e-ISSN: 2320-1215
p-ISSN: 2322-0112

RESEARCH AND REVIEWS: JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

Formulation and Evaluation of Floatable *In-situ* Gel for Stomach-Specific Drug Delivery of Vanlafaxine HCL.

Mahak Shaikh, Aarti Mandloi, Vishnu Yadav, Gopkumar P. and Sridevi G*.

GRY Institute of Pharmacy, Vidya Vihar, Borawan, Khargone, Madhya Pradesh – 451228, India.

Research Article

Received: 21/01/2014
Revised: 28/02/2014
Accepted: 05/03/2014

***For Correspondence**

GRY Institute of Pharmacy, Vidya Vihar, Borawan, Khargone, Madhya Pradesh – 451228, India.

Keywords: Vanlafaxine HCL, in-situ gel, Sodium alginate, floating.

ABSTRACT

The present investigation deals with the formulation and evaluation of sodium alginate and HPMC based floating oral *in-situ* gel of Vanlafaxine HCL. Sodium alginate and HPMC were used as a polymer and CaCO3 was used as a cross-linking agent to form in-situ gels. The drug gets released in sustained and controlled manner from these types of formulations for prolonged duration thus reduces the dosing frequency of the drug. Formulation method of present study utilizes the polymers that exhibit sol-to-gel phase transition due to change in specific physicochemical parameters. Developed formulations were evaluated for their suitability to control the drug release and ease of administration by measuring the amount of drug entrapped, floatation duration, rate of drug release and pH and viscosity during sol gel transition etc. Results of the study indicated among the different batches of formulations with range of polymeric concentration and gelling stimuli, the formulation batch F1 was most suitable preparation being able to control the drug release for 24hrs duration with administration and physiological suitability in terms of pH and Viscosity. Thus results of the study concluded that very useful antidepressant drugs like Vanlafaxine HCL can be reformulated into more patient friendly and therapeutically beneficial formulations using these types of oral in-situ floatable gel systems, which reduces manufacturing cost and duration.

INTRODUCTION

The present research is about gastro retentive drug delivery systems in the form of *in-situ* gels. Advanced research is carried out to develop novel drug delivery systems to alter the pharmacokinetics of the drugs. Drug release from the delivery devices are usually sustained at the target sites for many drugs using current release technologies. The main accent during the development of oral controlled release dosage forms is to prolong the residence time of the dosage form in the stomach or upper gastrointestinal (GI) tract until the drug is completely released[1]. To achieve the retention of dosage unit in stomach many approaches have emerged like bioadhesive systems, swelling and expanding systems, floating systems, modified shape systems, high-density systems and other delayed gastric emptying devices [2,3,4]. Gel dosage forms are successfully used as drug delivery systems to control drug release and protect the medicaments from a hostile environment. In situ gel formulation has received considerable attention over the past few years and increasing number of in situ gelling systems have been investigated and many patents for their use in various biomedical applications including drug delivery have been reported. In situ gels are the liquid formulations which undergo conversion in to semisolid form under influence of various stimuli like change in pH, temperature, ionic environment etc.

FDDS are widely explored for gastro retention purposes and have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents, the drug is released slowly at a desired rate from the system. The gel formed from in situ gelling system, being lighter than gastric fluids, floats over the stomach contents or adhere to gastric mucosa due to presence of bioadhesive nature of polymer and produce gastric retention of dosage form and increase gastric residence time resulting in prolonged drug delivery in gastrointestinal tract[5,6]. In situ forming

gels are formulations, applied as a solution, which undergoes gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way, the polymers, which show sol-gel phase transition and thus trigger drug release in response to external stimuli, are the most investigated. In-situ hydrogels are providing such 'sensor' properties and can undergo reversible sol-gel phase transitions upon changes in the environmental condition[7]. These "intelligent" or "smart" polymers play important role in drug delivery since they may dictate not only where a drug is delivered, but also when and with which interval it is released. Sodium alginate (SA) is a widely used natural polymer in various drug delivery systems. It exhibits favourable biological properties such as non-toxicity, biocompatibility, biodegradability and ulcer healing traits. Moreover, gelation of dilute solutions of SA occurs on addition of di-and trivalent ions by a co-operative process involving consecutive G-residues in the a-L-guluronic acid blocks of the alginate chain in a manner described by the 'egg-box' model[8,9].

Venlafaxine hydrochloride has been selected as a model drug because it exhibits required pharmacokinetic and physico-chemical properties for controlled release. Venlafaxine hydrochloride is a unique antidepressant that differs structurally from other currently available antidepressants. It is a bicyclic phenylethyl 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] cyclo hexanol hydrochloride with a molecular formula of C17H27NO2HCl. This medication is used to treat anxiety. It acts by inhibiting selectively the uptake of serotonin and noradrenaline but shows no affinity for neurotransmitter receptors1It is a white crystalline solid, freely soluble in water (534mg/ml) & possess serotonin/noradrenaline uptake inhibiting effect. The dose of venlafaxine hydrochloride ranges from 75 to 350 mg/day12. The steady state half-life of venlafaxine is 5hrs, necessitating the administration 2 to 3 times daily, so as to maintain adequate plasma level of drug 13. Venlafaxine hydrochloride is currently available as immediate release tablets and as extended release capsules under the brand names of Effexor® and Effexor XR® (Weyth Ayerst).Majority of oral sustained and controlled release delivery systems of venlafaxine hydrochloride are based on either gel forming matrix or coated formulations or the combination thereof[10-13]. However, when compared with single or multiunit sustained release tablets, in-situ gels are very easy to manufacture and as these have better floating properties gastric transit of SR tablets problem can be avaoided.

MATERIALS AND METHODS

Materials

Sodium citrate, Sodium alginate, CaCl2 and CaCO3 were obtained from Qualigens Fine chemicals, Mumbai. HPMC K4M was gift samples from Manbrove pharma, Mumbai, Gift sample of Vanlafaxine HCL was kindly provided by Sun pharmaceuticals Ltd. Vadodara. Gujarat. All the other ingredients used were of analytical grade and used as received.

Method of preparation of in-situ gelling solutions [4,5]

Sodium alginate solutions of concentrations 0.25, 0.5, 1.0, 1.5 and 2.0% (w/v) were prepared by adding the alginate to deionized water, the HPMC K4M, HPMC K15M and HPMC K100M were also added in respective batch in different concentration, containing 0.25% (w/v) sodium citrate with stirring and calcium carbonate (prescreened by 60 #) was dissolved in another beaker along with Methyl Paraben and Propyl Paraben in 2: 0.2 ratios in purified water in sufficient quantity. Vanlafaxine HCL (2000 mg) was initially dissolved in hot water, then dissolved in 10 ml of 0.1N HCl solution (pH 1.2) and added to above solution. Concentrations of cations in solution were sufficient to hold the molecular chains together and inhibit hydration. Sodium alginate solution was heated to 70^{o}C with stirring. After cooling to below 40^{o}C, different concentrations of calcium carbonate and the drug solution were added and dispersed well with continuous stirring. This results in sodium alginate in-situ gelling solution containing venlafaxine which were checked for lag time, viscosity and gelling property. To achieve repeatability in gelation we used a source of Ca++ ions in the solution itself. Due to the free calcium ions being complexed with sodium citrate, gelation was delayed until the administered solution reached the acidic environment of the stomach. Gelation was then occurred as the complex broke down and the Ca++ ions were released. The calcium carbonate present in the gelling formulation released carbon dioxide in gastric environment thereby making the formulation porous and buoyant and prolonging the residence time.

UV Absorbance Maxima and Calibration Curve of Vanlafaxine HCL in 0.1 N HCl

Stock solution of vanlafaxine HCL in acid buffer with proper dilution was initially scanned in UV visible spectrophotometer within wavelength of 200-700 nm. For calibration, 100 mg of vanlafaxine HCL was dissolved in100 ml of 0.1N HCl. The solution was then diluted with 0.1 N HCl to obtain 20, 40,60, 80 and 100 µg/ml solution. It was then measured by UV visible spectrophotometer.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Identification of Drug by FTIR

Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer (Shimadzu 8400S, Japan). The pure vanlafaxine HCL were mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm-1, from 4000 to 400 cm-1.

Identification of Drug by DSC

The DSC study was carried out using DSC-60 (Shimadzu, Tokyo, Japan). The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. The drug were heated in sealed aluminum pans under air flow (30 ml/min) at a scanning rate of 20°C/min from 50 to 300°C. Empty aluminum pan was used as a reference. The heat flow as a function of temperature was measured for the samples.

Physical Appearance and pH

All the prepared batches of polymeric solutions of vanlafaxine HCL were checked for their clarity and the pH. After administration of the prepared solutions in 0.1 mol L^{-1} HCl, pH 1.2, the time required for gel formation and consistency of gel formed was checked visually. The pH was also measured in each of the solution of sodium alginate based in situ solutions of vanlafaxine HCL, using a calibrated digital pH meter at 25°C.

Viscosity measurement of the in-situ gelling solutions

Viscosity of the sols were determined using a Brookfield digital viscometer (Model no LVDV 2P230) with the spindle number 1. The temperature of the 5 mL samples was kept at 28 ±1 °C during each measurement which lasted 30 sec, and the experiments were performed in triplicate.

In-vitro buoyancy

The in-vitro buoyancy study was performed using the 100 mL of simulated gastric fluid (pH = 1.2) in a beaker kept under slow stirring using magnetic stirrer. The medium temperature was kept at 37°C. A 10 mL sample of the prepared solution (in-situ gelling formulation) was drawn up with the help of a disposable syringe and injected into the beaker containing the medium without much turbulence [7]. The time for the gel to come to surface (floating lag time) and the time the gel remained floated on the medium surface (floating time) were recorded.

In-Vitro Gelling Capacity[5,7]

The in-vitro gelling capacity of prepared formulations was measured by placing five ml of the gelation solution (0.1N HCl, pH 1.2) in a 35 ml borosilicate glass test tube and maintained at 37±1°C temperature. One ml of gel formulation solution was added with the help of pipette. As the solution comes in contact with gelation solution, it was immediately converted into stiff gel like structure. The gelling capacity of solution was evaluated on the basis of stiffness of formed gel and time period for which the formed gel remains as such. The in-vitro gelling capacity was graded on the basis of gelation time and time period for which the formed gel remains.

Drug Content

Ten mL of the solution was added to 900 mL of simulated gastric fluid (0.1 mol L^{-1}HCl, pH 1.2) and stirred for 1 h on a magnetic stirrer. The solution was filtered, suitably diluted with simulated gastric fluid and the drug concentration was determined by using a UV-visible spectrophotometer a (UV-1601 Shimadzu, Japan) 227nm against a suitable blank solution.

Swelling Index[5]

A gel of 100mg was weighed accurately (W1). It was kept in a petridish and 50ml of 0.1 N HCl was added. The petridish was kept aside for 24 hrs. The weight of swollen matrix gel (W2) was measured and swelling index was calculated using following formulae: Swelling Index = (W2-W1/W1)*100 Where, W1 = initial weight of gel (100mg), W2 = weight of swollen matrix after 24 hrs.

In- Vitro Drug Release[13,14]

The release of drug from the formulations was determined using a USP/24 dissolution test apparatus with a paddle stirrer at 50 rpm. The dissolution medium used was 900 mL of simulated gastric fluid (0.1 mol L^{-1}HCl, pH 1.2) and temperature was maintained at 37 ± 0.2 °C. Ten mL of the formulation was added into the dissolution

e-ISSN: 2320-1215
p-ISSN: 2322-0112
vessel containing simulated gastric fluid avoiding any disturbance using test tube. At each time interval, a precisely measured sample of the dissolution medium was pipetted out and replenished with fresh medium. Drug concentration in the aliquot was determined spectrophotometrically. Each study was conducted in triplicate.

Kinetic analysis of release data [14,15,16,17]

The dissolution data obtained was fitted to Zeroorder, First order, Higuchi,Hixon -Crowell and Korsmeyer-Peppas equations to understand the rate and mechanism of drug release from the prepared formulations. The correlation coefficients values were calculated and used to find the fitness of the data.

Zero order equation Q t = Qo + Kot [14], describe the systems where the drug release rate is independent of concentration of the dissolved substance, where, Qo = initial amount of drug, Qt =cumulative amount of drug release at time t, Ko=zero order release constant, t = time in h

First order release equation Log Qt = Log Qo +Kt/2.303 [15], the drug release rate depends on its concentration, where, Qo = initial amount of drug, Qt = cumulative amount of drug release at time t, K = first order release constant, t = time in h

Hixon-crowell equation Mo1/3 - Mt1/3=K [16], describes the drug release by dissolution and with the changes in surface area and diameter of the particles or tablets. Mo = Initial amount of drug, Mt = Cumulative amount of drug release at time t, K = Hixson-crowell release constant, t = time in h. Higuchi release equation Q=KH t½ or Mt/Mo =Kt½[17] , the Higuchi equation suggests that the drug releases by diffusion mechanism. Q = cumulative amount of drug release at timet, KH = Higuchi constant ,t = time in h

Korsmeyer-Peppas: F = (Mt /M∞) = Km t n [17], which described drug release from a polymeric system, Where F=Fraction of drug released at time t, Mt=Amount of drug released at time t, M∞=Total amount of drug in dosage form, Km= Kinetic constant, ent, t = time in h. Similarity factor (f2) analysis

In-vitro drug release profile of Venlafaxine HCl floting in-situ gel drug release was compared with drug release profile of marketed formulation VENTAB® XL75 tablets under similar experimental conditions. The data obtained from in vitro drug release was used to determine the similarity factor between marketed and optimized product. Similarity factor was calculated using the formula, f2=50 log {[1+ (1/N) Σ (Ri –Ti)2] -0.5 X100}, where N is number of time points, Ri and Ti are dissolution of reference and test products at time i respectively. F2 values greater than 50 considered as product similarity between two products and have similar drug release behavior.

RESULTS AND DISCUSSION

Absorbance Maxima and Calibration Curve of Vanlafaxine HCL in 0.1 N HCl

Absorption spectrum of Vanlafaxine HCL indicated λmax at 227 nm which is very close to its reported λmax value that is 226nm.

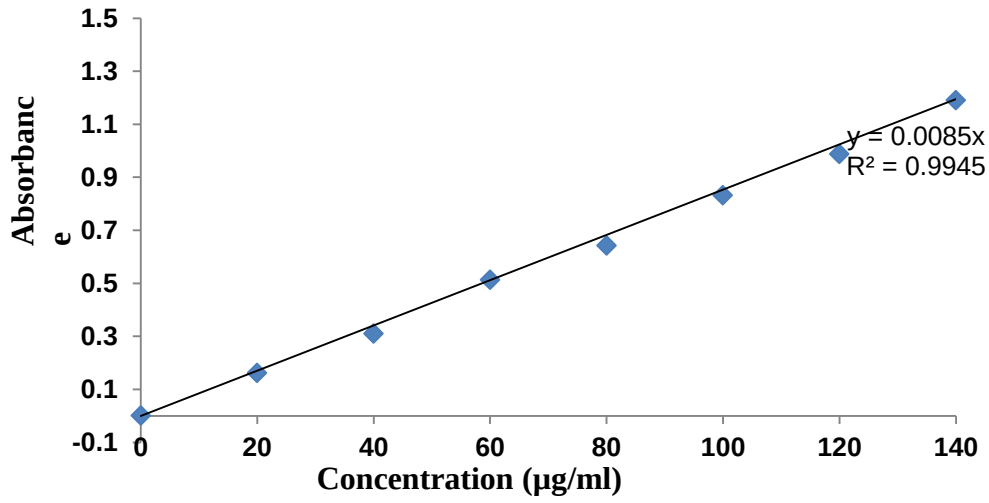

Figure 1: Calibration Curve of venlafaxine HCL

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Identification of Drug by FTIR

Identification of drug was performed using FTIR spectrophotometer. The characteristic absorption peaks of pure drug obtained in the spectra correlates with the peaks of official spectrum of Pharmacopeia which confirms the purity of drug. The stability of the drug and sodium alginate in presence of each other was studied by IR spectroscopy and DSC. The characteristic peaks remain unaltered in the combination formulation, which indicated that no major interaction occurred between the functional groups of drug with the other ingredients.

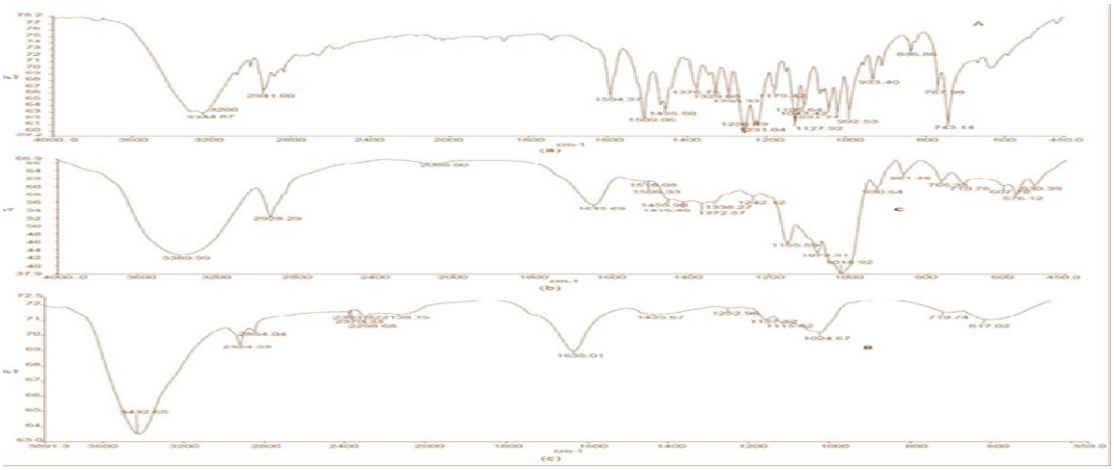

Figure 2: FT-IR spectra of A) Vanlafaxine pure drug B) Sodium alginate and C) Both in combination.

FTIR spectrum of venlafaxine which shows

Functional Group	Peaks of functional groups (cm^{-1})
CH- stretching (Aromatic)	3012.01
CH- stretching (Aliphatic)	2928.09
C=C stretching	1635.13
C-N stretching	1509.85
C-O stretching	1455.01
OH stretching	3344.64

Identification of Drug by DSC Spectra

The DSC thermograph of the pure drug, sodium alginate, and combination formulation were obtained (Figure 3). The DSC thermogram analyses was conducted to explore the melting activities of drug. DSC analysis figure (3-a) showed a endothermic onset of peak at 217.5°C corresponding to venlafaxine melting point.

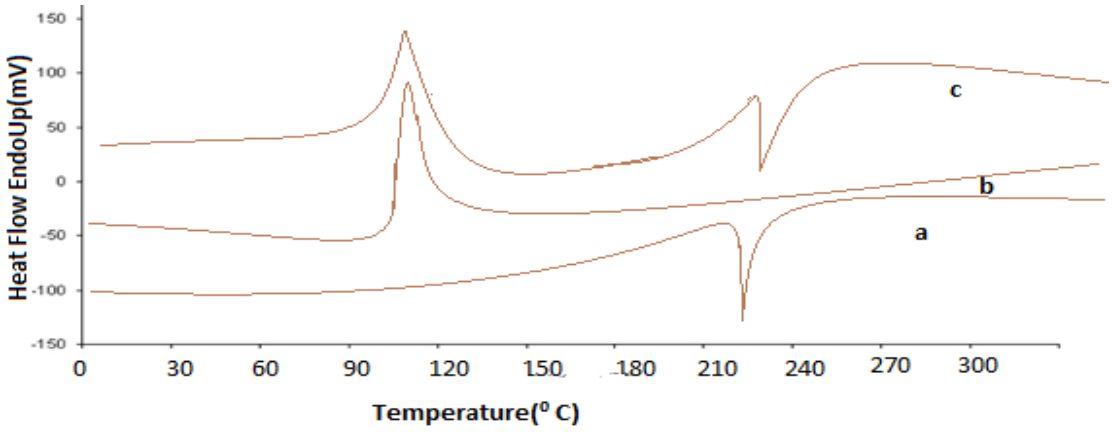

Figure 3: DSC thermograph of the pure drug, sodium alginate, and combination

e-ISSN: 2320-1215
p-ISSN: 2322-0112

Figure (3-b) shows that sodium alginate has a broad band ranging from 100 °C to 110 °C. Figure (3-c) shows the DSC thermograms of drug physical mixture with sodium alginate in a molar ratio of 1:1.. The thermograph of the drug-loaded formulation showed peaks related to drug (217.5°C,) and sodium alginate (105.54°C). This confirmed that the presence of other excipients did not affect the drug stability.

Physical Appearance and pH

Physical characterization parameters are reported in table 1. All the formulation had off white to pale yellow colored solution. They had pH in the range of 6.9 -7.5.

Viscosity of In Situ Gelling Solutions

The viscosity of the formulations increased with an increase in sodium alginate and HPMC concentration. This phenomenon is a consequence of increasing chain interaction with an increase in polymer concentration. Calcium carbonate, which is the source of cations, increased the viscosity of the formulation. This change in viscosity is due to the proportional increase in the amount of dispersed calcium carbonate. Formulation viscosities are tabulated in table 1.

Floating Behavior

The buoyancy lag time varied with the formulation variables. Formulation F5 exhibited the least buoyancy lag time (28s) while formulation F1 exhibited the highest lag time (111 s). Irrespective of formulation variables, buoyancy duration was more than 20 hours. All the prepared batches were evaluated for their floating properties in simulated gastric fluid. The time for formulation to come to the medium surface (floating lag time) and the time period for which the formulation maintained floated on the medium surface (duration of floating) were determined (Table 1).

Table 1: Table indicating the results of physical and formulation properties of optimum formulations

Evaluation Parameters	Formulation Code				
	F1	F2	F3	F4	F5
pH	7.0	7.5	7.1	7.4	6.95
Viscosity (cps)	315	320	310	310	315
In-Situ Gelling Time (Sec)	29	28	30	30	28
Floating Lag Time (min)	< 2	<2	<2	<2	<2
Floating Time (Hrs)	> 20	> 20	> 20	> 20	> 20
Type of gel and gelling capacity (Hrs)	Stiff, > 24hrs	Stiff,> 24hrs	Stiff,> 24hrs	Stiff,> 24hrs	Stiff,> 24hrs
Swelling Index (%)	80.9 ±3.25	80.1 ±2.73	85.5 ±2.51	80.3 ±1.73	80.2 ±1.887
% Drug Content	99.4±0.4	97.2±0.40	97.7±0.3	98.5 ±0.27	99.4±0.33

Upon contact with an acidic medium, calcium carbonate effervesced, releasing carbon dioxide and calcium ions. Then, gelation and cross-linking by Ca++ ions took place to provide a gel barrier at the surface of the formulation. The released carbon dioxide was entrapped in the gel network producing a buoyant preparation, which resulted in extended floating. *In-vitro* gelling capacity and % Swelling index of various formulations were reported in table no.1. The Drug content of all (F1-F5) formulations is given in table no 1. It ranges in between 99% - 97.%. The values are acceptable as per united states pharmacopeia standards.

In-Vitro Drug Release

The *in-vitro* drug release of the in situ floating gel were carried in 0.1N HCl from 0 to 24 hrs by USP type-II apparatus. The plot of % Cumulative drug release v/s time (hrs) was plotted and depicted as shown in figure no.4.

Initially, the drug was released at a faster rate due to the burst effect. As the percentage of calcium carbonate increased, the release rate decreased due to the stronger gel formation occurred. The lowest amount of calcium carbonate which produced a buoyant gel system for the 24 hrs duration of drug release study was found to be 0.7% at all polymer levels. On increasing the calcium carbonate concentration, the floating time was reduced significantly. Increasing calcium carbonate concentration in formulations increased the viscosity at all polymer concentrations studied. The drug release from the gel was characterized by an initial phase of high release (burst effect). However, drug was release was at a slower rate in the second phase due to swelling of gelation polymer, i.e. a moderate release rate. The initial burst effect was considerably reduced with an increase in polymer concentration.

e-ISSN: 2320-1215
p-ISSN: 2322-0112

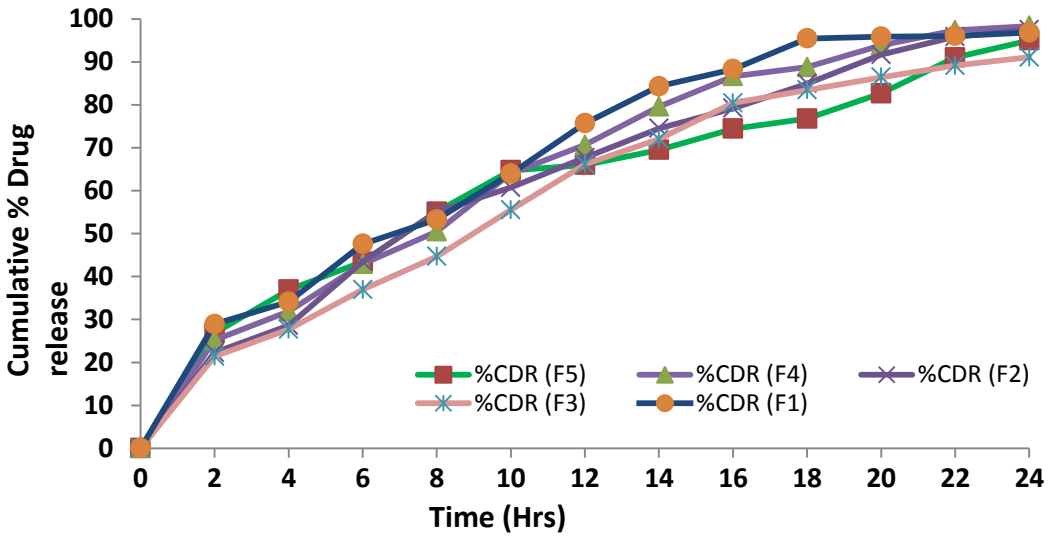

Figure 4: Graph of *In-vitro* drug release behavior from optimized formulations

Kinetic of Drug Release

Table No. 2: Table showing the release kinetic model with values of rate constant and regression coefficient.

Formulation Code	Zero-order Model		First-order Model		Higuchi- Model		Kors-peppas Model		Best-Fit Model
	K_0	R^2	K_1	R^2	K_H	R^2	K_{KP}	R^2	
F1	23.88	0.921	1.1733	0.967	5.304	0.984	-0.381	0.715	Zero, Higuchi
F2	21.89	0.818	1.294	0.87	4.02	0.961	-0.247	0.776	Zero, Higuchi
F3	20.91	0.913	1.7701	0.892	-0.212	0.983	-0.798	0.731	Zero, Higuchi
F4	11.56	0.856	1.677	0.85	4.29	0.993	0.0891	0.715	Zero, Higuchi
F5	9.22	0.8613	1.432	0.92	1.0377	0.996	-0.693	0.669	Zero, H

The dissolution drug release profile was plotted as cumulative % drug release v/s time curve as shown in figure 4. The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. Results were shown in table 2**.** The model that best fitted the release data was selected based on the correlation coefficient value (r2) obtained from various kinetic models. *In-vitro* drug release profile from all these formulations could be best expressed by Korsmeyer-Peppas and Higuchi equation as plot showed highest linearity with r2 value 0.976-0.998 (table 4). The release of drug from the in-situ gel followed higuchi model and the release process was found to occur by an non fickian diffusion-controlled mechanism as n value obtained for the best fit model was above 0.45 and below 0.85. The correlation coefficient (R2), Sum of square (SSQ) and Release constant also calculated to found fit the higuchi models in a more impeccable way than other.

ACKNOWLEDGEMENT

Authors wish to thank JNCETrust and Principal GRY Institute of Pharmacy, (India), for extending all the required laboratory facilities and support for the present work.

REFERENCES

1. Singh B, Kim K. Floating drug delivery systems: An approach to oral controlled drug delivery via gastric retention. J Control Rel. 2000;63:235-59.
2. Colombo P, Bettini R, Santi P, Peppas NA. Swellable matrices for controlled drug delivery: Gel layer behavior, mechanism and optimal performance. Pharm Sci Technol Today. 2000;3:1-8.
3. Deshpande AA, Rhodes CT, Shah NH, Malick AW. Controlled-release drug delivery systems for prolonged gastric residence: An overview. Drug Develop Ind Pharm. 1996;22:531-9.
4. Ganguly S and Dash AK, A novel in situ gel for sustained drug delivery and targeting. Int J Pharm. 2004; 276:83–92.

5. Ganapati R, Bhimagoni K and Sridhar AS. Floating Drug delivery of a locally acting H2 antagonist: An approach using an in situ gelling liquid formulation. Acta Pharmaceutica. 2009; 59:345–354.
6. Wamorkar V, Varma MM, and Manjunath SY, Formulation and Evaluation of stomach specific In-Situ gel of Metoclopramide using Natural, Bio-Degradable polymer. Int J Res Pharm Bio-Med Sci. 2011;2(1):193.
7. Rajinikanth P S, Balasubramaniam J and Mishra B. Development and evaluation of a novel floating in situ gelling system of amoxicillin for eradication of Helicobacter pylori. Int J Pharm. 2007;335:114–122.
8. Modasiya MK, Prajapati BG, Patel VM and Patel JK. Sodium alginate based insitu gelling system of famotidine: preparation and in-vivo characterizations. J Sci Technol. 2006;27:391.
9. Patel JK, Chavda JR and Modasiya MK "Floating In situ Gel based on Alginate as Carrier for Stomach-Specific Drug Delivery of Famotidine. Int J Pharm Sci Nanotechnol. 2010;3(3):1092-1104.
10. Muth EA, Moyer JA, JT Haskins, Andree TH, Husbands GEM. Biochemical, neurophysiological and behavioural effects of Wy-45,233, its enantiomers and otheridentified metabolites of the antidepressant venlafaxine. Drug Dev Res. 1991;23:191–199.
11. Cusack B., Nelson A. and Richelson E.,Binding of antidepressants to human brainreceptors: focus on newer generation compounds, Psychopharmacol. 1994;114:559–565.
12. Muth EA, Haskins JT, Moyer JA, Husbands GE, Nielson ST, Sigg EB. Antidepressant biochemical profile of the novel bicycliccompound Wy-45,030, an ether cyclohexanol derivative, Biochem Pharmacol. 1986;35: 4493–4497.
13. Madgulkar AR, Bhalekar MR, Kolhe VJ, Kenjale YD. Formulation and optimization of sustained release tablets of venlafaxine resonates using response surface methodology, Indian J Pharm Sci. 2009;71:387-394.
13. Wagner JG. Interpretation of percent dissolved-time plots derived from *in vitro* testing of conventional tablets and capsules. J Pharm Sci. 1969;58:1253-7.
14. Higuchi T. Mechanism of sustained-action medication: Theoretical analysis of rate of release of solid drugs dispersed in solid matrices. J Pharm Sci. 1963;52:1145-9.
15. Hixon AW, Crowell JH. Dependence of reaction velocity upon surface and agitation. Ind Engg Chem. 1931; 23:923-31.
16. Korsmeyer R, Gurny R, Peppas N. Mechanisms of solute release from porous hydrophilic polymers. Int J Pharm. 1983;15:25-35
17. Peppas NA. Analysisof Fickian and non-Fickian drug release from polymers. Pharm Acta Helv. 1985; 60:110-1.