RESEARCH ARTICLE

Venlafaxine Hydrochloride Granules Using Natural Polymers as Multiparticulate Drug Delivery System

B. Jeevana Jyothi[1], Jyosna Doniparthi[2]

[1]Department of Pharmaceutics, Institute of Pharmaceutical Technology, Sri Padmavathi Mahilaviswavidyalayam, Tirupati, Andhra Pradesh, India, [2]Department of Pharmaceutics, Sri Krishnadevaraya University College of Pharmaceutical Sciences, Sri Krishnadevaraya University, Anantapuramu, Andhra Pradesh, India

Abstract

Aim: The present investigation endeavors the importance of natural polymers for the sustained oral drug delivery. In an attempt to weigh up the efficiency of natural polymers in sustained oral delivery, an antidepressant venlafaxine hydrochloride, a highly water-soluble drug was selected as a challenging model. **Materials and Methods:** Different formulations (F1-F12) were prepared using drug, xanthan gum (XG), guar gum (GG) at 1:1, 1:2, and 1:3 ratios, and different polymer blends of chitosan, XG, and GG at 1:1, 1:4, and 4:1 ratios. Multiparticulates (granules) were prepared using wet granulation method and then were filled into empty hard gelatin capsules. The prepared multiparticulate drug delivery systems (MDDS) were characterized for drug-excipient compatibility study, physical evaluation, and *in vitro* drug release. **Results and Discussions:** Fourier-transform infrared spectroscopy study confirmed the absence of chemical interactions between drug and polymers. Differential scanning calorimetry analysis indicated the uniform dispersion of drug in the matrix. The physical and flow properties of the granules and MDDS were evaluated and found to be within the acceptable limits. The *in vitro* drug release study of the optimized formulation (F8) sustains the release of drug to 85.3% at the end of 20 h, while Venlor XR sustains the release of drug to 97.35% at the end of 12 h. Kinetic analysis of dissolution data indicated that the drug release follows first-order kinetics through Quasi-Fickian diffusion. **Conclusion:** It can be concluded from the study that the prepared MDDS using polymer blend of chitosan with XG at 1:4 ratio are the versatile release retardant material, which could release the drug for 20 h.

Key words: Chitosan, granules, guar gum, xanthan gum

INTRODUCTION

By designing a dosage form with aptitude to release its contents at an unremitting and controlled rate for a long extent of instance, constant plasma drug levels can be attained.[1] Such dosage forms which can accurately control the drug release rates and/or target the drug to specific body site will remain high demand in the future. Among various controlled release dosage systems, multiparticulate drug delivery systems (MDDS) have been developed in recent years to modify drug release and for improvement of bioavailability or stability and to target drug to specific sites.[2,3] MDDS consists of the variety of small discrete units that exhibit different characteristics. Simultaneously, these characteristic units such as granules, beads, microspheres, pellets, spheroids, and Minitab provide the overall desired controlled release of the dose.[4] MDDS provide the advantage of more uniform spreading throughout the gastrointestinal tract and invariably maximize drug absorption, reduce peak plasma fluctuation, and minimize the potential side effects without lowering drug bioavailability.[5,6] A distinction can be made between monolithic and multiparticulate controlled release formulation is relating to it's *in vivo* behavior because the subunits spread into the gastrointestinal tract as soon as the hard gelatin capsules or the tablet disintegrates, hence, drug release occurs over a large area avoiding high local drug concentrations.[7]

Address for correspondence:
Jyosna Doniparthi, Sri Krishnadevaraya University, College of Pharmaceutical Sciences, S.K University, Anantapuramu, Andhra Pradesh, India.
E-mail: jyosna.gms@gmail.com

Received: 29-09-2017
Revised: 30-10-2017
Accepted: 20-11-2017

Drug substances with high water solubility and short half-life (elimination half-life 2–3 h) get readily absorbed and eliminated, thus requiring frequent administration. This may lead to decrease in patient compliance and increase chances of side effects due to dose dumping.[8] Venlafaxine hydrochloride, a novel third-generation antidepressant and, is referred to as a serotonin, norepinephrine-dopamine reuptake inhibitor.[9] Due to high water solubility, first pass metabolism, low bioavailability, and short half-life extended release MDDS of venlafaxine hydrochloride became the key requirement to eliminate multiple daily dosages and minimize side effects.[10]

The use of biopolymers in controlled release applications has increased in recent years due to their efficient delivery and in extending the release time of short-lived drugs over those of the conventional type dosage forms.[11] Due to the major advantages, polymer blends offer as coating materials for controlled drug delivery systems,[12] it can be expected by the use of polymers such as xanthan gum (XG) and guar gum (GG) with chitosan. Such blended polymers protect the release of the drugs in the acidic environment and will swell and get hydrated on reaching the intestine when in contact with the alkaline medium and the release the drug slower over a long period.[13]

The aim of the present study was obtaining of MDDS using natural polymers for retarding release of the drug. In these regards, chitosan is selected as it has been used in pharmaceutical formulations as a release controlling agent, due to its appealing properties such as biocompatibility, biodegradability, low toxicity, and relatively low production cost from abundant natural sources.[14] Chitosan is a deacetylated derivative of chitin, which is a naturally occurring polysaccharide comprising copolymers of glucosamine and N-acetylglucosamine. The cationic amino groups on the C2 position of the repeating glucopyranose units of chitosan can interact electrostatically with the anionic groups (usually carboxylic acid groups) of other polyions to form polyelectrolyte complexes.[15] Although polyelectrolyte complex as the matrix of controlled release has some obvious advantages such as increasing the controlled-release ability and reducing the pH dependence, preparation of polyelectrolyte complex was a lengthy process. As an alternative for this lengthy process, here, we propose *in situ* chitosan–XG and chitosan-GG polyelectrolyte complexation as a tool for controlling drug release.[16]

Therefore, the main objectives of this study are (1) to develop MDDS of venlafaxine hydrochloride using natural polymers as release retardant and (2) to evaluate the release characteristics and mechanisms of drug release.

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride was purchased from Hermes chemical company Pvt., Ltd., Hyderabad, chitosan, XG, and GG from Sigma-Aldrich, Bengaluru. Dibasic calcium chloride, chitosan, alcohol, and PVP K-90 from Sisco Research Laboratories Pvt., Ltd. (SRL), Hyderabad, India, were used. All other materials were of analytical or reagent grade.

Drug-excipient compatibility study

Fourier-transform infrared (FTIR) spectroscopy

FTIR spectra of venlafaxine hydrochloride, physical mixtures of excipients of optimized formulation (placebo), and the optimized formulation were recorded on FTIR spectrometer (Model ALPHA T, Bruker). 2 mg sample was mixed with 200 mg potassium bromide (KBr). These mixtures were grinded into fine powder, and then compressed into KBr disc using a hydraulic press. Each KBr disc was scanned over a wave number region of 500–4000 cm^{-1} and the resolution was 4 cm^{-1}. The characteristic bands were recorded for all samples. FTIR analysis was used to analyze the stability of drug within the polymeric material.[17]

Thermal analysis

The thermal analysis of pure venlafaxine hydrochloride, physical mixture of optimized formulation was recorded using a differential scanning calorimetry (DSC) (Model-SDT Q600, USA) by heating from 40 to 600°C at a heating rate of 10°C/min under nitrogen atmosphere (flow rate, 20 ml/min).[9]

Preparation of granules of venlafaxine hydrochloride

In the present work, MDDS of venlafaxine hydrochloride were prepared in two stages. In the first stage, granules of different formulations were prepared by wet granulation method. In the second stage, prepared granules of all formulations equivalent to 75 mg were weighed and filled into hard gelatin capsule.

A total of 12 formulations were tried from F1 to F12 and their composition was shown in Table 1. In each formulation, specified quantities of venlafaxine hydrochloride, dibasic calcium chloride, XG, GG, chitosan, and PVP K-90 were weighed and passed through sieve #60.

In the first group, the drug was mixed with single release retardant polymer, i.e., XG or GG in a drug to polymer ratio (D:P) of 1:1, 1:2, and 1:2.8 along with dibasic calcium chloride, PVP K-90 and labeled as F1, F2, F3, F4, F5, and F6, respectively. In the second group, the drug was mixed with polymer blend of chitosan (CH) and (XG/GG) at 1:1, 1:4, and 4:1 ratios along with PVP K-90 and labeled F7, F8, F9, F10, F11, and F12, respectively. All the above formulations (F1-F12) were mixed well in a mortar using a spatula. The multiparticulates (granules) were prepared by utilizing alcohol into damp mass. Then, the wet mass was passed

Table 1: Formulae for the preparation of granules

Formulation codes	Quantity of ingredients (mg)							
	Drug	Chitosan	XG	GG	Dibasic calcium phosphate	PVP K -90	Alcohol (ml)	Total
F1	75	-	75	-	135	15	q.s.	300
F2	75	-	150	-	60	15	q.s.	300
F3	75	-	210	-	-	15	q.s.	300
F4	75	-	-	75	135	15	q.s.	300
F5	75	-	-	150	60	15	q.s.	300
F6	75	-	-	210	-	15	q.s.	300
F7	75	105	105	-	-	15	q.s.	300
F8	75	42	168	-	-	15	q.s.	300
F9	75	168	42	-	-	15	q.s.	300
F10	75	105	-	105	-	15	q.s.	300
F11	75	42	-	168	-	15	q.s.	300
F12	75	168	-	42	-	15	q.s.	300

XG: Xanthan gum, GG: Guar gum

through sieve #16. The wet granules were air dried for 2 h and then passed through sieve #22.

Evaluation of physical and flow properties of granules

Prepared granules were evaluated for flow properties and particle size distribution.

Flow properties

The flow properties of the prepared granules were determined by angle of repose θ, using fixed funnel method. The bulk and tapped densities for the prepared granules were determined by tapping method and the compressibility index using the data.[18]

Particle size distribution

To determine the particle size distribution of prepared granules containing venlafaxine hydrochloride, standard sieve method was used. Mechanical sifter with sieves between apertures 355 and 2000 µm was used using all the amount of blend prepared. The fraction collected on each of the sieves was calculated by the percentage value.

Preparation of MDDS

All prepared granules of 12 formulations are accurately weighed (equivalent to 75 mg of drug) were filled in size "1" hard gelatin capsules using hand-operated capsule filling machine.

Evaluation of physicochemical properties of MDDS

Filled capsules of different formulations (F1-F12) were evaluated for weight variation, disintegration time, drug content, and *in vitro* drug release.

Weight variation

Individual weights of 20 capsules were taken and the average weight was calculated using the following formula:

$$\text{Weight variation} = \frac{\left(\text{Weight of capsule} - \text{Average weight of capsules}\right)}{\text{Average weight of capsules}}$$

Weight variation should not be more than 5%.[19]

Disintegration time

One capsule was placed in each of six tubes of disintegration assembly (Electrolab and Model: ED-2L) and was suspended in water. Discs were added to each tube, temperature was maintained at 37 ± 2°C and assembly was operated for 30 min as per B.P.[20]

Drug content

A total of 10 capsules were selected and the contents were removed. From this, an accurately weighed amount of sample equivalent to 100 mg of venlafaxine hydrochloride was taken in a volumetric flask (100 ml). The content was dissolved in water and the volume was made up to 100 ml. This solution was filtered through Whatman filter paper No.41. The solution was suitably diluted and the drug content

was estimated by measuring the absorbance at 254 nm in ultraviolet-visible spectrophotometer (Shimadzu).[21]

In vitro drug release study

In vitro drug release studies for all formulations as well as commercial available product (Venlor XR) were carried out using dissolution test apparatus USP Type-II (Electrolab and Model: ESP-84) at 50 rpm. The dissolution test was performed using 900 ml of distilled water and the temperature was maintained at 37°C ± 0.5°C. Aliquots of 5 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted up to 50 ml with buffer, filtered and analyzed by measuring the absorbance at 278 nm.[15]

Kinetic treatment of dissolution data

To describe the kinetics of drug release, zero-order ($Qt = Q0 + K0t$), first-order ($\ln Qt = \ln Q0 + K1t$), Higuchi ($Qt = KHt^{1/2}$), and Korsmeyer-Peppas ($Qt/Q\infty = Kt^{n}$) models were fitted to the dissolution data of selected formulations (F7, F8, F9, F11, and Venlor XR), using linear regression analysis. A value of $n = 0.5$ indicates Case I (Fickian) diffusion, $0.5 < n < 1$ anomalous (Non-Fickian), $n = 1$ Case II transport, and $n > 1$ super Case II transport.[22]

RESULTS AND DISCUSSIONS

Drug-excipient compatibility study

FTIR spectroscopy

The FTIR spectra of drug, venlafaxine hydrochloride showed characteristic stretching bands at 3367.38, 3324.83,1611.52, 1512.08, and 1179.25 cm^{-1} corresponding to functional groups O-H, C=H,C-O, and C-N in the below Figure 1a. The FTIR spectra of placebo of optimized formulation showed characteristic stretching bands at 3390.01, 2923.65, 1724.05, and 1618.5 cm^{-1} corresponding to functional groups O-H, C-CH3, C=O, and C=C in below Figure 1b. The characteristic bands of the optimized formulation (F8) were slightly varied from the pure drug revealing no chemical interaction shown in Figure 1c.

Thermal analysis

The DSC analysis of venlafaxine hydrochloride and physical mixture of optimized formulation was carried out and the results

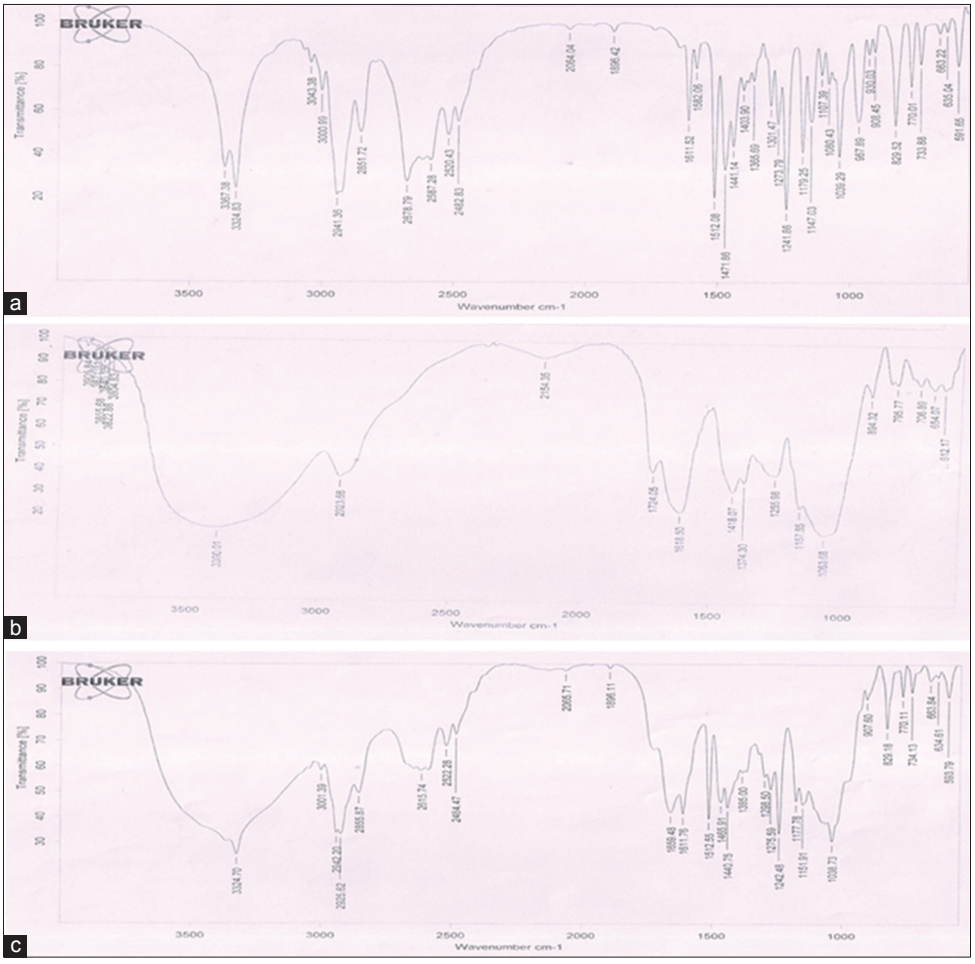

Figure 1: (a) Fourier-transform infrared spectra of venlafaxine hydrochloride, (b) Fourier-transform infrared spectra of placebo of optimized formulation (F8), (c) Fourier-transform infrared spectra of optimized formulation (F8)

were shown in Figure 2. The pure venlafaxine hydrochloride [Figure 2a] has shown a sharp endothermic peak at 217°C corresponds to the melting point of venlafaxine hydrochloride. In case of optimized formulation (F8) [Figure 2b], disappearance of the endothermic peak at 217°C suggests that the drug is uniformly dispersed in chitosan and XG matrix.

Physical and flow properties of granules

Prepared granules of different formulations from F1to F12 were evaluated and shown in Table 2. The angle of repose value for granules from F1 to F12 was found to be in the range of 24 and 31.62°.The Carr's index of granules from F1 to F12 was found to be in the range of 14.8–19.9. The bulk density of the prepared granules was in the range of 0.2490–0.3157. The bulk density, Carr's index, and angle of repose values of all prepared granules indicated that they possess average to good flow properties. Particle size distribution of all the prepared granules (F1-F12) was uniform and found to be 245–276 µm.

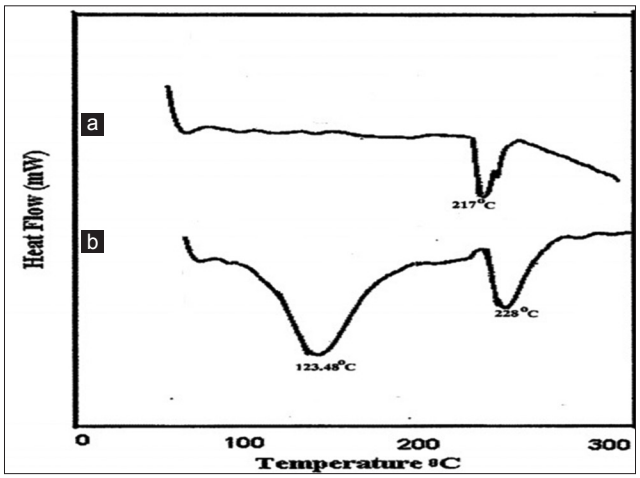

Figure 2: Differential scanning calorimetry thermograms of (a) venlafaxine hydrochloride, (b) physical mixture of the optimized formulation (F8)

Physicochemical properties of MDDS

The average weight of all formulations (F1-F12) was ranged from 391.4 to 398.6 mg. Disintegration time of all formulations (F1-F12) was found to be 24.59–29.92. The percent drug content of all formulations (F1-F12) was found to be 95.3–99.4 and was within the acceptable limits of I.P. All these values were depicted in Table 3.

In vitro drug release study

In vitro dissolution studies were performed in distilled water and the results were depicted in Table 4. The drug release from formulations F1-F6 made with XG or GG as a single release retardant material was shown in Figure 3a. From their release profiles, formulations F1, F2, F4, and F5 retard the release of the drug only for 4 h when as F3 and F6 retard up to 8 h. Due to the single component matrix, the prepared MDDS F1, F2, F4, and F5 resulted in faster drug release where 82.95%, 71.9%, 78.5%, and 74.7% of drug were released after 2 h and 97.2%, 84.7%, 95.6%, and 95.6% of drug were released after 4 h, respectively.

Although the single component matrix could not sustain the release of venlafaxine hydrochloride, the formulations F3 and F6 showed a lesser release rate compared to other formulations, i.e. F1, F2, F4, and F5. In case of F3 and F6, 54.9 % and 68.5% of drug were released in 2 h, and 69.2% and 85.5 % of drug were released in 4 h, and 96.3% and 99.6% release of drug in 8 h, respectively. The differences in release profile for these formulations could be attributable to failure in the formation of matrix network during dissolution due to less cohesiveness in the swollen matrix leading to

Table 2: Results of physical and flow properties of granules

Formulation codes	Angle of repose (°)[a]	Bulk density (g/ml)[a]	True density (g/ml)[a]	Carr's index (%)[a]	Average particle size (µm)[a]
F1	24±0.81	0.2490±0.003	0.2945±0.002	14.8±1.59	254.81±6.09
F2	26.25±0.92	0.2683±0.001	0.3283±0.001	18.2±0.07	263.48±7.16
F3	28±0.74	0.2661±0.001	0.3306±0.001	19.5±0.40	253.14±5.69
F4	31.3±0.68	0.2673±0.001	0.3193±0.001	16.2±0.35	272.14±2.98
F5	24±0.98	0.2697±0.003	0.3256±0.007	17.1±2.03	244.81±4.90
F6	27.5±0.84	0.2590±0.001	0.3216±0.001	19.4±0.17	266.64±6.04
F7	25.11±0.48	0.2707±0.002	0.3245±0.008	16.6±0.91	252.74±4.52
F8	29.28±1.2	0.2737±0.003	0.3351±0.003	18.3±1.61	273.08±2.42
F9	31.62±2.12	0.2744±0.004	0.3427±0.003	19.9±1.68	245.74±9.23
F10	25.08±0.51	0.3157±0.002	0.3801±0.002	16.9±0.82	274.08±5.58
F11	28.28±0.57	0.2674±0.005	0.3247±0.009	17.6±3.08	276.08±0.82
F12	30.03±0.34	0.2697±0.001	0.3351±0.002	19.5±0.18	248.09±3.41

[a](Mean±SD), *n*=3, SD: Standard deviation

faster release rates of drug. Hence, chitosan was incorporated to slower the release of the drug by forming polyelectrolyte complex with XG and GG. Formulations F7, F8, F9, F10, F11, and F12 extended the venlafaxine hydrochloride release for 12 h (97.6%), 20 h (85.3%), 12 h (99.9%), 8 h (97.2%), 12 h (95.6%), and 4 h (97.4%), respectively, were shown in Figure 3b. The effective sustained release was obtained with F8 formulation when compared with Venlor XR (commercially available product) by sustaining the release of drug up to 20 h (85.3 %) and 12 h (97.35 %), respectively, was

Table 3: Results of physicochemical properties of MDDS

Formulation codes	Weight variation (mg) *n*=20	Disintegration time (min)[b]	Drug content (%)[b]
F1	393±5.77	29.82±1.18	99.4±1.2
F2	392.9±6.04	28.82±0.35	98.6±1.5
F3	391.4±5.65	27.49±0.64	98.3±2.0
F4	394.3±7.89	25.82±0.35	99.1±1.9
F5	396.3±7.35	24.59±1.23	99.2±1.7
F6	397.3±7.58	29.92±0.66	97.6±2.6
F7	398.3±6.94	28.3±1.23	99.1±1.8
F8	396.5±4.74	29.63±1.07	98.1±2.8
F9	397.9±5.59	29.91±0.99	98.6±2.3
F10	394.8±4.89	27.42±0.59	99.3±1.8
F11	398.6±6.02	29.82±1.52	97.8±1.5
F12	394.9±7.02	26.16±1.01	95.3±2.3

[b](Mean±SD), *n*=3, SD: Standard deviation, MDDS: Multiparticulate drug delivery systems

Table 4: *In vitro* drug release studies for all formulations

Formulation codes/time (hours)	Mean percentage drug release[c]				
	2	4	8	12	20
F1	82.95±2.85	97.2±2.4	-	-	-
F2	71.9±3.15	84.7±4.78	-	-	-
F3	54.9±4.29	69.2±5.85	96.3±9.62	-	-
F4	78.5±7.71	95.6±9.17	-	-	-
F5	74.7±7.71	95.6±5.44	-	-	-
F6	68.85±3.45	85.5±1.21	99.6±3.9	-	-
F7	82.5±1.31	84.7±2.4	90.9±3.1	97.6±1.15	-
F8	57.6±1.08	61.8±1.82	74.1±2.38	81.1±0.75	85.3±2.29
F9	80.5±5.44	85.5±1.67	92.6±2.91	99.9±3.92	-
F10	86.7±4.18	91.3±3.12	97.2±2.01	-	-
F11	64.5±0.3	76.05±1.95	90.45±0.45	95.6±1.19	-
F12	82.4±1.23	97.4±4.39	-	-	-
Venlor XR	45±1.34	68.85±3.75	87.45±0.15	97.35±1.05	

[c](Mean±SD), *n*=3, SD: Standard deviation, XR

Table 5: Kinetic modeling of drug release

Formulation codes	Zero order	First order	Higuchi	Korsmeyer-Peppas	N
F7	0.996	0.919	0.969	0.921	0.092
F8	0.886	0.947	0.955	0.971	0.185
F9	0.996	0.997	0.995	0.992	0.101
F11	0.977	0.998	0.975	0.992	0.225
Venlor XR	0.907	0.985	0.961	0.969	0.427

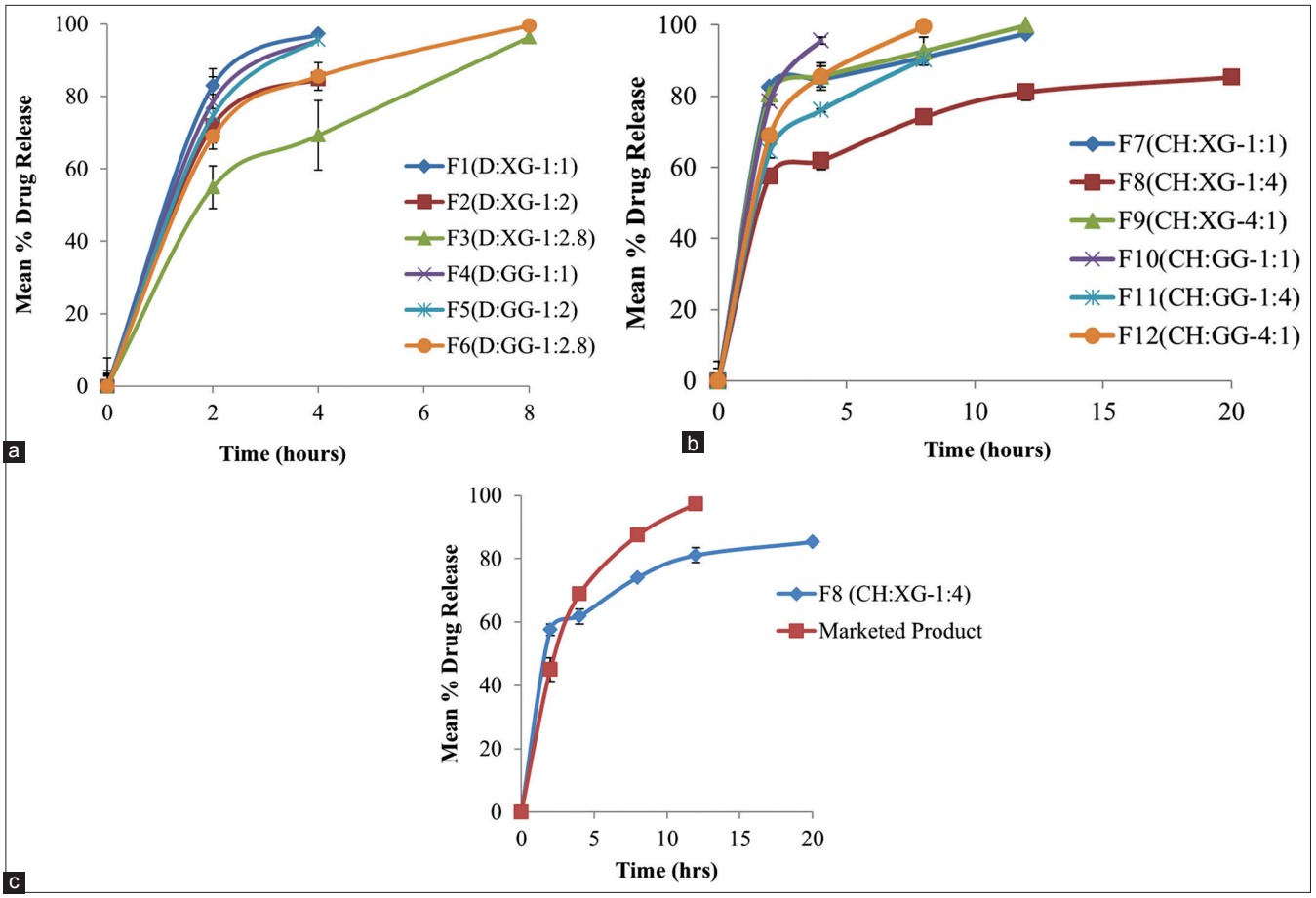

Figure 3: (a) *In vitro* drug release studies for formulations (F1-F6), (b) *In vitro* drug release studies for formulations (F7-F12) (c) In vitro drug release studies for optimized formulations (F8) and commercially available product (Venlor XR)

shown in Figure 3c. This retardation of drug release by the optimized formulation (F8) may be due to strong synergistic interactions between polymers resulted in the formation of polyelectrolyte complex with reduced porosity.

Kinetic modeling of drug release

In vitro release data of venlafaxine HCl from the MDDS were fitted to various kinetic models to understand the order and mechanism of drug release. Here, the formulations F7, F8, F9, F11, and Venlor XR were considered as they are capable to extend the drug release as that of commercial available product and the results were shown in Table 5. The kinetic model with the highest correlation coefficient value (r^2) was selected as the model that best describes the dissolution data. From the results, it is clear that the release of drug from the (F8) optimized formulation followed first-order Kinetics through Quasi-Fickian diffusion.

CONCLUSION

The MDDS of venlafaxine hydrochloride were successfully prepared using natural polymers as release retardant. FTIR studies showed that there is no much interaction between drug and polymers also with optimized formulation (F8). The DSC analyses indicated that the drug was uniformly dispersed in the chitosan and XG matrix. Different parameters such as percentage yield, flow properties, weight variation, disintegration time, drug content, and *in vitro* drug release were evaluated for all formulations. Based on these results, formulation (F8) was found to be most promising formulation. The release of the optimized formulation (F8) was capable of releasing drug up to 20 h and follows first-order kinetics through Quasi-Fickian diffusion. These findings suggest that the developed MDDS using chitosan, XG of venlafaxine hydrochloride could perform better than the commercially available reference product (Venlor XR), by achieving a retarding effect. Thus, the aim of this study was achieved. Hence, binary mixture of chitosan and XG could be a versatile release retardant for controlled the release of the drug.

REFERENCES

1. Moin A, Sandeep C, Deb TK, Shivakumar HG. Cationic guar gum polyelectrolyte complex microparticles. J Young Pharm 2014;6:11-9.

2. Nandy BC, Mazumder B. Formulation and characterizations of delayed release multi particulates system of indomethacin: Optimization by response surface methodology. Curr Drug Deliv 2014;11:72-86.
3. Koradia H, Butani S, Gohel M. Studies in oxacarbazepine microspheres employing plackett and burman design. Int J Pharm Pharm Sci 2014;6:305-10.
4. Jyothi BJ, Doniparthi J. Multiparticulate drug delivery systems using natural polymers as release retardant materials. Int J Pharm Pharm Sci 2014;6:61-5.
5. Narayan BA, Raosaheb NS. Development and evaluation of once a day oral controlled multiparticulate drug delivery systems of cefixime trihydrate. Indian J Pharm Educ Res 2008;3:283-94.
6. Seidenberger T, Siepmann J, Bley H, Maeder K, Siepmann F. Simultaneous controlled vitamin release from multiparticulates: Theory and experiment. Int J Pharm 2011;412:68-76.
7. Remon JP, De Brabander C, Vervaet C. Development and evaluation of sustained release mini-matrices prepared via hot melt extrusion. J Control Release 2003;89:235-47.
8. Subha MC, Siraj S, Sudhakar P, Rao US, Sekharnath KV, Rao KC. Interpenetrating polymer network microspheres of poly(vinyl alcohol)/methyl cellulose for controlled release studies of 6-thioguanine. Int J Pharm Pharm Sci 2014;6:101-6.
9. Pawar HA, Dhavale R. Development and evaluation of gastro retentive floating tablets of an antidepressant drug by thermoplastic granulation technique. BENI-SUEF Univ J Appl Sci 2014;3:122-32.
10. Nafee N, Gaber DM, Abdallah OY. Mini-tablets versus pellets as promising multiparticulate modified release delivery systems for highly soluble drugs. Int J Pharm 2015;1:1-9.
11. Kajjari PB, Manjeshwar LS, Aminabhavi TM. Novel blend microspheres of poly (3-hydroxybutyrate) and pluronic F68/127 for controlled release of 6-mercaptopurine. J Appl Polym Sci 2014;131:1-12.
12. Siepmann F, Siepmann J, Walther M, MacRae RJ, Bodmeier R. Polymer blends for controlled release coatings. J Control Release 2008;125:1-5.
13. Poornima G, Ahmed MG, Ramesh B. Comparative studies on polyelectrolyte complexes of chitosan for sustained release of simvastatin. double helix resolution. Int J Pharm Sci 2012;3:38-47.
14. Varshosaz J, Tavakoli N, Moghaddam F, Ghassami E. Polyelectrolyte complexes of chitosan for production of sustained release tablets of bupropion HCL. Farmacia 2015;63:65-73.
15. Moin A, Reddy MM, Reddy DJ, Shivakumar HG. Formulation of sustained release matrix tablet using Chitosan/Ghatti gum polyelectrolyte complex. Pharm Lett 2011;3:119-28.
16. Li L, Wang L, Shao Y, Ni R, Zhang T, Mao S, *et al.* Drug release characteristics from chitosan-alginate matrix tablets based on the theory of self-assembled film. Int J Pharm 2013;450:197-207.
17. El-Gawad HA, El-Gawad A, Ramadan EM, Soliman OA, Yusif RM. Formulation and *in-vivo* study of ketoprofen tablets prepared using chitosan interpolymer complexes. Bull Pharm Sci 2012;35:1-16.
18. Lankalapalli S, Kolapalli RM. Biopharmaceutical evaluation of diclofenac sodium controlled release tablets prepared from gum Karaya – chitosan polyelectrolyte complexes. Drug Dev Ind Pharm 2012;38:815-24.
19. Venkateswarlu P. Formulation and *in vitro* evaluation of lansoprazole delayed release capsules. Int J Innov Pharm Sci 2013;4:328-36.
20. Pujara ND, Parmar RB. Formulation and evaluation of hard gelatin capsule of losartan potassium. Inventi Rapid 2013;2:1-4.
21. Srinivas L, Lohithasu D, Madhupriya D, Siddhartha N, Tejaswi N. Formulation and evaluation of ibuprofen pulsin cap technique for controlled release. Pharm Lett 2013;5:60-68.
22. Karthikeyan D, Vijayalaxmi A, Kumar CS. Formulation and evaluation of biphasic delivery system of aceclofenac mini-tablets in hard gelatin capsules. Int J Novel Trends Pharm Sci 2013;3:39-45.

Source of Support: Nil. **Conflict of Interest:** None declared.