Acta Scientific Pharmaceutical Sciences (ISSN: 2581-5423)

Volume 7 Issue 9 September 2023

Research Article

Design, Characterisation and Evaluation of Venlafaxine Hydrochloride Sustained Release Microspheres

Janga Rameshbabu*, Sunkara Sivaprasad, Battula Sowjanya Lakshmi and Suryadevara Vidyadhara

Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, India

***Corresponding Author:** Janga Rameshbabu, Professor and H.O.D, Department of Pharmaceutics, Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur, India.

Received: June 19, 2023

Published: August 19, 2023

Abstract

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended and specified period of time. The aim of this study was to formulate and evaluate sustained release microspheres of Venlaflaxin Hydrochloride. Sustained release microspheres were obtained by solvent evaporation method for all the formulations from F1 to F9. Formulations F1, F2 and F3 were prepared Venlafaxine HCl with Chitosan polymer in the ratio of 1: 1, 1: 2 and 1: 3.Formulations F4, F5 and F6 were prepared Venlafaxine HCl with Sodium alginate polymer in the ratio of 1:1, 1:2 and 1:3; and formulations F7, F8 and F9 were prepared Venlafaxine HCl with Xanthan gum polymer in the ratio of 1: 1, 1: 2 and 1: 3 respectively: Based on the in vitro drug release characteristics and entrapment efficiency, the formulation F3 was found to be best formulation. By increasing the concentration of polymer, decreased the rate of drug released. According to stability study it was found that there was no variation in Percentage yield, Entrapment efficiency, and *in vitro* drug released profile of selected formulation F3 at specified period. Drug and Polymer interaction for formulated SR microsphere embedded on Venlaflaxin Hydrochloride was characterized by FT-IR and DSC studies.: The result showed that there is no interaction between the drug and polymer. Surface morphology of formulation carried out by SEM showed good spherical geometry and uniformity in size and shape. The formulation F3 was concluded best formulation among the prepared formulations.

Keywords: Microspheres; Drug Loading; Venlaflaxin Hydrochloride; Drug Release; Sustained Release

Introduction

The present study was based on preparation of microspheres of Venlaflaxin Hydrochloride by solvent evaporation method to overcome various life threatening health problems and to achieve better patient compliances.

It is a new generation antidepressant serotonin/ noradrenalin reuptake inhibitor drug showing effective anti-depressant properties. It has a short bioavailability 13% and biological half-life is <5hrs. 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. Venlaflaxin Hydrochloride is a water soluble drug with a solubility of 572mg/ml [2]. By preparing the sustain release dosage form, the initial burst effect of highly water soluble drugs like Venlaflaxin Hydrochloride can be prevented. It acts by inhibiting selectively the uptake of serotonin and noradrenaline 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 Venlaflaxin Hydrochloride and its active metabolite O-desmethyl venlafaxin is 5 hr and 11hr. respectively [4]. Venlaflaxin Hydrochloride overdose may be more serious than an overdose with selective serotonin reuptake inhibitors [5].

Materials

Venlaflaxin Hydrochloride was obtained as a gift sample from Dr. Reddy's labs, Hyd. Chitosan, Sodium alginate and Xanthan gum was obtained from yarrow Chem. Parma Limited, Mumbai. Dichloromethane, Span80 were procured from S.D Fine Chem. Ltd., Mumbai.

Methods

Estimation of venlaflaxin hydrochloride

In the present investigation, a simple, sensitive more accurate UV Spectrophotometric method was used for the estimation of Venlaflaxin Hydrochloride. The absorbance values of Venlaflaxin Hydrochloride were measured at a λ_{max} of 225 nm by using distilled water in the concentration range of 5-25 µg/ml using UV Spectrophotometric method shown in table 1 and figure 1.

Preparation of microspheres [7]

Nine formulations were prepared by using drug and three different polymers in the ratios of 1:1, 1:2 and 1:3 respectively shown in Table 2 and figure 2. The powder blend (drug with polymer) was dissolved at room temperature in ethanol and dichloromethane (1:1% v/v) with vigorous agitation to form uniform drug-polymer dispersion. This was slowly poured into the dispersion medium consisting of heavy liquid paraffin (50ml) containing 0.5% span 80. The system was stirred by using over head propeller agitator at speed of 750 rpm for 5 hours, to ensured complete evaporation of the solvent. The liquid paraffin was decanted and the microspheres were separated by filtration through a whatmann filter paper. The microspheres were separated and washed thrice with 180ml of n-Hexane and air dried for 24 hours.

Evaluation of microspheres

Percentage yield [8,9]

The dried microspheres were weighed and percentage yield of the prepared microspheres was calculated by using the following formula and results were shown in table 3.

Percentage yield = (Weight of Microspheres/Weight of Polymer +drug) X 100

Drug content estimation [10]

Drug loaded microspheres (100 mg) were powdered and suspended in 100 ml methanolic: water (1:99 v/v) solvent. The resultant dispersion was kept for 20min for complete mixing with continuous agitation and filtered through a 0.45 µm membrane filter. The drug content was determined spectrophotometrically at 225nm using a regression equation derived from the standard graph (R^2 = 0.9954) and results were shown in table 3.

Entrapment efficiency of the drug [8]

The micro beads equivalent to10mg of Venlafaxin Hydrochloride were weighed and dispersed in 0.1 N HCl. The resulting mixture was agitated on mechanical shaker for 24 hours. The solution was then filtered and drug content was estimated by UV Spectrophotometry and results were shown in table 3.

Encapsulation Efficiency = (W_1/W_2) X 100

W_1 = Actual Weight of Drug in SampleW_2 = Microspheres Sample Weight

Size distribution of microspheres [11]

Microspheres were separated into different size fractions by sieving for 10minutes using a Mechanical shaker containing standard sieves (Indian Pharmacopoeia 1996). The particle size distribution of the microspheres for all the formulations was determined and mean particle size of microspheres was calculated

by using the following formula and results were shown in table 3.

Mean Particle Size = $\sum (W_1XW_2)/(W_2)$

W_1 = Mean Particle Size of the Fraction

W_2 = WEIGHT FRACTION

In-vitro drug release study [8]

The dissolution test was carried out in USP Apparatus Type II (paddle) with 900ml of water as the dissolution medium. Fresh volume of the medium was replaced with the withdrawn volume to maintain the sink conditions and constant volume throughout the experiment. Samples withdrawn were suitably diluted with same dissolution medium and the amount of drug dissolved was estimated by Lab India double beam spectrophotometer at 225nm and subsequently analyzed for the cumulative percentage of drug released and results were shown in figure 3-5.

Assessment of dissolution parameters

Dissolution parameters such as zero order, first order rate constant, Higuchi constant and Peppa's constants were calculated from the dissolution data obtained from various formulations. A plot of cumulative percent drug released *Vs* time (hrs) was plotted and the zero order release rate constant (K_0) was calculated from the slope. A plot of log% undissolved *Vs* time (hrs) was plotted for all the formulations and the first order release rate constant (K_1) were obtained by multiplying slope with 2.303. A plot of cumulative amount of drug released *Vs* square root of time was plotted for all the formulations and the higuchi constant was calculated from the slope. A plot of log M^t/M^α *Vs* log time was plotted for all the formulations and the peppas constant was obtained by the slope and the 'n' values were noted from y-intercept of the straight line. The following mathematical expressions were used to calculate various pharmacokinetic parameters from the dissolution data and results were shown in table 4.

First order equation, Log % drug unreleased = K_1t ----------1

Where, K_1 = first order rate constant.

Higuchi equation, Cumulative amount of drug released = $K_Ht_{1/2}$ ----------2

Where, K_H = higuchi constant

Kors Meyer Peppas Constant, Log M^t/M^α = log K_p + n log t ----------3

Where, n = release exponent.

Characterization of microspheres

Based on the dissolution studies performed on all the formulations some of the optimized formulation were selected and further investigated for IR, DSC and SEM studies.

I.R. spectral studies (FTIR)

I.R Spectral studies were carried out on some selected pellets by using BRUKER FTIR. These studies on pellets were performed before they are subjected to dissolution studies to check the structural variation if any a raised between the drug and excipients used and results were shown in table 5 and figure 6.

Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of microspheres prepared by solvent evaporation method. About 10mg of sample was weighed in a standard open aluminium pans, were scanned from 20-300°C, at a heating rate of 10°C/minute while being purged with dry nitrogen. The DSC curves for optimised microspheres were shown in table 6 and figure 7.

Scanning electron microscopy (SEM)

The samples were coated with a thin gold layer by sputter coater unit (SPI, Sputter, USA). Then, the SEM photographs were taken by a scanning electron microscope (Scanning electron microscope JSM-6390, Japan) operated at an accelerated voltage of 5KV. The SEM photographs of pellets by pan coating and microspheres by solvent evaporation and results were shown in figure 8.

Accelerated stability studies

The formulations which showed good in vitro performance were subjected to accelerated stability studies. These studies were carried out by investigating the effect of temperature on the physical properties and chemical stability of microspheres. Optimised formulations F3 was subjected to accelerated stability studies. The above said formulations were kept in petridishes after

preparation and stored in thermo stated oven at a temperature and relative humidity of 25 ± 2^{0}C, 60 ± 5% RH for 6 months and 40 ± 2^{0}C, 75 ± 5% RH for 6 months. Then the samples of each type of formulations were evaluated for the earlier mentioned physical parameters. The microspheres were evaluated for physical parameters and drugs were analyzed for drug content uniformity by a known spectrophotometric method as described earlier. Further these were subjected to drug release studies as stated earlier and results were shown in figure 9.

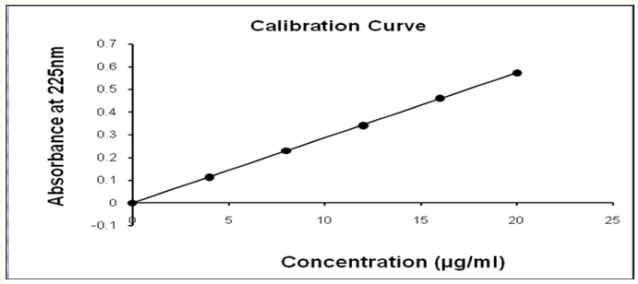

Figure 1: Calibration Curve of Venlaflaxin Hydrochloride in Distilled Water.

Results

S. No	Concentration (µg/ml)	Absorbance at 225nm
1	0	0.0000
2	5	0.113
3	10	0.229
4	15	0.340
5	20	0.461
6	25	0.571

Table 1: Calibration Data for the Estimation of Venlaflaxin Hydrochloride in water (N = 6).

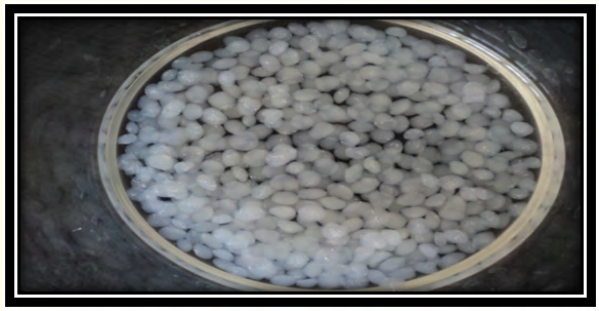

Figure 2: Composition of Sustained release Microspheres.

Ingredients	Formulations								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Venlafaxin Hydrochloride*	1	1	1	1	1	1	1	1	1
Chitosan*	1	2	3	-	-	-	-	-	-
Sodium Alginate*	-	-	-	1	2	3	-	-	-
Xanthan gum*	`	-	`	-	-	-	1	2	3
Liquid Paraffin#	50	50	50	50	50	50	50	50	50
Dichloromethane#	5	5	5	5	5	5	5	5	5
Ethanol#	5	5	5	5	5	5	5	5	5
Span80#	0.5%	0.5%	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %	0.5 %	0.5%
n-Hexane#	180	180	180	180	180	180	180	180	180

Table 2: Composition of Venlaflaxin Hydrochloride sustained release microspheres.

* All values are in grams. #All values are in ml (Formulations F1, F2, and F3 – Venlaflaxin Hydrochloride + Chitosan Formulations F4, F5, and F6 – Venlaflaxin Hydrochloride + Sodium alginate Formulations F7, F8, and F9 –Venlaflaxin Hydrochloride +Xanthan gum).

Evaluation of microspheres

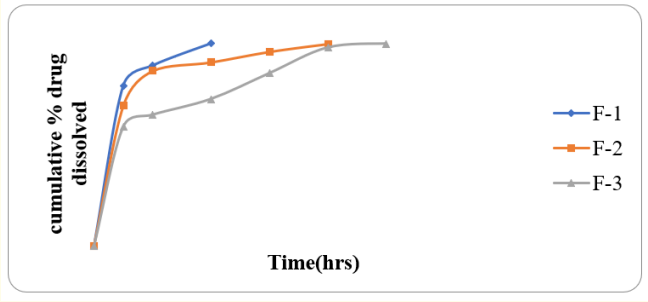

Figure 3: Dissolution Profile of Microspheres Prepared by Solvent Evaporation by using Chitosan.

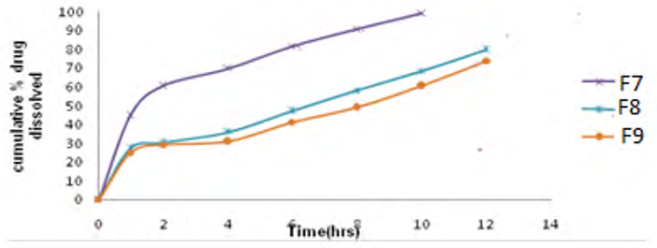

Figure 5: Dissolution Profile of Microspheres Prepared by Solvent Evaporation by using Xanthun Gum.

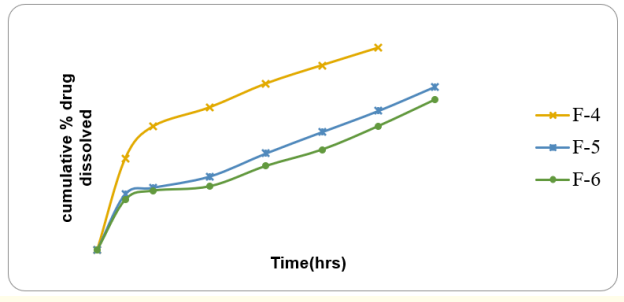

Figure 4: Dissolution Profile of Microspheres Prepared by Solvent Evaporation by using Sodium Alginate.

Formulation	Zero Order Constant		First Order Constant		Higuchi's Constant		Peppa's Constant	
	K (mg)	R^2	K (hr^{-1})	R^2	K ($mg^{1/2}$)	R^2	n (value)	R^2
F1	5.640	0.9621	0.307	0.9501	26.536	0.9723	0.432	0.9908
F2	5.454	0.9650	0.234	0.9705	26.939	0.9663	0.456	0.9909
F3	4.665	0.9900	0.112	0.9471	22.272	0.9530	0.402	0.9985
F4	4.809	0.9503	0.153	0.8439	22.987	0.9782	0.485	0.9908
F5	4.836	0.9592	0.115	0.8811	22.37	0.9729	0.365	0.9903
F6	4.85	0.9622	0.134	0.9307	21.04	0.9684	0.462	0.9903
F7	4.89	0.9540	0.112	0.8611	22.31	0.9770	0.398	0.9901
F8	4.86	0.9597	0.222	0.9162	22.68	0.9756	0.441	0.9907
F9	6.401	0.9647	0.256	0.9609	27.56	0.9663	0.356	0.9907

Table 4: Dissolution Parameters of Venlaflaxin Hydrochloride Sustained Release Microspheres.

Fourier transform-infrared spectroscopy (FT-IR)

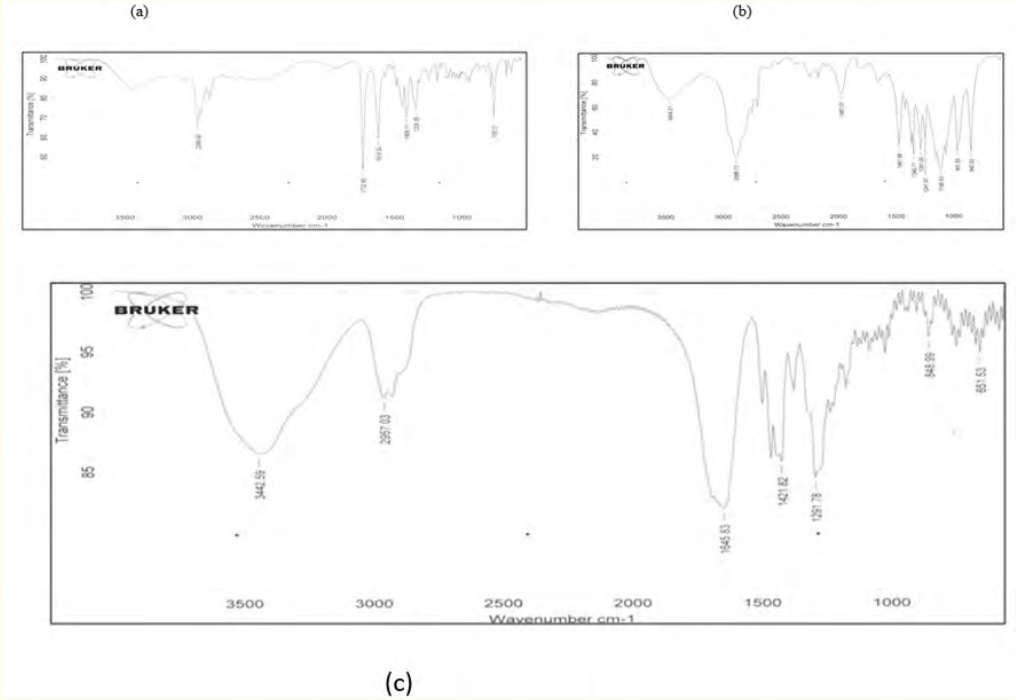

Figure 6: FTIR Spectrum of Venlafaxin Hydrochloride Microspheres (a) Pure Drug (b) Chitosan (c) F3.

Functional groups	Peaks observed (wave no.(cm^{-1}))	
	Pure drug	F3
C-H stretching	3075.55	3074.24
R-O-CH_3 stretching	2935.13	2935.09
NH_2 stretching	1317.95	1318.06
OH stretching	1153.46	1153.40
CH_2 stretching	1042.09	1042.56
C-H bending	836.5	836.68
OH bending	740.31	740.10

Table 5: Interpretation of FTIR Spectrum.

DSC studies

S. No	Formulation	Temperature	Type of peak
1.	Pure Drug	274.8 0C	Sharp Endothermic Peak
2.	Chitosan	410.7 0C	Broad Endothermic Peak
3.	F3	221.80C	Broad Endothermic Peak

Table 6

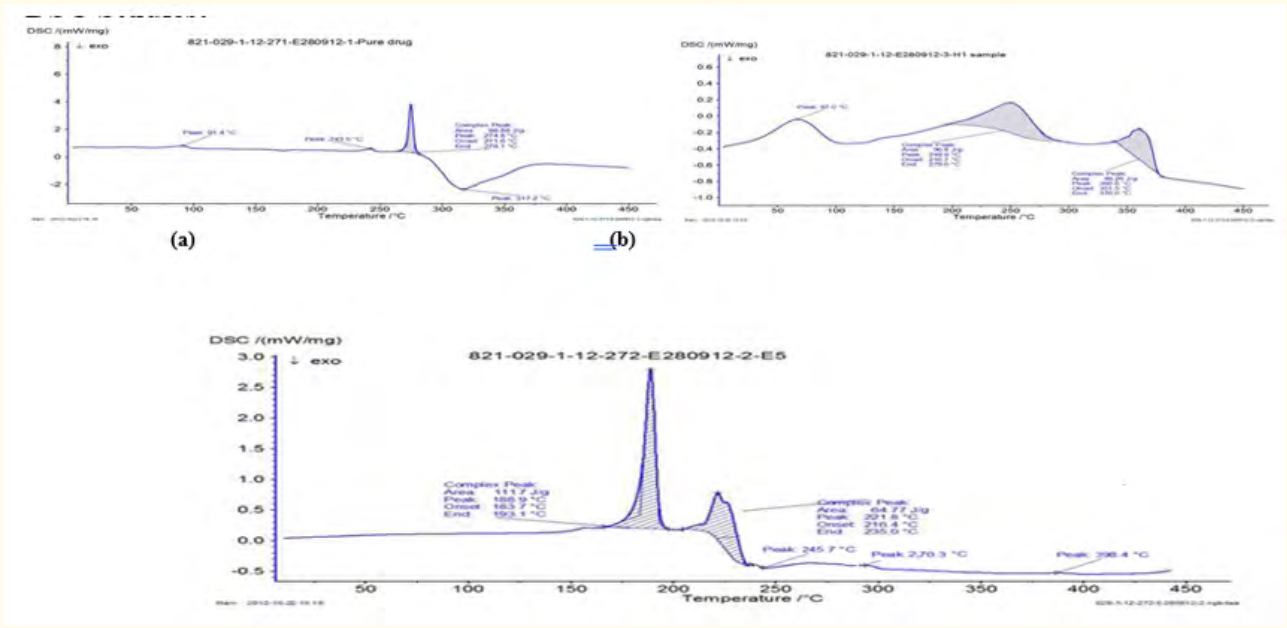

Figure 7: DSC Graph of (a) Pure Drug (b) Chitosan (c) Formulation F3.

SEM analysis

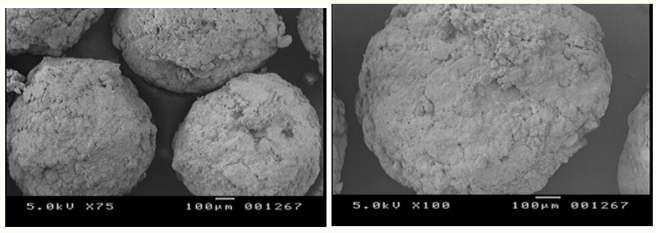

Figure 8: SEM Photographs of Pure drug and F3.

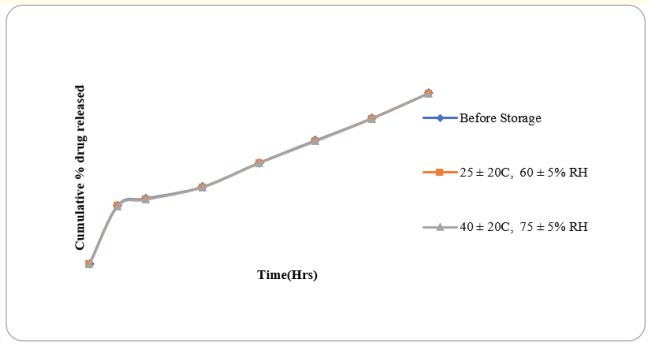

Figure 9: Release of Microspheres (F-3) Before And after Storage At Different Conditions.

Discussion of Results

The main goal of any drug delivery system was to provide the therapeutic amount of drug to the proper site in the body also to achieve and maintain the desired drug concentration in blood. Improving the therapeutic efficacy of existing drugs has been tried by different technologies one of the effective technologies exiting in recent years of pharmacy is Microspheres.

Sustained release drug delivery system was developed in pharmacy field and drug retention for a prolonged time has been achieved. Hence, it was made an effective attempt to formulate the Sustained release by using Venlaflaxin Hydrochloride as the model drug.

Venlaflaxin Hydrochloride was the serotonin-norepinephrine reuptake inhibitors used for the treatment of depression and anxiety disorders. Venlaflaxin Hydrochloride possess the mean half life of 5 hours and bioavailability was found to be only 27% and high water solubility Hence, it was chosen as the good candidate

for the sustained release microspheres in order to improve the bioavailability and prolong period of drug released.

The calibration curve for the estimation of Venlaflaxin Hydrochloride in distilled water was found to be linear and obeyed Beer's law in the concentration range of 5-25 µg/ml and measured at 225nm using UV spectrophotometer.

Sustained release microspheres were prepared by solvent evaporation method from F1 to F9. Formulations F1, F2 and F3 were prepared Venlaflaxin Hydrochloride with Chitosan polymer in the ratio of 1: 1, 1: 2 and 1: 3. Formulations F4, F5 and F6 were prepared Venlaflaxin Hydrochloride with Sodium alginate polymer in the ratio of 1:1, 1:2 and 1:3; and formulations F7, F8 and F9 were prepared Venlaflaxin Hydrochloride with Xanthan gum polymer in the ratio of 1:1, 1:2 and 1: 3 respectively. All formulations were evaluated for the Percentage yield, Entrapment efficiency, Particle size, Scanning electron microscopy, and *in-vitro* drug released profile.

On comparing the major criteria in evaluation such as percentage yield, drug content, entrapment efficiency and *In-Vitro* drug released profile, the formulation F3 was selected as the best formulation, as it showed the percentage yield as 83.16%, drug content as 69.26% and Entrapment efficiency as 92.09% and showed a good sustained release nature in the *In-Vitro* drug released was nearly 83.14% up to 10 hrs. Based on all the above evaluation parameters it was concluded that the formulation F3 was found to be best formulation among the formulations from F1 to F9. The *in-vitro* drug released data was applied to various kinetic models such as zero order kinetics, Higuchi plot, first order kinetics and Peppas plot by predicting the drug release kinetics mechanism. The formulation F3 was best fitted with Peppas kinetics (n value is 0.42) and it undergoes Fickian diffusion mechanism. By increasing the concentration of polymer, decreased the rate of drug released.

The identification of drug was carried out by FTIR spectroscopy. The analytical profile of drug was evaluated for determination of absorption maximum, development of standard curve and percentage purity of drug. Compatibility of drug and polymer mixture was done by performing DSC study. It was concluded that there was no interaction between the drug and polymer.

SEM analysis was performed for the optimized microspheres (F3) along with pure drug. The SEM photographs showed that microspheres were found to be discrete, free flowing and spherical in shape with rough surface and it exhibited a range of sizes. The photographs of microspheres showing pores on the surface were responsible for drug release.

According to stability study it was found that there was no variation in Percentage yield, Entrapment efficiency, and *in- vitro* drug released profile of selected formulation F3 at specified period of time. The formulation F3 was concluded best formulation among the formulations were prepared.

Future Prospects

Once the technology is fully accepted, these systems will probably increase with new pipeline drugs that need enhancement to their bioavailability. The sustained release can also be formulated for advanced drug delivery other than oral administration. In the present work the sustained microspheres were formulated using natural polymers such as Chitosan, Sodium alginate and Xanthan gum by solvent evaporation method. In this work only physiochemical property, formulation and *in vitro* evaluation of sustained release microspheres of Venlaflaxin hydrochloride was done. The study requires attention of researcher to develop sustained drug delivery systems using other synthetic polymers. Furthermore, the study can be extended to evaluate *in-vivo* performance and also *In-vitro-In-vivo* correlation of the microspheres.

Acknowledgements

The authors were expressing their gratitude to Dr. Reddys Ltd, Hyderabad for providing gift samples. The authors are thankful to the management of Chebrolu Hanumaiah Institute of Pharmaceutical Sciences, Guntur for providing the necessary facilities to carry out the research work.

Bibliography

1. Senthil A., *et al*. "Design and optimization of mucoadhesive microspheres of Venlaflaxin HCl using 23 full factorial designs". *Der Pharmacia Lettre* 3 (2011): 202-211.

2. Syed MA., *et al*. "Complexation between Venlafaxine Hydrochloride and βCyclodextrin Structural Study by Nuclear Magnetic Resonance Spectroscopy". *Bulletin of the Korean Chemical Society* 27 (2006): 1397.

3. Patel NM and Soniwala MM. "Influence of release enhancers on release of Venlafaxine hydrochloride from glyceryl behenate matrix tablet". *Indian Drugs* 45 (2008): 104.

4. Holliday SM and Benfieid P. "Venlafaxine A review of its pharmacology and therapeutic potential in depression". *Drugs* 49 (1995): 280-295.

5. Hanekamp BB., *et al*. "Serotonin syndrome and rhabdomyolysis in venlafaxine poisoning a case report Netherlands's". *The Journal of Medical Sciences* 63 (2005): 316-318.

6. Sundraganapathy R., *et al*. "Development and Validation of UV Spectrophotometric Method for the Determination of Venlafaxine Hydrochloride in Bulk and Solid Dosage Forms". *International Journal of Pharmacy and Industrial Research* 1 (2011): 28-31.

7. Kumar Darapu BN., *et al*. "Formulation andIn-Vitro Evaluation of Gastroretensive Floating Microspheres of Ranitidine Hydrochloride". *Research Journal of Pharmaceutical, Biological and Chemical Sciences* (2011): 789-801.

8. Bindumadhavi B., *et al*. "Formulation and Evaluation of Venlafaxine Hcl Microspheres". *Hygeia Journalfor Drugs and Medicines* (2011): 64-70.

9. Venkatesan P., *et al*. "Preparation and Evaluation ofSustained Release Loxoprofen". *Journal of Basic and Clinical Pharmacy* (2011): 159-162.

10. Prasant K Rout., *et al*. "Effect of Method of Preparation on Physical Properties and Invitro Drug Release Profile of Losartan Microspheres a Comparative Study". *International Journal of Pharmacy and Pharmaceutical Sciences* (2009): 208-228.

11. Kishore Kumar Reddy K., *et al*. "Formulation and Evaluation of Metformin Hydrochloride Microspheres". *International Journal of Pharmacy and Technology* (2011): 2228-2247.