INNSPUB

International Journal of Biosciences | IJB |
ISSN: 2220-6655 (Print), 2222-5234 (Online)
http://www.innspub.net
Vol. 6, No. 12, p. 90-107, 2015

RESEARCH PAPER OPEN ACCESS

Evaluation of Polysaccharides isolated from *Psyllium* husk and their potential for designing controlled release floats of levoflaxacin

Abdul Karim*, Tahir Mehmood, Muhammad A. Shaheen, Muhammad Imran Irfan, Qudsia Tabassam, Sehrish Shafique

Department of Chemistry, University of Sargodha, Sargodha, Pakistan

Key words: Levoflaxacin, floating tablet, psyllium husk, drug release study, kinetic models, Gel, GPC, TGA, Factorial design, Drug release, linear regression analysis.

http://dx.doi.org/10.12692/ijb/6.12.90-107 Article published on June 30, 2015

Abstract

The present investigation deals with the development and optimization of gastro-retentive tablets of levoflaxacin. The psyllium husk gel was isolated and further fractionated using solvent technique. The isolated polysaccharides fractions were used as matrix for tablet formulation and characterized by techniques FTIR, TGA and GPC. Tablets prepared by effervescence technique were characterized by SEM, and FTIR spectroscopy for surface morphology and excipients–drug interaction analysis respectively. The psyllium gel fractions in combination with stearic acid, linseed gel and tragacanth were selected as independent variables for different batches. Levoflaxacin floats were prepared by direct compression technique and evaluated for drug content, uniformity of weight, friability, buoyancy and *in vitro* drug release studies. Optimized formulations were selected using mathematical tools (kinetic study & linear regression analysis) to determine the effect of variables and closeness amongst predicated and experimental drug release data. The acetic acid extracted fraction (ANa) was found to be most drug release retardant and formulation S_4F_1 was found to be most suitable due to better swelling ability, lag time, drug release retarding ability and best fitness to Higuchi's square root model (R^2 = 0.976) and power law (R^2 = 0.971). The value of n = 0.476 showing that the drug release pattern was found to be Fickian diffusion.

* **Corresponding Author:** Abdul Karim ✉ karimiq65@gmail.com

Introduction

The natural polysaccharides and their derivatives represent a group of polymers which are abundantly used in pharmaceutical formulations of different types of dosage forms where they play a vital role as binders, film formers, release modifiers, viscosity enhancers and stabilizers (Guo, Skinner, Harcum, & Barnum, 1998; Beneke, Viljoen, & Hamman, 2009). In several cases, carbohydrates, proteins, gels and hydro-gels are being used as a matrix and their usage depend upon the way in which the drug is found within the polymer. The polymers which are generally used as retardant in controlled drug delivery systems have no specific therapeutic value. Now a day,main interest lies in therapeutic importance of drug release retardants. The PH (psyllium husk) is a traditional herbal product and its therapeutic importance is well known throughout the world. It is widely used as medicine in several parts of the world including Pakistan for treatment of chronic diseases i.e. attenuation of blood glucose, possessing anti carcinogenic effect for colon and breast cancer, constipation, coronary heart diseases etc. Its use as a matrix for different types of drugs is under trial (Iqbal, Akbar, *et al.*, 2011; Kokate, Purohit, *et al.*, 2005; Iqbal, Akbar, *et al.*, 2011; Kokate, Purohit, *et al.*, 2005; (Bharanda, Gohal, 2006). The swelling and reswelling is major requirement for sustained release of drug which is apparently present in Psyllium husk. Its swelling and gelling properties is reported in literature (Kennedy, Sandhu, *et al.,* 1999; Yasir, Asif, *et al.,* 2010; Seth, & Tossounian, 1991; Saghir, Iqbal, Koschella & Heinze, 2009; Iqbal, Akbar, *et al.,* 2011; Iqbal, Shazma, *et al.*, 2013; Iqbal, Jamshed, *et al.*, 2011). The thermal study reveals that it is stable at room temperature (Desai, Shidhaya, *et al.*, 2007). Recently a novel edible/biodegradable film has been prepared from HG using glycerol as plasticizer for preservation of food (Saboji, Gadve, *et al.*, 2012). In the present study, focus was towards the development of new hydro-gels as matricing agent for floats. It was preferred over synthetics material due to its multiple benefits i.e. chemically inert, non-toxic, low cost of production, ease of availability, high affinity for water (swelling index is about 20 times in volume). It is water insoluble and mechanical action of an alimentary canal cannot assimilate it. It forms supra molecular structures (matrices) which are appropriate for retaining and controlling the release of drug. There are so many mechanisms for controlling the drug release (Uhrich, Cannizzaro, *et al.*, 1999**)** and one such mechanism like swelling by hydration is apparently present in the psyllium husk gel which causes an increase in pore size of polymeric structure and allows the diffusion of aqueous medium for releasing the loaded drug.

The model drug is levoflaxacin which has antimicrobial effectt for the treatment of a variety of infectious diseases (Joseph, T., 2001; Data pharm. communications, 2002; Pharmacopoeia of India, 2007; Rang, H.P., Dale, M.M, *et al.*, 1954). It is safe and effective in first, second and third line for *H. pylori* eradication and this eradication rates is found to be > 90%. The failure of levoflaxacin for antibiotic therapy for the treatment of *H. pylori* is due to non-availability of effective concentration of drug at the site of action (Dicaro, S., Zocco, A. M., *et al.*, 2002; O' Morain, C., 2005; Watanabe, Y., Aoyama, N., *et al.*, 2006; Majithiya, R.J., Murthy, R.S.R., 2005; Cooreman, M.P., Krausgrill, P., *et al.*, 1993; Thakkar, V.T., Shah P.A., *et al.*, 2008). For effective eradication of *H. pylori,* extended resident time of the antimicrobial agents is most desirable (Shah, S., Qaqish, R., *et al.*, 1999). The rapid gastro-intestinal transit could result in incomplete drug release from the drug delivery system above the absorption zone leading to diminished efficacy of administered dose against *H. pylori* which have been recognized as a major gastric pathogen with worldwide distribution (Warren, J. R., Marshall, B. 1983). *H. pylori* are causative organisms in duodenal ulcers, chronic active gastritis, gastric adenocarcinoma and human-specific pathogen (Megraud, F., Lamouliatte, H., 1992; Forman, D., Webb *et al.*, 1994). *In vitro*, it is susceptible to eradicate it by many antibiotics but it is difficult *in vivo* (Evans, D. G., Evans *et al.*, 1992). Currently it is available in the forms of tablets, Single –use vials and infusions. Chemically it is a chiral fluorinated carboxyquinone and pure (-)(S)

enantiomer of racemic drug substance ofloxacin. Its solubility is 100 mg/mL in pH range from 0.6 to 5.8 and above this it increases rapidly to its maximum level (272 mg/mL) at pH 6.7 and is almost freely soluble.

The objective of present study was to prepare gastro-retentive control release floats to hang the drug for maximum time in gastric environment. These fractions me*et* all the physiological requirements which are needed for designing the floating drug delivery system i.e. insolubility in water, high swelling and re-swelling ability and low density. Citric acid/$NaHCO_3$ was added to decrease the lag time and increase the retention time in the upper GIT (gastrointestinal tract) to enhance the absorption and thereby improving the bioavailability. In the present study, an attempt has been made to formulate floats of levoflaxacin using a combination of hydrophilic and hydrophobic matricing agents. The change in composition of matricing agents may influence the change in mechanism of drug release. The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order, Power law and Higuchi release models (Costa, P., Lobo J, M.S., 1987; Wagner, J.G., 1969; Schefter, E., Higuchi, T., 1963). The interpretation of data was based on the value of resulting regression coefficients (R^2) (Table-4) and highest regression coefficient values for Higuchi's model indicates diffusion is the predominant mechanism of drug release. The main target was to improve bioavailability of drug by extending its residence in stomach and finding of best formulations by using low cost swellable therapeutic matrix for designing the floats. The prepared floats were evaluated for drug release % at different time intervals, lag time, similarity factors and difference factors (Milton, H., Fischer, *et al.*, 2004).

Material and methods

The psyllium seed husk (PH), linseed seed gel (LG), tragacanth gel (TG) was purchased from local market and levoflaxacin was taken from local pharmaceutical industry. Other chemicals were purchased from different international firms; CH_3COOH, C_2H_5OH, CH_3OH, Mg stearate (Merck), 38% HCl, NaOH, $NaHCO_3$ (ICI Ltd) and $CHCl_3$, $(CH_3)_2CO$ (Sigma-Aldrich). The double distilled H_2O was prepared on freshman–4 distillation unit. All chemicals were used without further purification.

Isolation of gel

The HG was isolated according a published method ((Saghir, Iqbal, Koschella & Heinze, 2009) with little modification. *Psyllium* husk (20 g) was placed in 1 L deionized water and kept overnight for complete swelling. The swelled mass was dissolved in appropriate amount of 0.4M NaOH solution with continuous stirring. After filtration, acetone was added in filtrate to coagulate the gel again. The separated gel was dialyzed, dried, ground to fine powder and used as matrix to make gastro-retentive floats. Other gel fractions were also obtained in similar way using other coagulating solvents such as methanol, ethanol and chloroform etc (Figure 1). After separation, each fraction was dialyzed thoroughly with distilled water. The purified gels were dried and ground to fine powder.

Characterization of gels (Instrumentation)

Elemental analysis

The elemental analysis of all the samples was performed on CHNS analyzer and their average was reported.

FT-IR

The FT-IR spectra of all samples were recorded on the spectrometer (IR Prestige-21 Shimadzu, Japan) using *anhydrous* KBr-pellet technique. The freeze dried samples were heated at 60°C under vacuum for 30 h. The dried samples were grinded to fine powder. The KBr discs of testing samples were prepared by applying 60 kN pressure. Thermal analysis was carried out with a simultaneous thermal analyzer, SDT, Q-600 (TA USA) under N_2 at multiple heating rate of 100 cm^3 $min^{-1}$with 10°C, 15°C and 20°C min^{-1} heating rate in the temperature range ambient to 600 °C using platinum crucible to determine the degradation pattern, thermal stability, heat flow, activation temperature and glass transition

temperature. Activation energy (Ea) and pre-exponential factor (A) for a major stage of decomposition were determined by Broido's method (Broido, 1969) using Eq. 1.

$$\ln\{\ln(1/y)\} = -Ea/RT + \ln ART^2_m/Ea \quad (1)$$

Where $y = (W_t - W_\infty)/(W_o - W_\infty)$, W_t is the weight of the sample at any time t, W_o= initial weight and W_∞= final weight; R=general gas constant; Θ = heating rate and Tm = temperature for maximum reaction rate. A plot of lnln(1/y) against1/T gives a straight line, the slope of which gives Ea and intercept gives A. The kinetic parameters are better estimated by use of multiple heating rate methods however, single heating rate methods are being used by several researchers (Madani, 2011; Spencer & Kohl, 2011).The integral procedural decomposition temperature (IPDT) and comprehensive index of intrinsic thermal stability (ITS) by Doyle's method (Doyle, 1961) was used to determine thermal stabilities of hydro-gels. Standard equations (Adel *et al.,* 2010; Ghaemy & Amini Nasab, 2010; Mallak pour & Dinari, 2010) were used to determine the entropy of activation (ΔS*), free energy of activation (ΔG*) and enthalpy of activation (ΔH*). Universal Analysis 2000 software, version 4.2E (TA Instruments, USA), and MS Excel® 2010 was used to analyze the data.

Gel proliferation chromatography (GPC)

Various GPC parameters including molar mass of husk fractions were determined by GPC. The GPC parameters are defined as: M_n is the average molar mass base on number of molecules (N_i) in a particular weight class (M_i)

$$M_n = \sum N_i M_i / \sum N_i$$

M_w is the average molar mass based on weight fraction of molecules (W_i) in a particular weight class (M_i):

$$M_w = \sum N_i M_i^2 / \sum N_i M_i$$

M_z is defined as:

$$M_z = \sum N_i M_i^3 / \sum N_i M_i^2$$

The polydispersity index was calculated from ratio of different average molar masses (Eq. 2) which is known as (PDI).

$$PDI = M_w / M_n. \quad (2)$$

The GPC analyses were carried out on an Agilent Technologies 1200 Series USA calibrated with pullulan and dextran standards (from Polymer Standards Service, Germany). The system was equipped with two columns using dimethyl sulphoxide (Me_2SO) as eluent with flow rate 0.5 mL min^{-1} at 70°C using 50 µL injection volumes.

SEM studies

The samples were taken in powder form. Before scanning electron microscopy (SEM), the pellets of husk fractions were prepared under high pressure (3000 psi) by hydraulic press. The pellets were mounted with the help of Ag-paint on Al-stubs and subsequently were coated with Au. The measurements of samples were carried out with SEM (JEOL, JSM-6480 LV, Japan). At accelerating voltage 10 kV, the micrographs at different magnifications were taken.

Thermal analysis (TA)

The TA of all samples, isolated by different solvents (fig. 2.1), was carried out under atmosphere of N_2 at 20°C min^{-1} in 20-700°C range using platinum crucible. Some samples were analyzed at multiple heating rates (10, 15, 20°C). The Broido method was used to calculate the activation energy (E_a) from the slope of line by least square methods by plotting the graph between lnln (1/y) along y-axis *versus* 1000/T along x-axis. According to Broido,1969.

$$\ln\ln(1/y) = -(E_a / R)(1/T) + \text{constant}$$

where T is temperature (K), R = general gas constant (8.31 JK^{-1} mol^{-1}), $y = (m_t - m_f) / (m_o - m_f)$ where m_t is weight of polymer at temperature T, m_o is the mass at initial temperature of particular decomposition stage and m_f is the mass at the final temperature of particular decomposition stage, so we can rearrange Broido equation as,

$$E_a = -(\text{slope} \times 8.314).$$

Statistical analysis

In this study 3^2 full factorial designs was used to design the formulations considering two factors at three levels (Table-1) and Regression analysis was used to analyze the effect of independent variables on drug release percentage. Results of all independent factors were calculated using the statistical model;

$S\% = ß_0 + ß_1 X_1 + ß_2 X_2 + ß_{12} X_1X_2 + ß_1 X_1^2 + ß_2 X_2^2$

Where S% is the level of response variable (% release of drug); ß is the regression coefficient; X_1 and X_2 stands for the main effect; X_1X_2 is the interactions between the main effects and X_1^2 and X_2^2 are quadratic terms of the independent variables.

Preparation of matrix tablets

Tablets were prepared by wet granulation technique using a wetting solution of ENa. Powdered drug and the ENa were passed separately through sieve no.16. Drug and excipients were mixed geometrically according to factorial model (Table 1). The ENa was poured in drug solution and kept for swelling. After maximum swelling, whole material was fed in to long tube of non-sticky surface having construction like air pump fitted with heater (45°C). The material was sprayed through small orifice on interior side of a drum fitted with heater from outer side. The dried granules were collected and compressed under force 10 kN on a rotary tablet press fitted with 9 mm flat punches; ^{i}PrOH was sprayed to smooth the swelling and Mg stearate was added as a glident before compressing for compression of tablets.

Calibration curve

A stock solution of Levo (100 mg/ mL) was prepared in 0.1 N HCl. It was further diluted to obtain the known standard solutions in the range of 1–10 µg/m L. Hydrochloric acid (0.1 N HCl, pH 1.2) was prepared by adding 8.5 mL concentrated acid to 991.5 mL of double-distilled water with cooling. The absorbance was measured spectro-photometrically (Shimadzu UV/Vis spectrophotometer 2100, Tokyo, Japan) at 293 nm with the mean data (n = 6) used for the calibration curve. The concentrations of dissolved drug in the formulations were calculated from the regression equation obtained from the calibration curve (Figure 2).

$y = 0.055 \times \text{concentration} + 0.009$.

Analysis of drug content, friability and stability study

Ten tablets of each batch were finely grinded and an amount equal to 100 mg was accurately weighed and transferred to 100 mL volumetric flask and filled with solution of pH 1.2 to the mark after mixing the contents. The mixture was filtered and 1mL of filtrate was suitably diluted to obtain a solution containing 100 µg mL^{-1} of levoflaxacin and analyzed at λ_{max} 293 nm using UV/Vis spectrophotometer. After analysis, friability was determined under standard conditions using tablet tester. Weighed tablets were placed in a drum revolving at 30 rpm min^{-1} for 100 revolutions for 5 min. The tablets were dusted off and weighed again. The friability was calculated from % loss in mass.

Friability = (initial mass of sample - final mass) / initial mass of sample × 100.

Dissolution study

The drug release profile was studied by using USP paddle dissolution apparatus II at 37°C± 0.1°C and 50 rpm. The buffer solution of pH 1.2 (900 mL in each beaker) was used as dissolution medium. At predetermined time intervals, 5 mL sample was withdrawn with special collecting syringe, filtered, suitably diluted and analyzed spectro-photometrically using Schimadzu UV-1700 double beam spectrophotometer at λ_{max} 293 nm. After removal of sample solution, same amount of dissolution medium stored at same temperature was added to keep the total volume 900 mL. The amount of drug released was expressed as the percentage of the total loaded drug.

Result and discussion

Characterization of gel

Elemental analysis

The elemental analysis shows that the HGs are free from nitrogenous matter (proteins).Three different

samples of each were analyzed and no evidence of N_2 in any sample was found. The percentage of C was found to be lower (40.2% against 45.0%) and H higher (6.5% against 6.0%) as observed in other natural polysaccharides. This difference was due to its better H_2O upholding capability. When same procedure was repeated with air dried samples, the % of H was lesser (5.8%) than freeze dried samples (6.5%). This difference was might be due to better drying on exposure to air. This is evident from its physical state which indicates that freeze dried samples were soft and flexible where air dried samples became hard and crunchy.

Table 1. Formulations for floating release tablets of Levo (250 mg).

Batches	Variables	Materials	Low (-1)	Medium (0)	High (+1)	Constant*
1st	X_1	ANa	80	160	220	$NaHCO_3$ = 10
	X_2	SA	10	20	30	CA = 5
2nd	X_1	ANa	80	160	220	$NaHCO_3$ = 10
	X_2	SA	5	10	15	CA = 5
3rd	X_1	ANa	80	160	220	$NaHCO_3$ = 5
	X_2	LG	5	10	15	CA = 2.5
4th	X_1	ANa	80	160	220	$NaHCO_3$ = 5
	X_2	TG	5	10	15	CA = 2.5

*$CHCl_3$ = 5 mL, ^{i}PrOH = 2 mL, and Mg-stearate = 5 mg in each tablet.

Fourier transform-infrared spectroscopy

The FT-IR spectra of ANa and ENa are shown in (Figure 3). The absorption bands in FT-IR spectra were assigned by comparing with earlier work for similar materials. The assignments are: 3375-3442 cm^{-1} (OH stretching broad band), 2880-2916 cm-1 (saturated C-H stretching), 1562-1639 cm^{-1} (deformation due to absorbed H_2O), a sharp band at 1012-1051 cm-1 (β-glycosidic bond) and 642-690 cm^{-1}, 528-549 cm^{-1} (polymer backbone). The isolated husk fractions by different methods were found to be almost similar.

Table 2. GPC parameters of *psyllium* husk fractions.

Parameters	AANa	ANa	ENa	MNa	ClfNa
Mn (g mol-1)	4.964 ×103	4.488×103	3.320×103	3.541×103	2.144×103
Mw (g mol-1)	1.326×104	1.288×104	1.232×104	1.112×104	8.054×103
Mz (g mol-1)	2.621×104	2.918×104	2.942×104	2.095×104	2.099×104
Mp (g mol-1)	7.360×103	8.498×103	8.231×103	1.586×104	4.136×103
Vp (cm3)	7.444	7.38	7.394	7.099	7.704
PDI	2.671	2.8641	3.712	3.139	3.755

Gel Permeation Chromatography (GPC)

The molar mass distribution in HGs was determined by GPC. The polydispersity index (PDI) was used to determine heterogeneity of a polymer which is the ratio M_w/M_n. For an ideal monodisperse polymer, the molar mass averages are equal and therefore, PDI value is close to 1. For a poly disperse system, $M_n<M_w<M_z$ resulting in PDI value greater than 1. For isolated HGs, the molar mass distribution was almost similar (Table 2) and their PDI were found to be; AANa = 2.671, ANa = 2.86, ENa = 3.71, MNa = 3.13, ClfNa = 3.75. These results indicated that their heterogeneity indexes were trending from 2.671 to 3.75 showing that these fractions are poly disperse in nature.

Microscopy

All fractions showed different surface morphology with different pore-size distribution. For representative purpose, SEM images of ENa and ANa are shown in Figure 4.

Thermal Analysis

Thermal behavior of the isolated husk fractions was studied by TGA and DSC from ambient to 600°C. The TGA showed an endothermic weight loss of ~10% up to 200°C, which could attributed to the loss of absorbed moisture (Iqbal, Shazma, Jamshed, Ashraf & Rashid, 2013). The first major weight loss (~45%) occurred in the range 225-325°C (Figure 5), that might be due to major degradation of structure. This step is associated with an exothermic enthalpy change. The second major decomposition stage, with a weight loss of ~25%, was observed at 450-560°C. It might be attributed to the complete degradation of HGs to gaseous molecules like CO, CO_2, H_2O etc. leaving behind a carbon rich residue. Glass transition temperature (T_g) could not be observed in the experimental temperature range. These fractions did not show any significant difference in their thermal behavior. The average *Ea* values calculated by Broido method, at multiple heating rates were found to be 134 kJ mol^{-1}comparable to other commercial polysaccharides such as CMC. An overall thermal stability of the husk fractions was assessed by integral procedural decomposition temperature (*IPDT*) and comprehensive index of thermal stability (*ITS*) values (Doyle's method). The *IPDT* and *ITS* ranges are 269-302°C and 0.44-0.49 respectively. These values indicate a good thermal stability of the isolated fractions, comparable with those of other commercially available polysaccharides (Ahmadi, Kalbasi-Ashtari, Oromiehie, Yarmand & Jahandideh, 2012). The apparent E_a values for major stage of decomposition were also calculated by FWO method. Typical α-*T* and FWO plots for ANa are shown in Fig. 5a, 5b and 6 respectively. The E_a varied greatly with α indicating a multistep degradation for HGs. The average activation energies by FWO method are also given in (Table 3).

Table 3. Thermal parameters of *psyllium* husk gel fractions.

Sample code	Temp. range[a] (°C)	Mass loss (%)	E_a kJ mol^{-1}	ΔH^* kJ mol^{-1}	ΔS^* JK^{-1} mol^{-1}	ΔG^* kJ mol^{-1}	lnA	IPDT (°C)	ITS	Mass at 600°C (%)
AANa	240-315	56.79	139.61	134.74	-74.06	178.07	21.22	269.42	0.44	0.40
MNa	220-310	41.46	141.43	138.7	-54.78	169.87	23.51	308.44	0.47	11.2
ENa	220-315	48.10	143.57	138.84	-52.32	168.56	23.81	287.21	0.47	0.99
ANa	245-315	45.60	136.53	131.67	-78.34	177.5	20.71	302.27	0.49	0.53
ClfNa	230-320	47.18	148.77	143.9	-56.79	177.18	23.3	300.99	0.49	14.59

Isolation of gel fractions

Different gels in different concentrations were coagulated (Fig.1). The relative amount of gel fractions extracted from husk gel is, AANa 80% (water white) > ENa 64% (off white) > ClfNa 60% (yellowish) > MNa 50 % (off white) > ANa 40% (transparent water white).

Drug release study and In vitro Buoyancy Studies

It was found that all husk fractions are better retardant than C std (Figure 2). The calibration graph with drug release profile of all fractions is shown in Fig. 7.

The % release of drug *vs* time for all fractions showed different release percentage ranging from 35.6 (ANa) > 38.1(AANa) > 39.1(ENa) > 40.9 (ClfNa) > 44.0 (MNa) > 44.4 (C std) > 47.5% (H). The crushing strength of the tablet was found between 9.9 to 9.1 kN which was maintained to minimize its effect on drug release rate. The physical parameters like thickness, content uniformity, weight variation (less than ± 5%), length of the tablet and floating lag time (25 to 55 min) were found in acceptable limits (Table 4). $NaHCO_3$ and CA were used as a gas-generating agent although $NaHCO_3$ induces carbon dioxide in presence of dissolution medium (pH 1.2) and Mg-stearate was used as glident.

Table 4. Physiochemical properties and floating lag time of levoflaxacin floats.

Tablet matrix	Crushing strength (kN)	Content uniformity (%)	Friability (%)	Floating lag time (min)
MNa	9.5± 0.5	98.5± 0.5	0.35	32
ENa	9.7± 0.3	98.7± 0.3	0.32	34
AANa	9.9± 0.1	99.9± 0.1	0.25	47
ANa	9.4± 0.6	99.4± 0.6	0.39	29
ClfNa	9.2± 0.8	99.2± 0.8	0.65	49
H	9.1± 0.6	98.1± 1.4	0.85	50
Cstd	9.3± 0.7	97.3± 1.1	0.56	55

The amount of drug remained within the matrix was relatively greater, therefore new batches were prepared to increase the bioavailability of drug. The design parameters for target profile were as follow: after 2 h; 20 ± 5%, after 5 h; 40 ± 5% and after 10 h; 60 ± 5%. 1st batch failed to meet the stated criteria. In 2nd batch; the drug release % in 2 h was close to 20% but after 5 h it was less than stated criteria. Therefore 2nd batch also failed to meet the stated criteria. In 3rd batch; the drug release rate in 2 h was greater than 20% and in 5 h was greater than 40% but after 10 h was much less than stated criteria. Therefore initial three batches were neglected. In 4th batch; the release rate in 2 h; was > 20%, in 5 h > 40% and in 10 h; ≈ 60%. So this batch was found to be suitable for set criteria (Table 5).

Table 5. Drug release % at different time intervals from all batches.

Levo	S1 $_{2\,h}$	S1 $_{5\,h}$	S1$_{10\,h}$	Levo	S2 $_{2\,h}$	S2 $_{5\,h}$	S2 $_{10\,h}$
S1F1	16.4	23.0	38.1	S2F1	22.7	33.1	46.0
S1F2	14.6	21.6	35.3	S2F2	21.1	31.1	44.7
S1F3	13.2	20.5	32.4	S2F3	20.2	28.0	40.9
S1F4	13.2	19.2	31.0	S2F4	19.6	25.9	43.1
S1F5	10.8	17.7	29.4	S2F5	17.1	24.6	38.6
S1F6	9.8	17.6	28.1	S2F6	15.7	24.0	37.7
S1F7	11.7	18.0	31.8	S2F7	19.5	29.6	40.0
S1F8	9.8	17.7	27.5	S2F8	17.1	25.6	38.0
S1F9	8.9	16.4	26.5	S2F9	16.7	23.9	36.3
Levo	S3 $_{2\,h}$	S3 $_{5\,h}$	S3 $_{10\,h}$	Levo	S4 $_{2\,h}$	S4 $_{5\,h}$	S4 $_{10\,h}$
S3F1	20.6	33.4	46.9	S4F1	22.0	32.6	43.2
S3F2	22.3	34.2	47.9	S4F2	24.3	41.4	46.1
S3F3	25.2	36.8	49.8	S4F3	28.3	48.9	58.5
S3F4	19.9	31.6	44.4	S4F4	27.1	40.4	44.7
S3F5	20.8	32.1	46.6	S4F5	29.6	44.4	48.5
S3F6	23.1	34.7	48.2	S4F6	34.6	49.8	58.9
S3F7	18.1	26.5	40.3	S4F7	30.5	43.5	54.2
S3F8	19.1	28.1	42.8	S4F8	36.1	49.7	59.3
S3F9	20.5	29.6	45.1	S4F9	43.7	58.9	67.2

Due to best retarding ability of ANa, it was taken as a major component (X_1) in matrix formation. In 1st batch, ANa and SA were taken as independent variables. In initial three formulations, as the amount of SA was increased, the release rate was decreased but from 4th formulation of this batch, as the amount of ANa was increased, the lag time was also increased due to increase in water entrapping ability which made the system little bit heavier. The drug release data shows that SA acts as release retardant due to its least hydrophilicity and lower density. In this batch the lag time remained between 30 and 80 min. For

further decreasing the lag time, the amount of SA was reduced to half in 2nd batch and it was found that the lag time was decreased from 40 min (S_1F_1) to 15 min (S_2F_1). It showed that by decreasing the amount of SA, the effervescence was increased due to increase in penetration of H_2O and thereby reduces the lag time. The drug release rate was relative slow and drug release percentage was below the require limit. The formulation containing greater amount of SA exhibited very slow release rate. In order to increase the release rate, SA was replaced by linseed gel (LG) in 3rd batch. The retarding ability of LG is lesser than ANa. So drug release rate was increased with lag time but release rate was still lesser than required limit. So in order to increase the release rate, LG was replaced by Tragacanth gel (TG) in 4th batch. TG consists of a component tragacanthin (30 - 40%) which is water soluble. Now drug release rate was increased but lag time was also increased (S_3F_1, 25 min) to (S_4F_1, 35 min). In other formulations, lag time was not much different from formulations of 3rd batch (Figure 8).

Floats of all batches showed variable swelling ability with different lag time (Table 6).

Table 6. Lag time (min) of formulation of all batches of levoflaxacin.

S1F1	S1F2	S1F3	S1F4	S1F5	S1F6	S1F7	S1F8	S1F9
40	35	30	60	48	42	80	72	68
S2F1	S2F2	S2F3	S2F4	S2F5	S2F6	S2F7	S2F8	S2F9
15	12	10	18	14	12.5	20	16	14
S3F1	S3F2	S3F3	S3F4	S3F5	S3F6	S3F7	S3F8	S3F9
25	28	34	27	32	45	61	NF	NF
S4F1	S4F2	S4F3	S4F4	S4F5	S4F6	S4F7	S4F8	S4F9
35	28	21	60	48	42	NF	NF	N F

Table 7. Kinetic study of 4th batch of matrix tablets.

	Zero Order			First Order		Higuchi Model		H-Crowell Model		Power law		
Levo	$S_{10\,h}$	k_o	R^2	k_1	R^2	k_H	R^2	k_{HC}	R^2	k_P	R^2	n
S4F1	43.2	0.074	0.935	-0.001	0.963	2.326	0.976	-0.024	0.935	0.020	0.971	0.476
S4F2	46.0	0.086	0.967	-0.01	0.992	2.691	0.989	-0.028	0.967	0.035	0.985	0.478
S4F3	58.5	0.096	0.929	-0.001	0.973	3.061	0.98	-0.032	0.929	0.020	0.984	0.561
S4F4	44.7	0.077	0.986	-0.001	0.992	2.364	0.981	-0.025	0.986	0.014	0.978	0.606
S4F5	48.5	0.086	0.987	-0.001	0.996	2.647	0.990	-0.028	0.987	0.016	0.990	0.626
S4F6	58.9	0.116	0.993	-0.001	0.988	3.557	0.972	-0.039	0.993	0.0002	0.949	1.317
S4F7	54.2	0.116	0.959	-0.002	0.991	3.64	0.992	-0.038	0.959	0.0011	0.964	1.038
S4F8	59.3	0.128	0.98	-0.002	0.979	3.931	0.966	-0.042	0.98	0.0003	0.966	1.228
S4F9	67.2	0.133	0.991	-0.002	0.968	4.035	0.96	-0.044	0.991	0.0002	0.976	1.312

The swelling characteristics were noted in simulated gastric fluid (pH 1.2) for 10 h and it was found that the diameter of tablet (S_4F_1) was increased 1.5 times than the original diameter. So its passage from stomach to intestine via pyloric sphincter was prevented due to greater swelling ability. The formulation S_4F_1 was found to be better due to best swelling ability, lag time and drug release rate. Greater the retention of tablet in stomach is considered to be better toward eliminating the *H. pylori* and efficacy of drug. The higher initial drug dissolution was observed in tablets containing higher proposition of TG (F7, F8, F9) as compared to F1, F2, F3. It showed that as the concentration of TG increases, the drug release rate increases due to greater H_2O absorbing ability along with its disintegration that was supported by kinetic study (power law and n value = 0.476 - 1.313).

In order to investigate the drug release kinetics, data were fitted to various kinetic models such as zero order, first order, Higuchi model, Hixson Crowell

model and power law. Various kinetic models were applied to understand the release rate and its mechanism. Kinetic data of 4th batch for the formulations S_4F_1-F_9 is shown in (Table 7). In this investigation, the next step was selection of best formulation. Higuchi's square root model showed highest correlation coefficient for S_4F_1 (R^2 = 0.976). The power law also showed highest correlation coefficient (R^2 = 0.971) with n value 0.476 showing that the drug release pattern of levoflaxacin was Fickian diffusion. The n value increases as the concentration of TG increases because disintegration increases and this values goes up to 1.312 which is beyond 1 which is standard value for super case- II showing that release mechanism is diffusion plus disintegration. These results can be used for setting *in vitro* and *in vivo* calculation.

Table 8. Similarity (f_2) and difference factor (f_1).

Levo		F1	F2	F3	F4	F5	F6	F7	F8	F9
S1	f1	8.91	9.63	14.83	20.03	24.23	26.37	26.02	28.15	30.28
	f2	76.28	72.61	66.86	62.09	58.20	56.72	57.41	55.78	54.46
C std	f1	19.27	22.97	27.64	32.06	35.62	37.44	37.15	38.96	40.77
	f2	58.23	55.48	52.27	49.51	47.21	46.37	46.84	45.85	45.03
S2	f1	33.86	25.14	15.29	17.72	7.09	7.22	17.05	8.36	7.56
	f2	53.61	59.97	68.18	67.14	81.97	82.50	65.19	80.32	80.55
C std	f1	13.73	8.15	11.6	9.27	15.28	14.84	12.98	14.49	16.16
	f2	66.01	74.69	72.42	74.89	65.13	65.00	69.72	65.45	62.47
S3	f1	20.70	33.48	40.08	24.06	31.14	40.81	26.01	33.1	39.38
	f2	62.65	53.69	50.33	60.89	55.84	50.01	59.48	54.44	50.81
C std	f1	13.03	13.95	19.01	8.37	11.54	19.64	7.06	13.08	18.42
	f2	68.32	63.38	59.46	73.84	67.9	60.54	77.38	69.15	62.8
S4	f1	45.14	48.86	55.34	33.73	39.28	46.67	21.67	28	32.97
	f2	49.48	47.8	45.22	55.63	52.44	48.91	64.54	59.63	56.21
C std	f1	14.32	17.26	22.36	6.32	9.71	15.53	9.38	7.92	9.61
	f2	66.25	62.60	58.35	79.1	74.13	64.44	75.81	78.64	72.98

Table 9. Regression analysis of all batches

1st Batch:
2 h study $S1_{2\,h} = 0.08173\,t - 0.16266\,X_1 - 0.1934\,X_2 + 0.000201\,X_1X_2 + 0.000241\,X_1^2 + 0.001288\,X_2^2 + 33.79$ *(CRC = 0.968763, R^2 = 0.938501, Adj.R^2 = 0.920052, n = 27)*
Effect of variables: X_1(1.48255)>X_1^2(1.100215)>X_2(0.35253)>X_1X_2(0.127957) > X_2^2(0.093935)
5 h study $S1_{5\,h} = 0.041668t - 0.21243X_1 - 0.22565X_2 + 0.00047X_1X_2 + 0.000325X_1^2 + 0.000499X_2^2 + 41.011$*(CRC=0.990904, R^2 = 0.98189, Adj.R^2 = 0.979578, n = 54)*
Effect of variables: X_1(1.20776)>X_1^2(0.924912)>X_2(0.25658)>X_1X_2(0.187151) > X_2^2(0.02268)
10 h study $S1_{10\,h} = 0.094453t - 0.095647X_1 - 1.267915X_2 + 0.00296X_1X_2 + 0.00032X_1^2 + 0.00567X_2^2 + 50.53$ *(CRC = 0.996215, R^2 = 0.992444, Adj.R^2 = 0.991951, n = 99)*
Effect of variables: X_1(0.93636)>X_1^2(0.762275)>X_2(0.1862)>X_1X_2 (0.121958)>X_2^2 (0.036231).
2nd batch:
2 h study $S2_{2h} = 0.058025t - 0.24528X_1 - 00.33169X_2 + 0.000214X_1X_2 + 0.000527X_1^2 + 0.0036X_2^2 + 43.2529$*(CRC = 0.974154, R^2 = 0.948976, Adj.R^2 = 0.933669, n = 27)*
Effect of variables: X_1(2.22573)>X_1^2(1.913669)>X_2(0.60198)>X_2^2(0.267215)>X_1X_2(0.11665).
5 h study $S2_{5\,h} = 00.049355t - 0.42018X_1 - 0.46594X_2 - 0.00012X_1X_2 + 0.000968X_1^2 + 0.007567X_2^2 + 62.62$ *(CRC=0.981261, R^2= 0.962873, Adj.R^2 = 0.958133, n = 54)*
Effect of variables: X_1(1.96972)>X_1^2(1.814176)>X_2(0.43684)>X_2^2 (0.28378)>X_1X_2 (0.03278)
10 h study $S2_{10\,h} = 0.047505\,t - 0.36667\,X_1 - 0.56482\,X_2 + 0.000419\,X_1X_2 + 0.000789\,X_1^2 + 0.007007\,X_2^2 + 59.78$ *(CRC* = 0.992648, R^2 = 0.98535, *Adj.*R^2 = 0.984395, *n = 99)*
Effect of variables: X_1 (1.07078)>X_1^2(0.92217)>X_2 (0.32989) > X_1X_2(0.07347) > X_2^2(0.02685).

Similarity and difference factor

All formulations were compared with Cstd (market tablet) and showed their f_2 values greater than 50 in all batches showing that their release pattern was non –Fickian diffusion (Table 8).

Table 10. Regression analysis of all batches.

3rd batch:
2 h study $S3_{2\ h}$= 0.086972t – 0.13021X_1– 0.59816X_2 – 0.0002X_1X_2 + 0.000265X_1^2 + 0.009783X_2^2+ 30.90156 *(CRC = 0.95608, R^2 = 0.91409, Adj.R^2 = 0.888317, n = 27)*
Effect of variables: X_2(0.59816)>X_1(0.13021)>X_1^2(0.245617)> X_1X_2 (0.12771) > X_2^2 (0.09471)
5 h study $S3_{5\ h}$ = 0.054285 t + 0.030125 X_1+ 0.178275 X_2 – 0.00026 X_1X_2 – 7.6E-05 X_1^2 – 0.00047 X_2^2 + 31.3277 *(CRC*=0.976905, R^2= 0.954344, *Adj.*R^2 = 0.948516, *n = 54)*
Effect of variables: X_2 (0.393612)>X_1X_2 (0.17054)>X_1^2 (0.13376)>X_1(0.133026)>X_2^2 (0.10347)
10 h study $S3_{10\ h}$ = 0.052286t + 0.029355X_1+ 0.178324X_2 – 0.00032X_1X_2 – 1.7E-05 X_1^2 – 0.00031X_2^2+ 6.357 *(CRC = 0.990788, R^2 = 0.98166, Adj.R^2 = 0.980464, n = 99)*
Effect of variables: X_2(0.234055)>X_1X_2(0.12586)> X_1 (0.077057) > X_2^2(0.04072) > X_1^2(0.0175).
4th batch:
2 h study $S4_{2\ h}$ = 0.058883t – 0.10609X_1– 0.02414X_2 + 6.42E-05X_1X_2 + 0.000151X_1^2 + 0.000766X_2^2 + 27.8202 *(CRC = 0.986649, R^2 = 0.973477, Adj.R^2 = 0.96552, n = 27)*
Effect of variables: X_1(0.84392)>X_1^2(0.481081)> X_2^2(0.304505) > X_2 (0.096) > X_1X_2(0.076577).
5 h study $S4_{5\ h}$ = 0.056496t – 0.06708X_1– 0.027X_2 + 9.49E-05X_1X_2 + 3.05E-05X_1^2 + 0.00065X_2^2 + 25.29769 *(CRC*=0.992532, R^2= 0.985119, *Adj.*R^2 = 0.98322, *n = 54)*
Effect of variables: X_1(0.27669)>X_2^2(0.133977)>X_2(0.05569) >X_1X_2(0.058748) > X_1^2(0.050248)
10 h study $S4_{10\ h}$ = – 0.052758t – 0.00816X_1+ 0.022315X_2 + 4.9E-05X_1X_2 – 0.00011X_1^2 + 0.000193X_2^2 + 19.25426 *(CRC* = 0.996738, R^2 = 0.993487, *Adj.*R^2 = 0.993062, *n = 99)*
Effect of variables: X_1^2(0.1361)> X_2^2(0.039586) > X_2(0.028989) >X_1X_2(0.005934) > X_1(0.0013).

The difference factors are in between 0-15 but most of the formulations deviate from these standard values showing that their release pattern varies from Cstd to some extent showing that their behavior is anomalous and need to explore further.

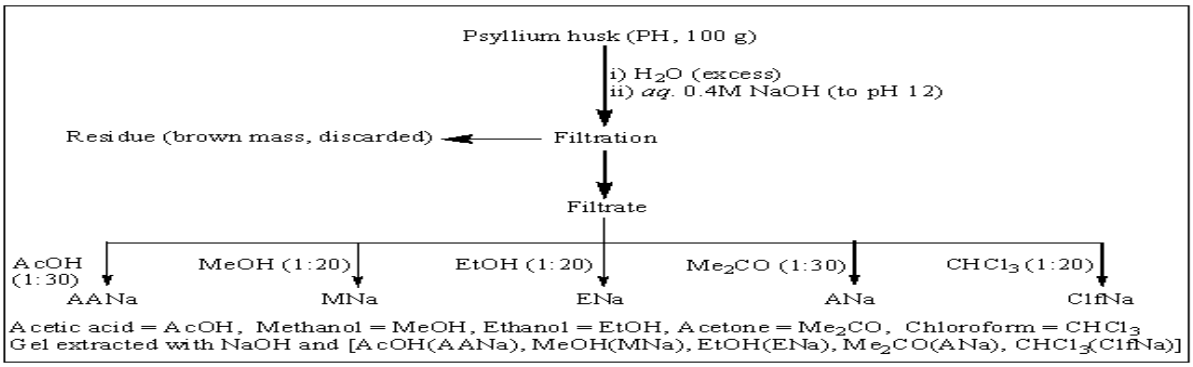

Fig. 1. Flow diagram for extraction/ Isolation of gel.

Regression analysis

By applying LRA on the drug release data at various time intervals to identify the effect of variables, Regression equations were derived from standard regression analysis.

1st Batch

2 h study: The *SRA* shows that the effect of X_1X_2, X_1^2 and X_2^2 is positive while effect of X_1 and X_2 is negative. This relation shows that effect of X_1 and X_1^2 is significant while effect of X_2^2 is negligible (Table 9).

5 h study: The *SRA* shows that the effect of X_1 and X_2 is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_1^2 is most significant while effect of X_2^2 is negligible (Table 9).

10 h study: The *SRA* shows that the effect of X_1(0.93636) and X_2(0.1862) is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and $X_1^2$is most significant while effect of X_2^2 is negligible (Table 9). The S - plot between P - release and Exp - release is shown by (Figure 9.1-e).

2nd batch

2 h study: The *SRA* shows that the effect of X_1 and X_2 is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_1^2 is most significant while effect of X_1X_2 is least significant.

5 h study: The *SRA* shows that the effect of X_1, X_2 and X_1X_2 is negative while effect of X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_1^2 is most significant while effect of X_1X_2 is negligible (Table 9).

10 h study: The *SRA* shows that the effect of X_1 and X_2 is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_1^2 is most significant while effect of while effect of X_1X_2 and $X_2^2$is negligible (Table 9). The S - plot between P - release and Exp - release is shown by (Figure 9. 2-e).

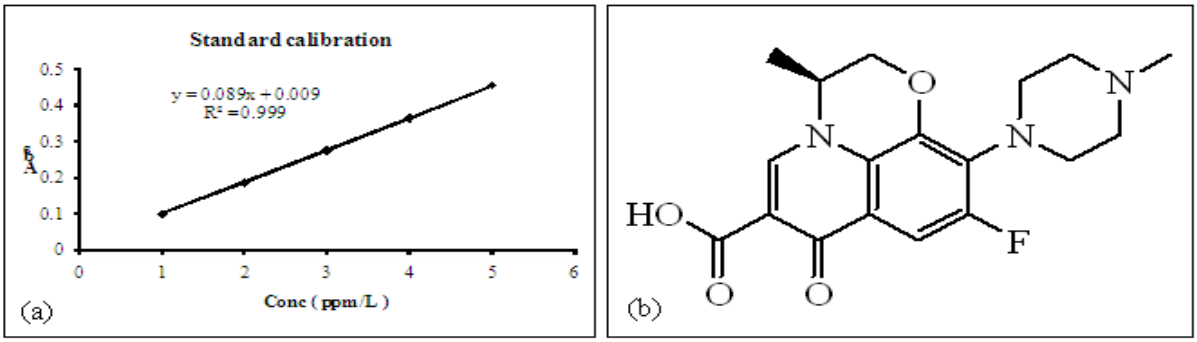

Fig. 2. (a) Calibration graph of pure drug (b) Drug structure.

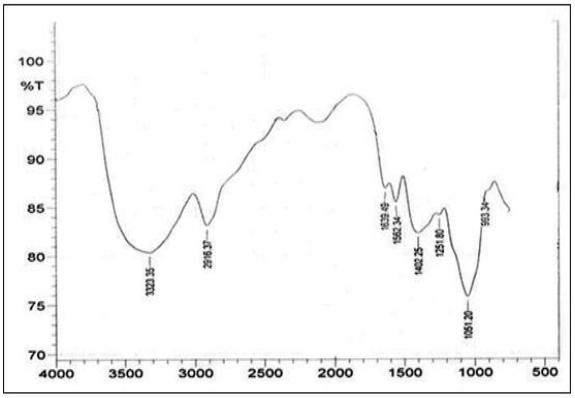

Fig. 3. FTIR spectrum of Ana.

2 h study: The *SRA* shows that the effect of X_1, X_1X_2 and X_2 is negative while effect of X_1^2 and X_2^2 is positive. This relation shows that effect of X_2 and X_1 is significant while effect of X_1X_2 and X_2^2 is negligible (Table 10).

5 h study: The *SRA* shows that the effect of X_1 and X_2 is positive while effect of X_1X_2, X_1^2 and X_2^2 is negative. This relation shows that effect of X_2 is most significant while effect of X_1X_2, X_1^2 and $X_1$is of intermediate level. The effect of X_2^2 is least significant (Table 10).

3rd batch

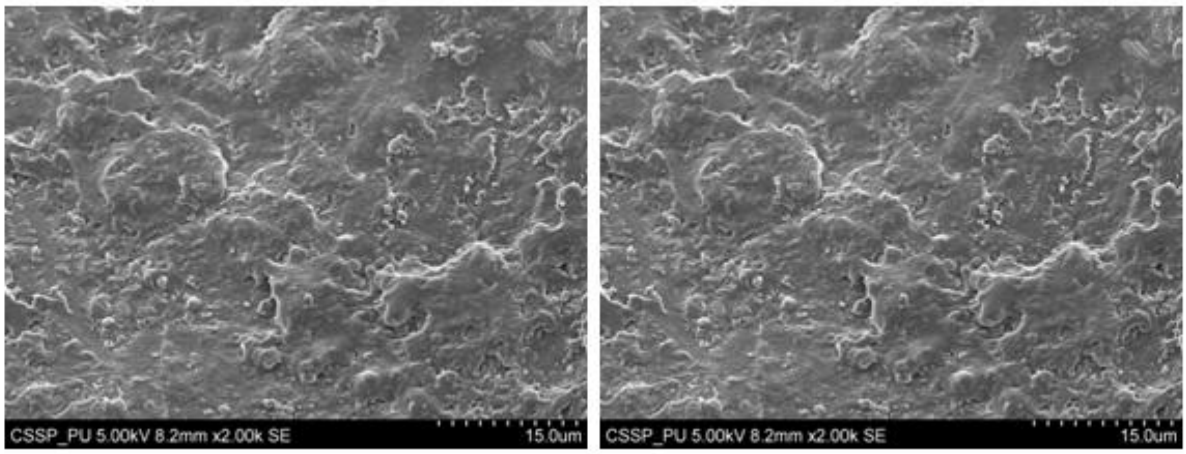

Fig. 4. Scanning electron microscopy of (a) ENa. (b) ANa.

10 h study: The *SRA* shows that the effect of X_1 and X_2 is positive while effect of X_1X_2, X_1^2 and X_2^2 is negative. This relation shows that effect of X_2 is most significant while effect of X_1, X_2^2 and X_1^2 is negligible (Table 10). The S - plot between P - release and Exp - release is shown by (Figure 9. 3-e).

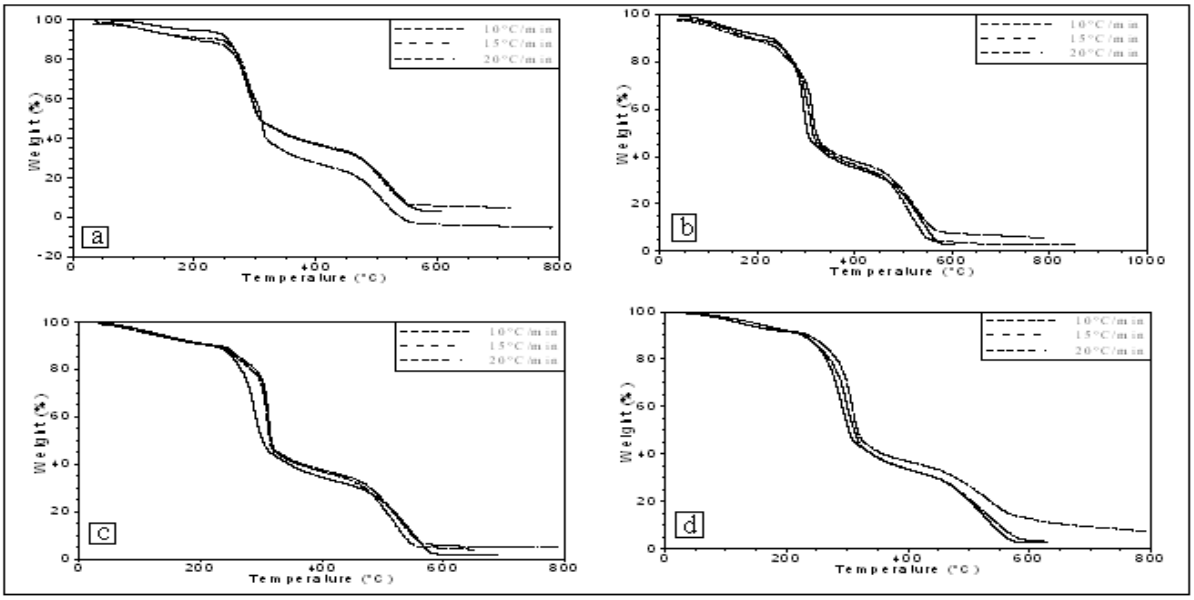

Fig. 5. Thermogravimetric curves: (a) AANa (b) ANa (c) ClfNa (d) MNa.

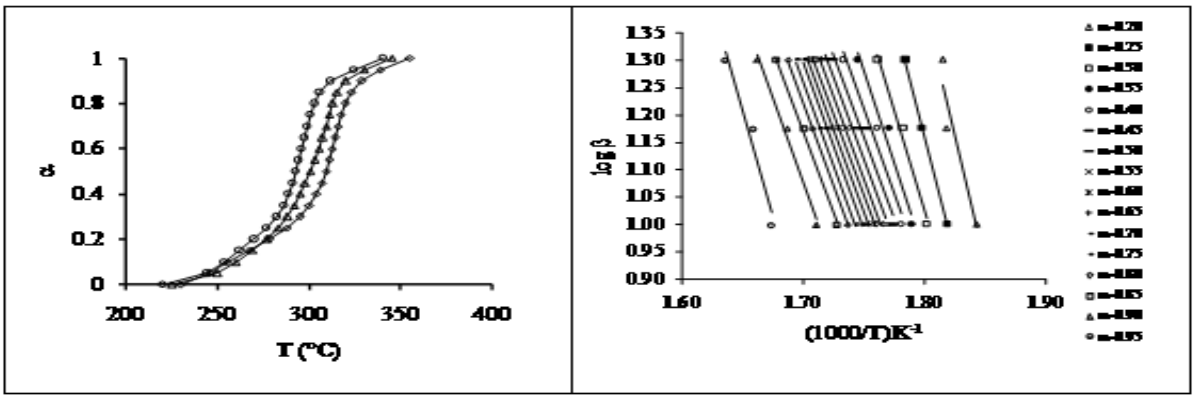

Fig. 6. Representative α -T curve and log β for ANa.

4th batch

2 h study: The *SRA* shows that the effect of X_1 and X_2 is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_1^2 is significant while effect of X_2 and X_1X_2 is negligible (Table 10).

5 h study: The *SRA* shows that the effect of X_1 and X_2 is negative while effect of X_1X_2, X_1^2 and X_2^2 is positive. This relation shows that effect of X_1 and X_2^2 is most significant while effect of X_2, X_1X_2 and X_1^2 is negligible (Table 10).

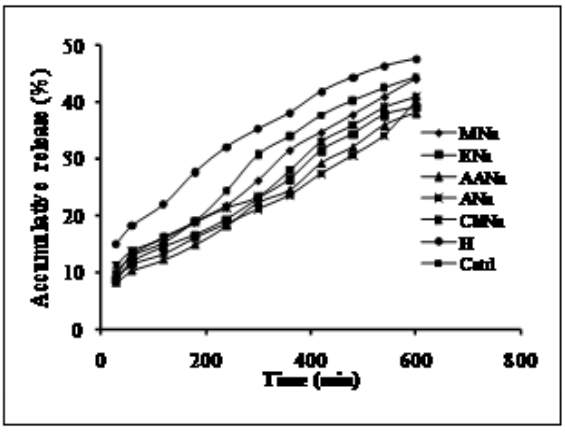

Fig. 7. Drug release profiles from pure fractions, C std and husk.

10 h study: The *SRA* shows that the effect of X_1 and X_1^2 is negative while effect of X_2, X_1X_2 and X_2^2 is positive. This relation shows that effect of X_1^2 is most significant while effect of other variables is negligible (Table 10). The S - plot between P-release and Exp-release is shown by (Figure 9.4-e).

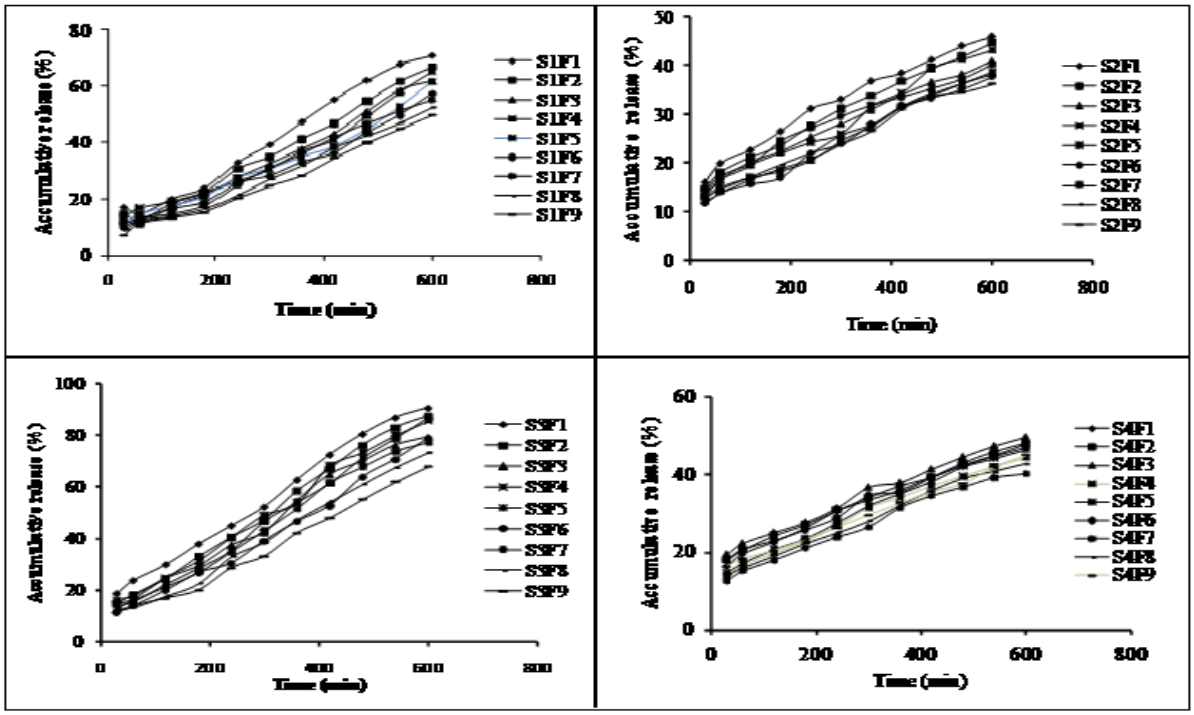

Fig. 8. Drug release profiles of all batches.

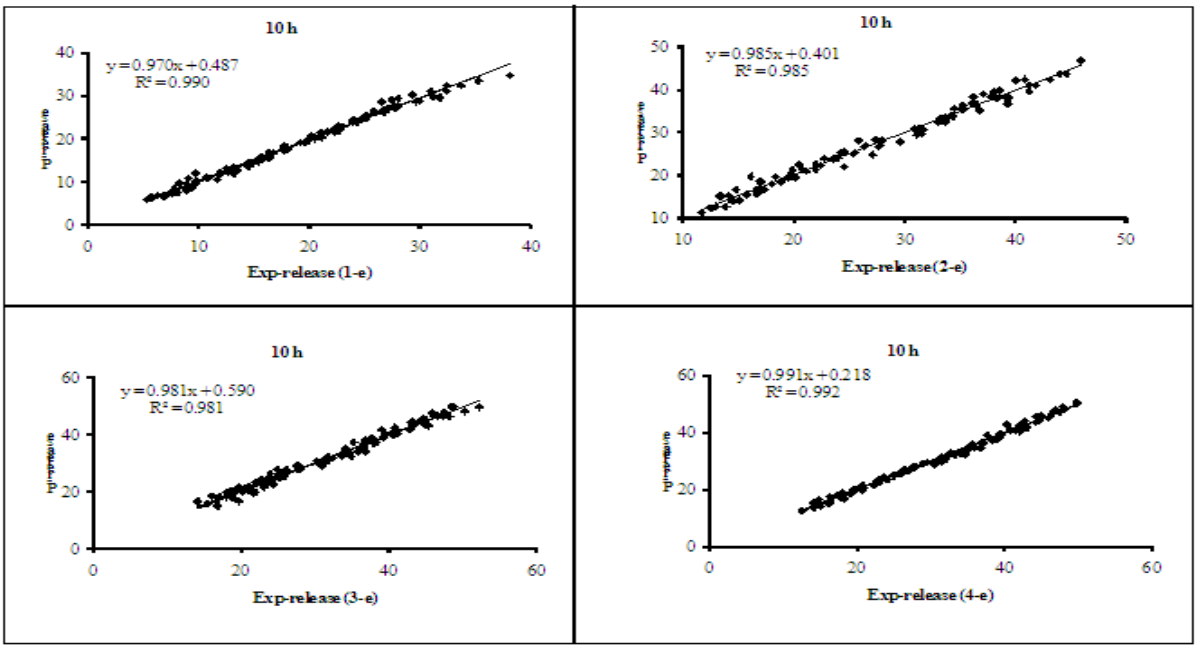

Fig. 9. (1-e, 2-e, 3-e, 4-e). Scattered plot between experimental release and predicted release for 10 h.

Conclusion

The psyllium husk fractions are hydrophilic swell able polysaccharides which have been successfully used for designing floating matrix tablets for controlled drug delivery. Due to having excellent pharmaceutical properties, Psyllium husk and its fractions are choice solution for drug delivery problems. The full factorial design 3^2 revealed that all independent factors of each

formulation (float) showed significant effect on drug release rate, lag time and floating time of floats. *SRA* shows that the level of X_1 and X_2 are parameters to achieve the desired drug release profile. Their values may be negative; it indicates that its amount must be decreased or positive; its amount must be increased to get required drug release profile. So their amounts are adjusted as regression demands for desired drug release profile. Similarity (n_2) and dissimilarity factors (n_1) help to find the deviation or resemblance with existing floating device. The thermal study reveals that all polymer fractions are almost equally stable and can withstand the environmental changes, although GPC study of all fractions vary from each other with respect to PDI value (ranging from 2 to 3.75). But this difference has no prominent effect on dissolution behavior. Excipients used are mostly herbal in nature which are also biocompatible to body and enlisted in GRAS list. So it can be concluded that the use of psyllium husk gel and its fractions as tablet matrix is totally safe and biocompatible. Keeping in view the exceptionally useful properties of psyllium husk gel and its fractions, these materials have potential in biomedical field and food industry including capsule shells, tablet matrix, food preservative films and binder (Ahmadi, R., *et al.,* 2012). The data obtained from drug release study was applied to kinetic models and interpretation was based on value of regression coefficient (R^2) and highest value of R^2 was found for power law with n value ranging from .47 to 1.322. It indicates that the release mechanism in S4F1 to S4F4 was swelling/diffusion (n≈ 0.47) and in remaining formulation dispersion occurred to some extent and release mechanism was found to be super case-11 (n > 1).

References

Adel AM, El-Wahab ZHA, Ibrahim AA and Al-Shemy MT. 2010. *Characterization* of microcrystalline cellulose prepared from lignocellulosic materials. Part Acid catalyzed hydrolysis. Bioresource Technology **101(12),** 4446–4455.
http://dx.doi.org/10.1016/j.biortech.2010.01.047

Ahmadi R, Kalbasi Ashtari A, Oromiehie A, Yarmand M, Jahandideh F. 2012. Development and *characterization* of a novel biodegradable edible film obtained from psyllium seed (Plantago ovata Forsk). Journal of Food Engineering **109,** 745-751.
http://dx.doi.org/10.1016/j.jfoodeng.2011.11.010

Beneke CE, Viljoen AM, Humman JH. 2009. Polymeric Plant derived Excipients in drug delivery, Molecules **14,** 2602-2620.
http://dx.doi.org/10.3390/molecules14072602

Bharanda PD, Gohael MC. 2006. Formulation and Evaluation of Diclophenac Sodium Modified Release using Ispaghula Husk, The Indian Pharmacist **51**, 92-97.

Bourne DW. 2002. Pharmacokinetics In: Banker, G.S., Rhodes, C.T. eds. (2002). Modern Pharmaceutics. 4th edt. New York, NY: Marcel Dekker Inc. 67-92.

Cooreman MP, Krasugrill P, Hengels KJ. 1993. Local gastric and serum amoxicillin concentrations after different oral application forms. Antimicrob. Agents Chemother **37,** 1506–1509.
http://dx.doi.org/10.1128/AAC.37.7.1506

Costa P. 2001. An alternative method to the evaluation of similarity factor in dissolution testing. International Journal of Pharmaceutics **220,** 77-83.
http://dx.doi.org/10.1016/S0378-5173(01)00651-2

Desai A, Shidhaya S, Kadam VJ. 2007. Possible use of psyllium husk as a release retardant. Indian Journal of Pharmaceutical sciences **69(2)**, 206-210.
http://dx.doi.org/10.4103/0250-474X.33144

Dicaro S, Zocco MA, Cremonini F, Candellim EC, Nista F, Bartolozzi A, Armuzzi G, Cammarota L, Santaerilli Gasbassini A. 2002. Levofloxacin based regimens for the eradication of Helicobacter pylori. Eur. Journal Gastroenterol Hepat **14(12),** 1309–1312.

Doyle CD. 1961. Estimating thermal stability of experimental polymers by empirical Thermogravimetric Analysis. Analytical Chemistry **33(1),** 77–79.
http://dx.doi.org/10.1021/ac60169a022

Evans DG, Evans DJ, Graham DY. 1992. Adherence and internalization of H. pylori by HEp- 2 cells. Gastroenterology **102(5),** 1557–1567.

Forman D, Parsonnet J. 1994. H. pylori and gastric cancer. Lancet **343,** 243–244.

Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. 2007. Development and in-vitro evaluation of oral floating matrix tablet Formulation of Diltiazem HCl, American Association of Pharmaceutical Scientists **8,** 166-174.
http://dx.doi.org/10.1208/pt0803073

Ghaemy M, Amini NSM. 2010. Synthesis and identification of organosolublepolyamides bearing a triaryl imidazole pendent: Thermal, photophysical,chemiluminescent and electrochemical *characterization* with a modified carbonnanotube electrode. Reactive and Functional Polymers **70(5),** 306–313.
http://dx.doi.org/10.1016/j.reactfunctpolym.2010.02.004

Guo J, Skinner GW, Harcum WW, Barnum PE. 1998. Pharmaceutical applications of naturally occurring water soluble polymers. Pharmaceutical Science and technology today 254-261.
http://dx.doi.org/10.1016/S1461-5347(98)00072-8

Iqbal MS, Akbar J, Hussain MA, Saghir S, Sher M. 2011. Evaluation of hot-water extracted arabinoxylans from ispaghula seeds as drug carriers. Carbohydrate Polymer **83 (3),** 1218 – 1225.
http://dx.doi.org/10.1016/j.carbpol.2010.09.024

Kennedy JF, Sandhu JS, DAT. 1999, Structural data for the*carbohydrates* of ispaghula husk ex Plantago ovata Forsk. Carbohydrate Research **75,** 265-274.
http://dx.doi.org/10.1016/S0008-6215(00)84646-7

Kokate K, Purohit AP and Gokhale SB. 2005, Pharmacognosy, 30th edt. Nirali Prakashan, Pune.

Korsmeyer RW, Gurny DRE, Buri P, Peppas NA. 1983. Mechanisms of solute release from porous hydrophilicpolymers. International Journal of Pharmaceutics **15,** 25–35.
http://dx.doi.org/:10.1016/0378-5173(83)90064-9

Madani M. 2011. Structure, optical and thermal decomposition characters of LDPEgraft copolymers synthesized by gamma irradiation. Current Applied Physics **11(1),** 70–76.
http://dx.doi.org/10.1016/j.cap.2010.06.021

Majithiya RJ, Murthy RSR. 2005. Chitosan-Based Mucoadhesive Microspheres of Clarithromycin as a Delivery System for Antibiotic to Stomach. Curr. Drug Del **2(3),** 235–242.

Mallakpour S, Dinari M. 2010 .Eco-friendly fast synthesis and thermal degradationof optically active polyamides under microwave accelerating conditions, Chinese Journal of Polymer Science **28(5),** 685–694.
http://dx.doi.org/10.10071s10118-010-9120-2

Mehta B, Doshi P, Joshi M, Dattat M. 2003. Floating Osmotic Device for Controlled Release Drug Delivery, U.S. Patent, 992 897.

Medicines Compendium. 2002. published by Datapharm communications, Ltd, 4th edition, 1901-1905.

Megraud F, Lamouliatte H. 1992. Pylori and duodenal ulcers. *Digestive Diseases* and Sciences **37,** 769–772.

Milton H, Fischer Y, Nanxiong R, Gary, Gray R, John, Laurens, Anderson, Judith AM. 2004. Endogenous carbohydrates, especially oligo- *and* polysaccharides, participate in the regulation of a

broad range *of* biological activitiesCarbohydrate Research **11,** 2009-2017.

Moes AJ. 1993. Gastro retentive dosage forms. Critical Reviews in Therapeutic Drug Carrier Systems **10**, 143–195**.**

Mohammad SI. 2013. Thermal analysis of some natural polysaccharide materials by isoconversional method. Food Chemistry **140 (1-2),** 178-182. http://dx.doi.org/10.1016/j.foodchem.2013.02.047

Mohammad SI. 2011. Thermal studies of plant carbohydrate polymer hydrogels Carbohydrate Polymers **86(4),** 1775-1783. http://dx.doi.org/10.1016/j.carbpol.2011.07.020

Moore JW, Flanner HH. 1996. Mathematical comparison of dissolution profiles.Pharmaceutical. Technology **20(6),** 64–74.

Naonori K, Yatabe H, Iseki Kand Katsumi M. (1991).A new type of pH independent controlled release tablet.International journal ofpharmaceutics **68,** 255–264. http://dx.doi.org/10.1016/0378-5173(91)90147-G

Niemegeers CJ. 1980. The antiemetic effects of domperidone, a novel potent gastrokinetic, Archives internationales de pharmacodynamie et de thérapie **244,** 130–140.

Nista EC, Candelli M, Zocco MA, Cremonini F, Ojetti V, Finizio R, Spada C, Cammarota G, Gasbarrini G, Gasbarrini A. 2006. Levofloxacin-Based Triple Therapy in First-Line Treatment for Helicobacter pylori EradicationThe American Journal of Gastroenterology **101(9),** 1985-1990. http://dx.doi.org/10.1111/j.1572-0241.2006.00716.x

O'Morain C. (2005). Treatment of H.pylori infection. Eur. Gastroenerol. Rev **1,** 56–59.

Pharmacists Drug Hand book. 2001. forward by Joseph, T.Dipro, Pharm, 663-665.

Pharmacopoeia of India 2007. The Indian pharmacopoeia commission publications Ghaziabad **2,** 1296-1297.

Punitha K, Hadhir SK, Ravichandiran SK, Umadevi. (2010). Intragastric floating drug delivery system of ranitidine hydrochloride: formulation and evaluation. Int. J. Pharmaceutical Sciences **2(4),** 105-108.

Riger PL, Peppas NA. 1987. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. Journal of Control Release **5,** 37-42. http://dx.doi.org/10.1016/0168-3659(87)90035-6

Rosa M, Zia H, Rhodes T. 1994. Dosing and testing in-vitro of a bio-adhesive and floating drug delivery system for oral application. International Journal of pharmaceutics **105,** 65-70.

Rouge N. 1997. Prevention of the sticking tendency of floating minitablets filled into hard gelatin capsules, European Journal of Pharmaceutics and Biopharmaceutics **43,** 165–171. http://dx.doi.org/10.1016/S0939-6411(96)00003-3

Rang H, Dale MM, Ritter JM, Moore PK, Lamb P. 2003. A Text book of Pharmacology, 5th edition, Elsevierpublications, 647-649.

Saboji JK, Gadve RB, Patil SM. 2012. Development of Oral Colon Specific pH Dependent Microcapsules of NSAID Drug Naproxen Journal of Applied Pharmaceutical Science **02(05),** 202-211.

Saghir S, Iqbal MS, Koschella A, Heinze T. 2009. Ethylation of arabinoxylan from Ispaghula (*Plantago ovata*) seed husk. Carbohydrate Polymers **77,** 125–130. http://dx.doi.org/10.1016/j.carbpol.2008.12.009

Schefter E, Higuchi T. 1963. Dissolution behavior

of crystalline solvated and non-solvated forms of some pharmaceuticals, Journal of Applied Pharmaceutical Science **52,** 781–791. http://dx.doi.org/10.1002/jps.2600520815

Seth PR, Tossounian JL. 1991. Process for Dehusking Seeds of *Psylluim*. US Patent 5020732.

Sweta S, Roula Q, vijay P, Mansoor A. 1999. Evaluation of factors influencing stomach specific delivery of antibacterial agents for Helicobacter pylori infection. The Journal of Pharmacology and Pharmacotherapeutics **51,** 667–672.

Shuto K, Shiozaki Z, Kojima T, Tanaka M. 1980. Antagonism of KW-5338 (domperidone) against emesis and depression of intestinal motility induced by L-DOPA, Journal of Pharmacobiodyn **3,** 709–714. http://dx.doi.org/http://doi.org/10.1248/bpb1978.3.709

Siepmann J, Peppas NA. 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advance Drug Delivery Review **48,** 139.

Talukder R. Fassihi R. (2004).Gastro retentive delivery systems, a mini review, Drug Development-and-Industrial-Pharmacy **30,** 1019–1028.

Thakkar VT. 2008. Fabrication and evaluation of levoflaxacin hemihydrate floating tablet. Research in Pharmaceutical Sciences **3(2),** 1-8.

Thomma K, Zimmer T. 1990. Retardation of weakly basic drug with diffusion tablet International journal of pharmaceutics **58,** 197–202. http://dx.doi.org/10.1016/0378-5173(90)90195-A

Umamaheshwari RB, Ramteke S, Jain KN. 2004. Anti Helicobacter pylori effect of mucoadhesive nano-particle bearing amoxicillin in experimental gerbils. American Association of Pharmaceutical Scientists.-Tech **325**,5-2.

Uhrich KE, Cannizzaro SM, Langer RS Shakesheff KM. 1999. Polymeric systems for controlled drug release. Chemical Review **99,** 3181-3198**.** http://dx.doi.org/10.1021/cr940351u

Wagner JG. 1969. Interpretation of percent dissolved-time plots derived from *in vitro* testing of conventional tablets and capsules. Journal of Pharmaceutical Sciences **58,** 1253–1257. http://dx.doi.org/10.1002/jps.2600581021

Whitehead L, Fell JT, Collett JH, Sharma HL and Smith AM. 1998. Floating dosageforms: an in vivo study demonstrating prolonged gastric retention. Journal of controlled release **55,** 3–12. http://dx.doi.org/10.1016/S0168-3659(97)00266-6

Warren JR, Marshall B. 1983. Unified curved bacilli on gastric epithelium in active chronic gastritis. Lancet **321,** 1273–1275.

Watanabe Y, Aoyama N, Shirasaka D, Maekwa S, Karoda K, Miki I, Fukuda M, Wambura T, Tamura, Kasugam. 2003. Levofloxacin based triple therapy as a second-line treatment after failure of Helicobacter pylori eradication with standard triple therapy. Digest. Liver Dis **35,** 711–715. http://dx.doi.org/10.1016/S1590-8658(03)00432-8

Yasir M, Asif M, Bhattacharya A, Bajpai M. (2010). Development and Evaluation of Gastro retentive Drug Delivery System for Theopylline using *Psyllium* Husk, International Journal of ChemTech Research **2(2),** 792-799.

Yeole PG, Khan Sand Patel VF. 1995. Selective adherence of a sucralfate-tetracycline complex to gastric ulcers: implications for the treatment of Helicobacter pylori. Biopharmaceutics & Drug Disposition **16,** 475–479. http://dx.doi.org/10.1002/bdd.2510160605