2 was used as dissolution medium (900 ml) and was maintained at $37^oC \pm 0.5^o$ C. Approximately 0.1 g microcarriers were used for each experiment. The paddle speed was controlled at 50 rpm. Aliquots of 5 ml were withdrawn at different time intervals up to 7 hr and a 5 ml of fresh medium was added to replace the sample that was withdrawn. Drug content of the beads was determined by UV/Visible spectroscopy at 266 nm, after suitable dilution of the samples [17].

RESULTS AND DISCUSSION

The shape of the microcarriers was found to be spherical and white in color. FTIR and DSC results were suggesting that the drug and excipients used in the formulation were compatible with each other and shown in the Fig No 2 and 1. The floating ability of microcarriers was depending upon the amount of oil entrapped in the each microcarrier. The formulation F1 had 0% floating ability and the remaining all formulation remained buoyant for more than 10 hrs. There was no lag time was observed. Results of the angle of repose, Carr's index (compressibility index) and Hausner's ratio of all microcarriers confirms better flow properties, values were reported in the Table no.2. The particle size of the floating microcarriers was in the range of 0.54-1.26 mm. A gradual increase in the size of the microcarriers was observed upon increasing the concentration of oil in the formulation. The particle size of the floating microcarriers was shown in the Fig No 3. The drug entrapment was found in the range of 41.93-71.88. Oil leak ease from the microcarriers was controlled by varying the curing time. F1 formulation had having highest % drug entrapment efficiency and F6 formulation had having lowest % drug entrapment efficiency. Gradual decrease in the % drug entrapment in floating microcarriers of Venlafaxine hydrochloride upon increase in the amount of the liquid paraffin was due to the most of the volume of the microcarrier was occupied by the liquid paraffin . In vitro drug release studies were conducted in the gastric simulated

Table 1. Formulae of floating microcarriers

Formulation	Venlafaxine hydrochloride	Sodium alginate	Liquid paraffin	Distilled water	Curing time (min)
F1	500mg	1.5g	0g	50ml	10
F2	500mg	1.5g	5g	50ml	10
F3	500mg	1.5g	7.5g	50ml	10
F4	500mg	1.5g	10g	50ml	15
F5	500mg	1.5g	15g	50ml	15
F6	500mg	1.5g	20g	50ml	15

Fig 1. DSC report of pure Venlafaxine hydrochloride drug and formulation

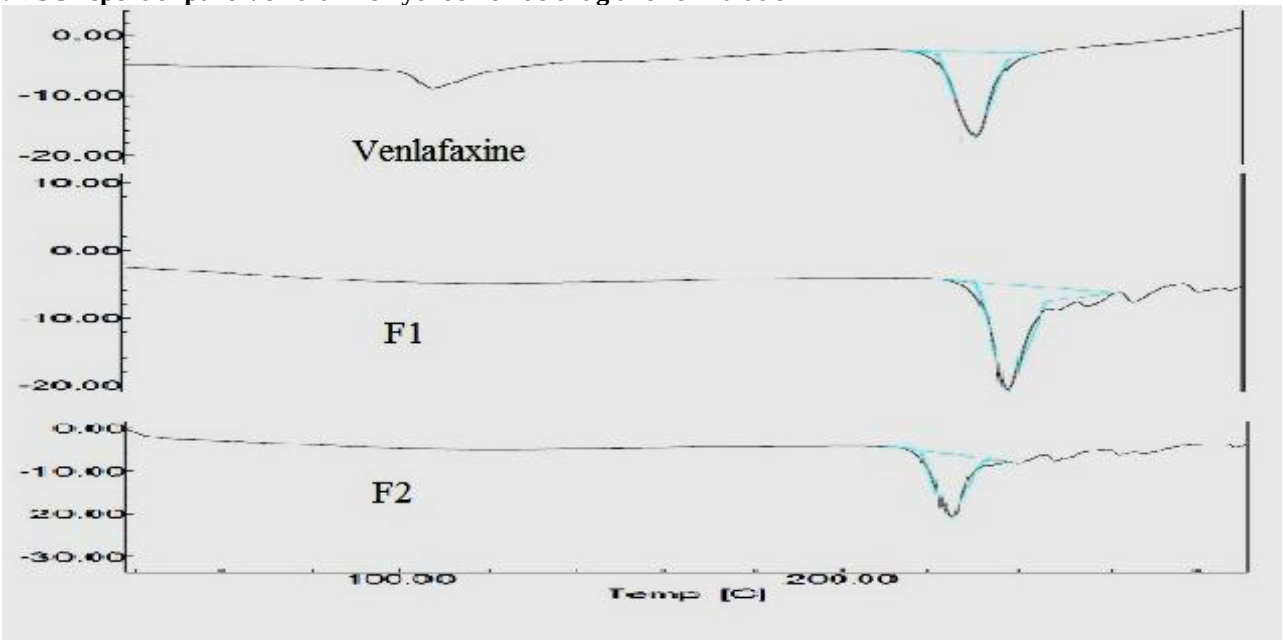

Fig 2. FTIR report of pure Venlafaxine hydrochloride drug and formulation

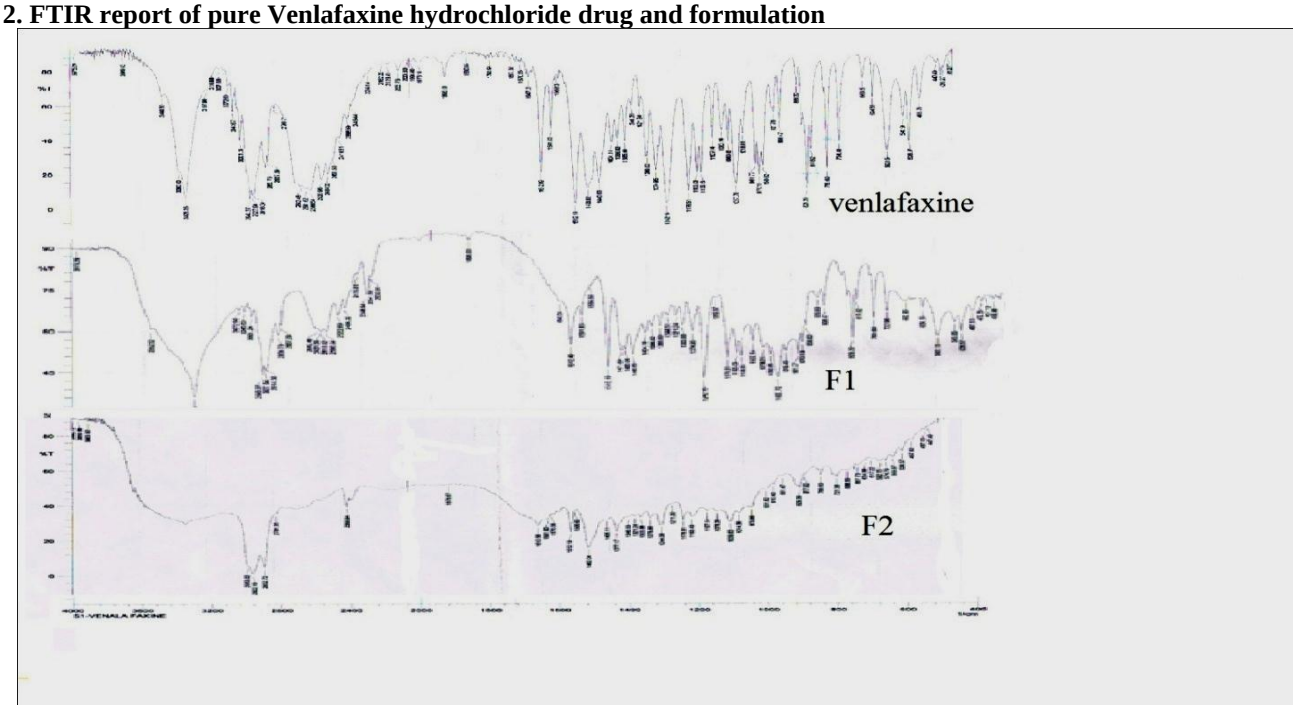

Fig 3. Particle size of floating microcarriers of Venlafaxine hydrochloride

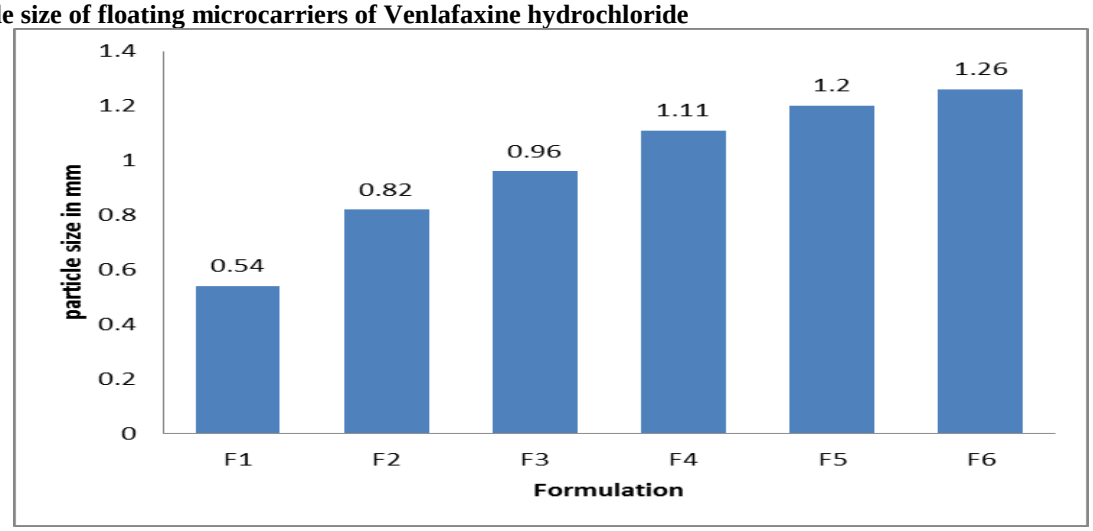

Fig 4. In Vitro dissolution profile of the floating microcarriers of Venlafaxine hydrochloride

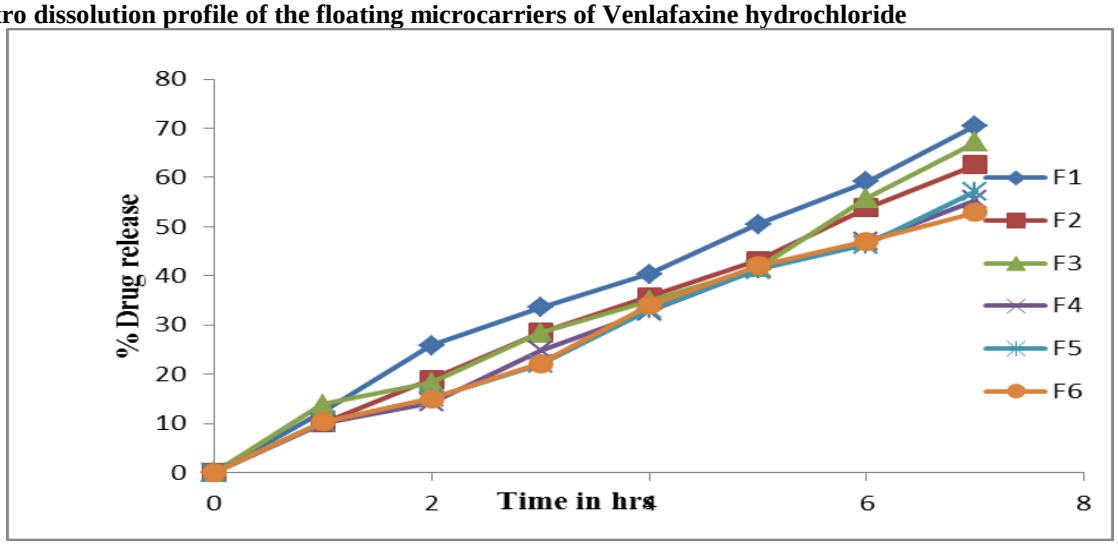

Table 2. Flow properties of all floating microcarriers formulations

S.NO	Formulation	Angle of repose	Carr's index	Hausner's ratio
1	F1	20.56 ±0.92	14.46 ± 0.91	1.17 ± 0.03
2	F2	21.54 ± 1.25	16.42 ± 0.97	1.14 ± 0.03
3	F3	21.79 ± 0.72	15.58± 1.29	1.21 ± 0.03
4	F4	21.96 ± 0.97	13.08 ± 0.29	1.14 ± 0.03
5	F5	22.46 ± 1.02	15.56 ± 0.97	1.15 ± 0.01
6	F6	22.86 ± 0.7	13.31 ±0.35	1.16 ± 0.02

Table 3. Entrapment efficiency and particle size of all floating microcarriers formulations

Formulation	Entrapment efficiency (%)	Particle size (mm)
F1	71.88	0.54
F2	66.47	0.82
F3	60.77	0.96
F4	47.84	1.11
F5	57.59	1.20
F6	46.93	1.26

pH 1.2 buffer (without enzymes). In vitro-drug release profile of all formulations were shown in the Fig No 4. The % drug release for batches F1, F2, F3, F4, F5, and F6 was found to be 71.576, 61.596, 60.152, 54.896, 58.208, and 53.589% respectively at the end of the 12- hours. The % of oil entrapped in each microcarrier had a great significance in the drug release from the floating microcarrier. Drug release from the microcarriers can be controlled by increasing amount of entrapped oil in each microcarrier. Oil also acts as barrier for the drug release from the microcarrier.

CONCLUSION

Venlafaxine hydrochloride loaded floating microcarriers were prepared by using emulsion gelation method using the sodium alginate as a polymer and varying liquid paraffin concentration. The prepared microcarriers were free flowing and discrete. The microcarriers were found to be spherical in nature. The %drug entrapment was found in the range of 46.93 to 71.88. F1 formulation showed highest entrapment efficiency (71.88). There was no lag time was observed, the microcarriers immediately floated and remained floating for more than 10 hours. The particle size of the floating microcarriers was in the range of 0.54-1.26 mm. The drug release was studied up to 7hours and results indicate that F6 formulation was found to be best suitable one.

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