MARMARA
PHARMACEUTICAL JOURNAL

Research Article

www.marmarapharmj.com

Development and optimization of venlafaxine hydrochloride floating microspheres using response surface plots

Sachin Kumar [1, 2, *], Rupa Mazumder [3]

1 NKBR College of Pharmacy & Research Centre, Meerut Hapur Road, Meerut, India

2 Dr. A.P.J. Abdul Kalam Technical University, Sector 11, Jankipuram, Lucknow, India

3 Pharmacy Institute, Noida Institute of Engineering and Technology, 19, Knowledge Park-II, Institutional Area, Greater Noida, Uttar Pradesh 201306, India

* Correspondence: sachin.mpharm86@gmail.com (S.K.); Tel: +91-7055018882; ORCID No: 0000-0001-6109-0116.

Received: 6 November 2017 / Revised: 7 December 2017 / Accepted: 7 December 2017

ABSTRACT: The current study deals with the development of floating microspheres of venlafaxine hydrochloride. This drug is known as a serotonin-norepinephrine reuptake inhibitor and used to treat depression. Due to the short elimination half life of 4-5 h, the drug has to be administred 2-3 times in a day to maintain the plasma concentration. Thus an attempt was made to decrease the dosing frequency. The microspheres were prepared by non-aqueous solvent evaporation method. The microspheres were evaluated for particle size and morphology using a photomicroscope and scanning electron microscopy, respectively. The incorporation efficiency of microspheres of batch F2 and F6 showed entrapment of 60.6% and 57.2%, respectively. The mean diameters of particles for all batches were found in the range of 226.15 ± 24.37 to 283.37 ± 21.56 µm. The Fourier transform infrared spectroscopy revealed absence of any drug - polymer interactions. The microsphers remained buoyant for more than 12 h. The drug release from developed microspheres followed Fickian diffusion with swelling. The results suggested that the developed floating microspheres containing venlafaxine hydrochloride could enhance drug entrapment efficiency, reduce the initial burst release and modulate the drug release.

KEYWORDS: Floating microspheres; gastroretentive floating system; response surface plots; venlafaxine hydrochloride.

1. INTRODUCTION

Depression is a chronic, recurring, and potentially life-threatening illness that affects up to 20% of the population across the globe [1]. This disease is one of the top ten causes of morbidity and mortality worldwide and represents a high cost to country's economy [2]. Available therapy for depression treatment is often associated with several undesirable side effects, and its effectiveness achieves only a certain portion of the population. Therefore, the identification of alternative therapeutic tools for the treatment of depression is of high importance.

Oral controlled drug delivery system are useful to maintain therapeutically effective plasma drug concentration for a longer duration, thereby reducing the dosing frequency and to minimize fluctuations in the plasma drug concentration at the steady state by delivering the drug in a controlled and reproducible manner. Moreover, it is easy for administration, patient compliances, and flexibility in the formulation [3].

Many studies have been performed concerning the sustained release dosage form of drug, which have aimed at the prolongation of gastric emptying time, *i.e.*, gastroretentive drug delivery systems, which will provide as with new and important therapeutic options, which utilize several approaches such as intra gastric floating system, high density system, mucoadhesive system , and super porous hydrogel systems [4]. In floating systems, drugs can remain in the gastric region for several hours and significantly prolong the gastric resistance time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility of drugs that are less soluble in a high pH environment. This approach has applications for drugs showing absorption from stomach and proximal small intestines. Micro-particulate delivery system

How to cite this article: Kumar S, Mazumder R. Development and optimization of Venlafaxine hydrochloride floating microspheres using response surface plots. Marmara Pharm J. 2018; 22 (2): 277-285.

ISSN: 1309-0801

https://doi.org/10.12991/mpj.2018.65
Marmara Pharm J 2018; 22(2): 277-285

has emerged as one of the best controlled drug delivery system, which delivers the drugs in a controlled rate over a period of time [5].

Venlafaxine hydrochloride, is a highly water soluble and structurally novel antidepressant for oral administration. It is a dual serotonin and norepinephrine reuptake inhibitor [6]. It inhibits the serotonin transporter at 30 fold lower concentrations than norepinephrine transporter, respectively. It display differential effects on norepinephrine reuptake in healthy versus depressed patients [7]. It is highly soluble in 0.1 N HCl and it decreases with increasing pH over the physiological range. The half-life of venlafaxine hydrochloride is 5 ± 2 h, necessitating the administration, two or three times daily to maintain adequate plasma drug concentration [8].

Response surface methodology (RSM) is a group of mathematical and statistical techniques which plays an important role in experimental design. The objective of RSM is to optimize the response of various independant variables. RSM has applications in the situations where several input variables (indepandant variables) potentially influence some performance measure or quality characteristic (depandant variables) of the process. Thus, performance measure or quality characteristic is called the response [10]. The purpose of this study was to improve the release profile of velnafexine HCl in the stomach in a controlled manner to improve the therapeutic benefit of selected drug. It is hypothesized the improved bioavailability might be due to increased surface area and swelling and hydration nature of polymers used.

2. RESULTS AND DISCUSSION

2.1. Fourier Transform Infrared (FTIR) Spectroscopy

The results of FTIR studies of venlafaxine HCl and drug loaded microspheres (formulation F2) to determine interactions and structural changes in drug and excipients are shown in Figure 1. The FTIR spectrum of venlafaxine HCl exhibited peaks at 3321 cm^{-1} assigned to symmetric stretching peaks of –OH, 2943 cm^{-1} (aliphatic CH stretching), 1514 cm^{-1} (stretching of C6H5), 1039 cm^{-1} (C-O-C stretching). Characteristic peaks of drug were also present in FTIR spectrum of microspheres. Some peaks were shifted with a very slight change in the wave number. These results suggested that there was no interaction between venlafaxine HCl and excipients.

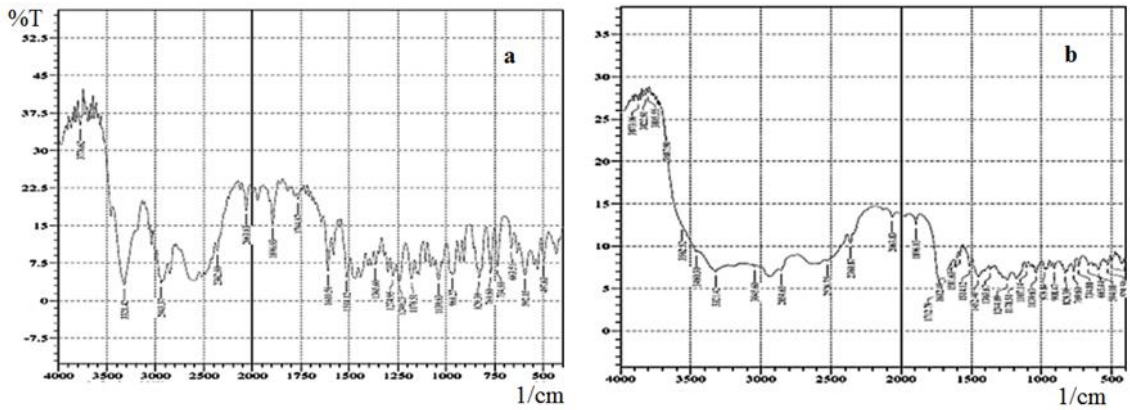

Figure 1: FTIR spectra of (a) venlafaxine HCl and (b) formulation blend (Formulation F2).

2.2. Percentage yield

The maximum percentage yield was found to be for batch F2 and minimum of 77.45% for batch F7 (Table 1).

2.3. Particle size and bulk density of microspheres

The analysis was performed for all eight batches by photomicroscope using micrometric tools. The results were as shown in table 1. The mean diameters of particles for all batches were found in the range of 226.15±24.37 to 283.37±21.56 µm. The bulk density determination was performed for all eight batches. The bulk densities for all samples were found to be in the range of 0.75±0.02 mg/ml to 0.82±0.03 mg/ml, respectively. Tapped density was in the range of 0.88±0.02 mg/ml to 0.99±0.07 mg/ml. the difference in bulk density was small, which confirms small and uniform particle size.

Table 1: Results of *in vitro* characterization of floating microspheres (Data presents mean±SD, n=3).

Formulation	Drug content (%)	Yield (%)	Mean particle size (μm)	Bulk density (mg/ml)	Tapped density (mg/ml)
F1	41.7±1.21	88.53±3.24	283.37 ± 21.56	0.75 ± 0.02	0.89±0.03
F2	60.6±0.09	92.14±2.28	267.53 ± 7.71	0.77 ± 0.03	0.92±0.06
F3	56.6±1.04	78.87±5.23	232.00 ± 23.64	0.79 ± 0.03	0.97±0.01
F4	32.9±.076	90.82±6.22	229.33 ± 31.50	0.81 ± 0.02	0.99±0.07
F5	42.7±1.23	89.18±7.12	256.33 ± 32.47	0.77 ± 0.01	0.91±0.08
F6	57.2±2.09	79.37±2.78	266.27 ± 28.91	0.78 ± 0.02	0.88±0.02
F7	49.3±1.30	77.45±4.33	226.15 ± 24.37	0.82 ± 0.03	0.96±0.03
F8	54.7±1.76	87.19±3.98	239.33 ± 19.43	0.79 ± 0.01	0.94±0.05

2.4. Buoyancy percentage

The purpose of preparing floating microspheres was to extend the gastric residence time of the drug. The buoyancy test was carried out to investigate the floatability of the prepared microspheres. The particles were spread over the surface of a simulated gastric fluid and the fraction of microspheres settled down as a function of time was quantitated. The fraction of floating microspheres reduced up to 12 h suggesting that the absorption of the drug in vivo pertaining to sustained release would be linear with time (Table 2). As the time passed, water gradually entered into the microspheres and subsequently the density was increased and microspheres sink to the bottom. The sinking was observed maximum in formulation containing gum at highest concentration. Buoyancy of batch F2 was found to be 76 %, which indicate that most of the microspheres were floatable.

Table 2: Results of buoyancy study of microspheres (Data presents mean±SD, n=3).

Formulation	Total mass (mg)	Total mass remained floating (mg)	Buoyancy lag time (sec)	Buoyancy percentage (%)	Floating time (h)
F1	200	125±3.98	8	62.5±1.34	17.0±0.34
F2	200	140±4.12	5	76.3±2.88	17.0±1.11
F3	200	105±2.32	7	52.5±3.11	23.0±1.55
F4	200	130±3.97	9	65.1±2.14	22.5±1.34
F5	200	115±2.69	10	57.5±3.67	17.0±2.02
F6	200	123±3.34	11	61.5±2.87	17.5±2.22
F7	200	137±1.97	10	68.5±4.12	23.0±0.67
F8	200	152±3.22	10	70.7±2.56	22.5±1.78

2.5. Drug entrapment efficiency

The microspheres of batch F2 and F6 showed entrapment of 60.6% and 57.2%, respectively while least entrapment was observed in F1 and F4 particles were least entrapped (Table 1). It attributed to the permeation characteristics of each polymer [16].

2.6. Surface morphology

Detailed observation of morphological characters of the dried microspheres (Formulation F2.) was done by SEM. The SEM photomicrographs confirmed the spherical shape with rough surface of the microspheres (Figure 2). The results showed that the polymer type had significant effect on morphology of beads.

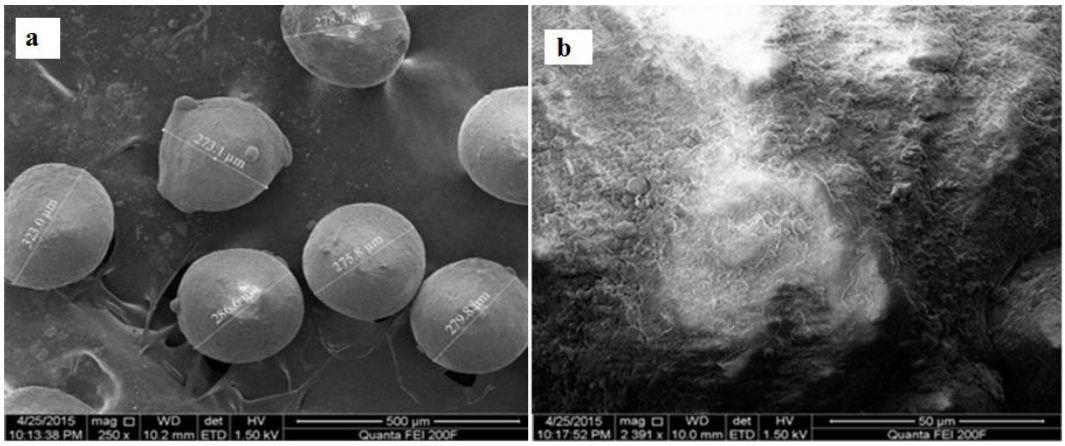

Figure 2: Scanning electron microscopy of optimized formulation (Formulation F2).

2.7. *In-vitro* dissolution studies

In vitro drug release profiles showed that the polymer combination had excellent control on the release of the drug from microspheres in gastric fluid (figure 3) [17]. An attempt was made to control the drug release by use of polymer combination. The results of in vitro drug release study showed that the drug release rate from prepared microspheres was 89.2 ± 3.12 % to 96.88 ±2.44 % in 0.1 N HCl (pH 1.2) after 24 h. The drug release was found to occur through swelling process.

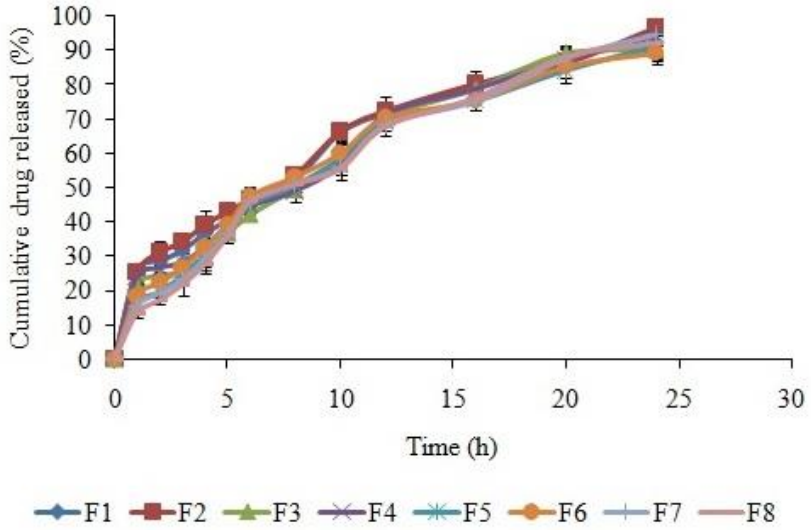

Figure 3: *In vitro* drug release profiles from formulation F1-F8 (Data presents mean ± SD, n = 3).

From Table 3, it can be seen that all the formulations had 'n' values greater than 0.5 and less than 1, which confirms that the release mechanism of venlafaxine HCl from the floating microspheres in acidic media (pH 1.2) was Fickian diffusion with swelling.

Table 3: Kinetic parameters for drug release from different batches.

Formulation Code	Zero order (r^2)	First order (r^2)	Higuchi model (r^2)	Korsmeyer Pappas' model	
				(r^2)	n
F1	0.9558	0.9618	0.9807	0.972	0.910
F2	0.9481	0.9511	0.9852	0.9951	0.700
F3	0.9725	0.9628	0.9792	0.9896	0.802
F4	0.9709	0.9598	0.9771	0.9792	0.767
F5	0.9479	0.9421	0.989	0.9729	0.911
F6	0.9415	0.9323	0.9876	0.9896	0.687
F7	0.9668	0.9255	0.9904	0.9913	0.701
F8	0.9576	0.9124	0.9897	0.9853	0.731

2.8. Response surface plots

The relationship between the dependent and independent variables was further elucidated using response surface plots. Figure 4 shows that the percentage buoyancy of the microspheres decreased with an increase in the polymer concentration. This could be due to an increase in viscosity of the organic phase, which, in turn, increases the particle density. Figure 5 suggests that the polymer concentration have a significant effect on drug release and control the release of drug from the microspheres. The increased density of the polymer matrix at higher polymer concentration results in an increased diffusion path length, which may decrease the overall drug release from the polymer matrix. Also, smaller particles formed at lower polymer concentration exhibit larger surface area for exposure to the dissolution medium. The drug release pattern may be changed by appropriate selection of the polymers levels [18-19].

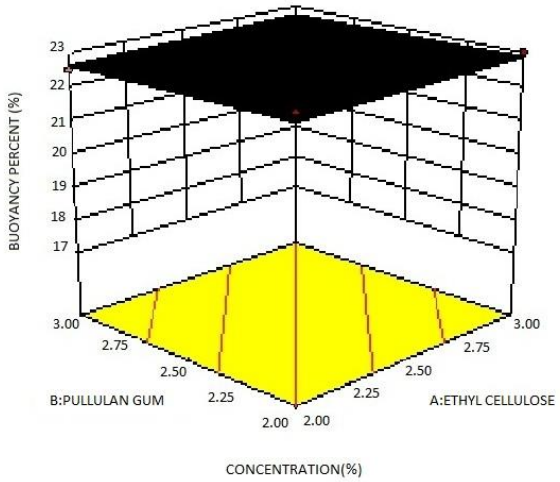

Figure 4: Response surface plots showing the influence of pullulan gum, and ethyl cellulose on mean percentage buoyancy of floating microspheres.

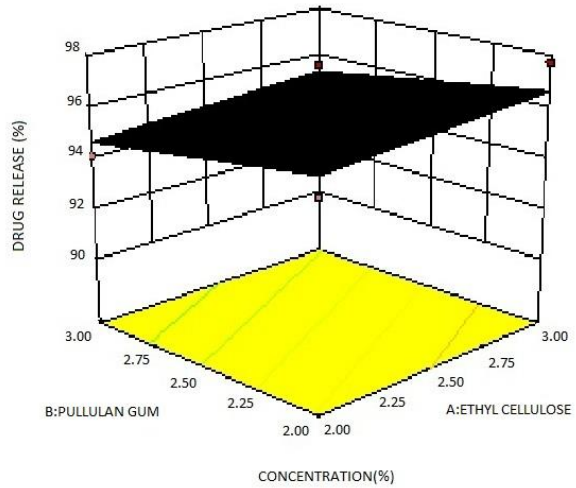

Figure 5: Response surface plots showing the influence of pullulan gum and ethyl cellulose on percentage drug release of floating microspheres.

3. CONCLUSION

The major limitation of gas generating floating system is that these systems cause alkaline micro envornment due to the presence of alkali salt. The prepared microspheres showed great potential in replacing the alkaline microenvironment created by gas-generating microspheres. It was found that the developed microspheres had ideal physical properties and drug release profiles to be used as controlled release microparticulate floating drug delivery system. Based on the results obtained from this study, it is hoped that further research with a variety of natural gum will lead to the development of more effective floating drug delivery systems.

4. MATERIALS AND METHODS

4.1. Materials

Venlafaxine HCl was received as gift sample from Torrent Pharmaceuticals, Ahmadabad. Ethyl cellulose and HPMC K100M were purchased from Fine Chem. Labs., Mumbai. Pullulan gum was received as gift sample from Aurobindo Pharmaceuticals Ltd., Hyderabad. Microcrystalline cellulose, sodium bicarbonate, liquid paraffin, Tween 80, petroleum ether, citric acid, hydrochloric acid, magnesium stearate, and talc were purchased from CDH (P) Ltd., Mumbai, India.

4.2. Methods

4.2.1. Preparation of venlafaxine HCl floating microspheres

Microspheres containing venlafaxine HCl were prepared using non-aqueous solvent evaporation method. Accurately weighed quantities of drug and polymers were dispersed in a solvent mixture containing dichloromethane and ethanol (Table 4). The mixture was slowly introduced into 60 ml of light liquid paraffin containing Tween 80 as an emulsifier with continuous stirring using a precision digital stirrer (LT400A, Yamato, Japan). The temperature was maintained at 25°C and stirring was continued for 2 h for complete evaporation of solvent. The microspheres were collected, washed repeatedly with petroleum ether and dried at room temperature (25°C) until free flowing particles were obtained [9-11].

Table 4: Composition of different floating microsphere formulations containing venlafaxine HCl.

Ingredients	Formulation code							
	F_1^a	F_2^a	F_3^b	F_4^b	F_5^a	F_6^a	F_7^b	F_8^b
Drug (g)	1	1	1	1	1	1	1	1
Ethyl cellulose (g)	2	2	2	2	3	3	3	3
Pullulan gum (g)	2	3	2	3	2	3	2	3
Ethanol (ml)	25	25	25	25	25	25	25	25
Dichloro methane (ml)	25	25	25	25	25	25	25	25
Tween 80 (ml)	0.18	0.18	0.18	0.18	0.18	0.18	0.18	0.18
Liquid paraffin (ml)	60	60	60	60	60	60	60	60

a: indicates 600 rpm stirring, b: indicates 1200 rpm stirring

4.2.2. Characterization of floating microspheres

4.2.2.1. Determination of percentage yield

The percentage yield was calculated as the mass of the microspheres recovered from each batch divided by the total mass of drug and polymers used in the preparation of the particular batch.

$$\text{Yield (\%)} = \frac{\text{Total mass of microspheres}}{\text{Total mass of drug and polymers}} \text{X } 100$$

4.2.2.2. Drug polymer compatibility study by Fourier transform infrared (FTIR) spectroscopy

The molecular interaction between drug and excipients was examined by FTIR spectroscopy using KBr disc (IR affinity-1, Shimadzu, Japan). The samples were triturated with dried KBr at a weight ratio of 1:100 and compacted into a disc using a KBr press at 10 tons for 2 min. The sample disc was placed in the sample holder and scanned from 4000 to 400 cm^{-1} at a resolution of 4 cm^{-1}.

4.2.2.3. Determination of particle size

The analysis of particle size was carried out using a photomicroscope (QUASMO, Quality Scientific, Ambala) fitted with micrometric tools (Winzoe). The particle size distribution was determined and the average diameter was calculated for each batch of microspheres. The analysis was done in triplicate for each batch.

4.2.2.4. Determination of bulk density and tapped density

Samples (1 g) were taken into a 10 ml graduated measuring cylinder separately and the volume was recorded. The graduated measuring cylinder was tapped 50 times using USP bulk density apparatus (ETD 1020, Electrolab, Mumbai, India). The analysis was done in triplicate for each batch. The bulk density and tapped density were determined using the following formula [12]:

$$\text{Bulk density} = \frac{\text{Mass of floating microspheres}}{\text{Initial volume of microspheres}}$$

$$\text{Tapped density} = \frac{\text{Mass of floating microspheres}}{\text{Final volume of microspheres after tapping}}$$

4.2.2.5. Determination of angle of repose

For the determination of angle of repose, the microspheres were poured through a funnel, which was fixed at a position such that its lower tip was at a height of 2 cm above the surface. The microballoons were poured till the time when the tip of the microballoons pile surface touched the funnel. The $\tan^{-1}$ of ratio the height of the pile (h) and radius (r) of its base gave the angle of repose. The analysis was done in triplicate for each batch. The angle of repose was determined by following formula [12]:

$$\tan^{-1} = \frac{h}{r}$$

4.2.2.6. Determination of Carr's index

The analysis was done in triplicate for each batch. The density determinations were used to determine the Carr's index by following formula [12]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

4.2.2.7. Determination of Hausner's ratio

The analysis was done in triplicate for each batch. The density determinations were used to determine the Hausner's ratio by following formula [12]:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

4.2.2.8. Determination of percentage buoyancy

The analysis was done in triplicate for each batch. The microspheres were spread over the surface of USP Type II dissolution apparatus filled with 900 ml of HCl (1.2 pH) containing 0.01% w/v of Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 h. The floating and the settled portions of microspheres were recovered, dried and weighed separately. Buoyancy percentage was calculated as the ratio of the mass of particles that remained floating and the total mass of the recovered microspheres.

4.2.2.9. Determination of percentage entrapment efficiency

The practical drug content was determined by UV analysis in triplicate for each batch. Entrapment efficiency was calculated using following formula [13]:

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

4.2.2.10. Determination of surface morphology

The morphological characterization of floating microspheres was carried out by Scanning electron microscopy (Quanta FEI 200F). The dried microspheres were coated with gold foil (100 Å) under an argon atmosphere in a gold coating unit and micrographs were obtained at both higher and lower resolutions.

4.2.2.11. Determination of in-vitro drug release profiles

In vitro drug release studies were carried out at 37°C for all batches using USP Type II dissolution test apparatus. Microspheres equivalent to 150 mg of the Venlafaxine HCl were used for the study. The dissolution studies were carried out using UV spectrophotometer (UV 3000$^+$, Lab India, Mumbai.) at 223 nm using dissolution media (pH 1.2 HCl Buffer and SGF). Sample (5 ml) were withdrawn at predetermined time interval, diluted suitably and analyzed at 223 nm. Analysis was done in triplicate for each batch [14].

Kinetics of drug release [15]: Zero order release kinetics refers to the process of constant drug release from a drug delivery device such as oral osmotic tablets, transdermal systems, matrix tablets with low-soluble drugs and other delivery systems.

$$Q = Q_0 + K_0 t$$

where Q is the amount of drug released (assuming that release occurs rapidly after the drug dissolves), Q_0 was the initial amount of drug in solution and K_0 was the zero order release constant. A plot of the percent of drug released against time will be linear, if the release obeys zero-order kinetics. The value of release rate constant k_0 was obtained in each case from the slope of cumulative percent drug released versus time plot.

The first-order equation describes the release from systems where the rate was concentration dependent. Where Q_0 was the initial amount of the drug, time 't' in minutes and k_1 described the dissolution rate constant for first-order release kinetics. A plot of the logarithm of cumulative percent of drug remained against time would be linear if the drug obeyed first-order release kinetics.

$$\log Q_t = \log Q_0 + \frac{k_1 t}{2.303}$$

Values of release rate constant k_t were obtained in each case from the slope of the log cumulative percent of drug remained versus time plots.

A plot of the fraction of drug released against square root of time would be linear if the release obeyed Higuchi's equation.

$$Q(t) = k_H t^{1/2}$$

where Q(t) is the percent of drug dissolved, time't' in minutes, k_H is the dissolution rate constant for square root of time kinetics in percent drug dissolved. Values of release rate constant k_H were obtained in each case from the slope of the cumulative percent of drug released versus square root of time plots.

Korsmeyer *et al*. (1983) derived a simple relationship which described drug release from a polymeric system. To find out the mechanism of drug release, first 60% drug release data were fitted in Korsmeyer-Peppas' model.

$$Mt / M\infty = Kt^n$$

where $Mt / M\infty$ is a fraction of drug released at time t, k is the release rate constant and n is the release exponent. The n value is used to characterize different release for cylindrical shaped matrices. In this model, the value of n characterizes the release mechanism of drug. To study the release kinetics, the values of the release exponent (n) and the kinetic constant (k) were determined in each case from the slope and y-intercept of logarithmic plot of cumulative percent of the drug released versus time, respectively.

Author contributions: Concept – S.K., R.M.; Design – S.K., R.M.; Supervision –R.M.; Resource – S.K., R.M.; Materials – S.K., R.M.; Data Collection and/or Processing - S.K., R.M.; Analysis and/or Interpretation - S.K., R.M.; Literature Search – S.K., R.M.; Writing – S.K., R.M.; Critical Reviews – S.K., R.M.

Conflict of interest statement: The authors declared no conflict of interest" in the manuscript.

REFERENCES

[1] Berton O, Nestler EJ. New approaches to antidepressant drug discovery: beyond monoamines. Nat Rev Neurosci. 2006; 7(2): 137-151.

[2] Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002; 34(1): 13-25.

[3] Awasthi R, Kulkarni GT, Ramana MV, Pinto TJA, Kikuchi IS, Ghisleni DDM, Braga MS, Dua K, Bank PD. Dual crosslinked alginate-pectin network as sustained release matrix for repaglinide. Int J Biol Macromol. 2017; 97: 721-732.

[4] Pawar VK, Kansal S, Garg G, Awasthi R, Singodia D, Kulkarni GT. Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems. Drug Deliv. 2011; 18(2): 97-110.

[5] Awasthi R, Kulkarni GT. Decades of research in drug targeting to the upper gastrointestinal tract using gastroretention technology: Where do we stand?. Drug Deliv. 2016; 23(2): 378-394.

[6] Blier P, Saint-André E, Hébert C, de Montigny C, Lavoie N, Debonnel G. Effects of different doses of venlafaxine on serotonin and norepinephrine reuptake in healthy volunteers. Int J Neuropsychopharmacol. 2007; 10(1): 41-50.

[7] Holliday SM, Benfield P. Venlafaxine: a review of its pharmacology and therapeutic potential in depression. Drugs. 1995; 49(2): 280-294.

[8] Omprakash B, Ajay S, Santosh G, Amin P. Formulation development of venlafaxine hydrochloride extended release tablet and *in vitro* characterizations. Int J PharmTech Res. 2012; 4(4): 1777-1784.

[9] Fentie M, Belete A, Gebre-Mariam T. Formulation of sustained release floating microspheres of furosemide from ethylcellulose and hydroxypropyl methylcellulose polymer blends. Nanomed Nanotechnol. 2015; 6: 1-5.

[10] Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: design and optimization using combination of polymers. Acta Pharm. 2008; 58(2): 221-229.

[11] Li Z, Xu H, Li S, Li Q, Zhang W, Ye T, Yang X, Pan W. A novel gastro-floating multiparticulate system for dipyridamole (dip) based on a porous and low-density matrix core: *In vitro* and *in vivo* evaluation. Int J Pharm. 2014; 461: 540-548.

[12] Awasthi R, Kulkarni GT. Development and characterization of amoxicillin loaded floating microballoons for the treatment of *Helicobacter pylori* induced gastric ulcer. Asian J Pharm Sci. 2013; 8(3): 174-180.

[13] Awasthi R, Kulkarni GT. Development of novel gastroretentive floating particulate drug delivery system of gliclazide. Curr Drug Deliv. 2012; 9(5): 437-451.

[14] Eberle VA, Schoelkopf J, Gane P, Alles R, Huwyle J, Puchkov M. Floating gastroretentive drug delivery systems: comparison of experimental and simulated dissolution profiles and floatation behavior. Eur J Pharm Sci. 2014; 58: 34-43.

[15] Awasthi R, Kulkarni GT. Development of novel gastroretentive drug delivery system of gliclazide: Hollow beads. Drug Dev Ind Pharm. 2014; 40(3): 398-408.

[16] Stepensky D, Friedman M, Sroar W, Raz I, Hoffman A. Formulation of controlled release dosage forms for metformin containing methocel K100M. J Control Release. 2011; 71: 107-115.

[17] Samani MS, Montaseri H, Kazemi A. Effects of polymer blends on the in vitro release profile of diclofenac sodium. Eur J Pharm Biopharm. 2003; 55: 351-355

[18] Christoper GVP, Raghavan CV, Siddharth K, Kumar MSS, Prasad RH. Formulation and optimization of coated PLGA – zidovudine nanoparticles using factorial design and *in vitro-in vivo* evaluations to determine brain targeting efficiency. Saudi Pharm J. 2014; 22: 133–140.

[19] Awasthi R, Kulkarni GT, Pawar VK, Garg G. Optimization studies on gastroretentive floating system using response surface methodology. AAPS PharmSciTech. 2012; 13(1): 85-94.