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DEVELOPMENT AND EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF LORATADINE

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ABSTRACT

Objective:

The low bioavailability and narrow absorption window of Loratadine (LD), stable in acidic pH following oral administration favors development of a gastro retentive formulation.

Methods:

Gastro retentive floating tablets of LD were prepared by using direct compression method with hydrophilic polymers like HPMC K100M, CARBOPAL 940 and standard excipients like micro crystalline cellulose (MCC), sodium bicarbonate, magnesium stearate and talc. These polymers and excipients were utilized to make 14 formulations (F1-F14), the physical characteristics of tablets were evaluated, including hardness, friability, floating time, thickness, weight variation, *in-vitro* buyoncy studies, *in -vitro* dissolution studies, *in –vivo* xray studies.

Results:

The drug- polymer compatibility studies indicated that there was no compatibility problems with the polymers used in the study, the effect of polymer concentration on buoyancy and drug release was

studied. the optimized formulation (F7) sustained the drug release in 12 hours than the marketed product, maintained total floating time of 12 hours with floating lag time of 30 seconds, Carbopal 940 had shown a more sustained release profile because it remains un ionized in acidic dissolution media, showed a non fickian diffusion and followed the zero order, higuchi model, After three months of storage at 45^0C with 75 % RH, it showed no significant changes in physical appearance, dug content, floatability. *In-vivo* x-ray studies were conducted to note the gastric residence time of floating tablets, time was found to be 4 hours.

Conclusion:

The floating principle improved gastro retention time, which was considered to be favorable for expanding the absorption window of drugs.

Key words: Floating tablets, Gastric residence time, Gastro retentive drug delivery system, Loratadine, In-*vitro* buoyancy.

INTRODUCTION

Oral sustained release medication distribution is complicated by the fact that not all the drug candidates are absorbed uniformly throughout the gastrointestinal tract. GIT is typically limited by poor bioavailability with traditional dose forms due to partial drug release and short residence time at the absorption site. Over the last three decades, gastro retentive dosage forms have been developed to address these issues. High density, swelling and expanding, polymeric mucoadhesive, ion exchange, raft forming, magnetic, and floating drug delivery systems are some of current technical approaches used to expand stomach residency time. A gastro retentive sustained release system of LD was formulated to increase the residence time and to modulate the release behavior of the drug, LD is a tricyclic antihistamine, which selectively antagonizes peripheral histamine H_1-receptors.The main aim of present work is to develop floating drug delivery system of LD, which increases the gastric residence time, minimizes the problems associated with oral sustained release dosage forms, LD is given orally it is well absorbed from the gastrointestinal tract, used to treat allergy, and other skin allergies, elimination half life is approx. 8.4 hours, shows narrow absorption window **[1,2].**

MATERIALS AND METHODS

Materials

Loratadine was obtained as a gift sample from Vasudha Pharmaceutical Hyderabad, carbopol 940,hpmc k100M, microcrystalline cellulose, sodium bicarbonate, magnesuim stearate, talc were obtained from S.D fine chemicals Mumbai, all other chemicals and solvents used were analytical grade.

METHODS

Construction of standard graph of Loratadine in 0.1 N hydrochloric Acid

Accurately weighed amount of 100 mg of LD was transferred into a 100 ml of volumetric flask. 5 ml of methanol was added to dissolve the drug and the primary stock was made with 0.1 N hydrochloric acid to obtain concentration of 1.0 mg/ml, of LD stock solution. From this primary stock 10 ml was transferred into another volumetric flask and made up to 100 ml with 0.1 N hydrochloric acid. From this secondary stock 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 ml, was taken separately and made up to 10 ml with 0.1 N hydrochloric acid to produce 5, 10, 15, 20, 25, 30, 35and 40 microgram/ml. The absorbance was measured at 280 nm using a U.V Visible Spectrophotometer (Elico SL 159 Pvt ltd, Hyderabad) **[2, 3]**.

Preparation of floating tablets of Loratadine

LD tablets were prepared with CARBOPAL 940, HPMC K100M and MCC were triturated in a mortar to get fine powder, Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and pestle, pulverized powder was passed through sieve # 40 and blended with the drug blend, which was subsequently passed through sieve # 40, mixed in a plastic bag for 5 minutes to get uniform mixing, then Magnesium stearate was added and mixed for 5 minutes, then Talc was added and mixed for 2 minutes. Afterwards, the uniform mixture was directly compressed into tablets weighing 200 mg using a 16-station punching machine equipped with an 8-mm flat-faced round punch (Cadmach, Ahmadabad, India**) [4]**.

The drug and different polymer concentration ratios was used to formulate floating tablets as shown in **Tables 1, 2**.

Table 1: Formulation of floating tablets with CARBOPAL 940

Ingredients	F1	F2	F3	F4	F5	F6	F7
Loratadine	10	10	10	10	10	10	10
CARBOPAL 940	20	30	60	90	100	110	120
MCC	137	127	97	67	57	47	37
$NaHCO_3$	30	30	30	30	30	30	30
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg.Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200

Weight in (mg)

Table 2: Formulation of Floating tablets with HPMC K100M

Ingredients	F8	F9	F10	F11	F12	F13	F14
Loratadine	10	10	10	10	10	10	10
HPMC K 100M	20	30	60	90	100	110	120
MCC	137	127	97	67	57	47	37
$NaHCO_3$	30	30	30	30	30	30	30
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg.Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	200	200	200	200	200	200	200

Weight in (mg)

Pre-compression evaluation

Standard procedure have been used to determine the angle of repose, bulk density, tapped density, compressibility index (Carr's index), and Hausner's ratio of the powder **[5]**.

Evaluation of tablets

The prepared tablets were evaluated for their physical parameters like weight variation and uniformity in thickness using analytical balance and digital micrometer (Mitutoyo, Japan), respectively. Hardness was measured with Monsanto hardness tester, friability with Roche type friabilator. Triturating 20 tablets in a mortar and adding powder equivalent to average weight in 100 ml of 0.1 N HCL was used to determine the drug concentration in each formulation, followed by shaking for overnight. The solution was filtered through 0.45µm membrane filter, diluted suitably and analyzed by using UV/VIS double beam spectrophotometer (Elico SL 159 pvt ltd, Hyderabad) at 280 nm against 0.1 N HCl as blank **[6, 7]**.

Floating properties of tablets

The tablets were dissolved in 0.1N HCL in a 100 ml glass beaker

1. Floating Lag Time: Floating lag time is the time it takes for the tablet to rise to the surface of the medium and float.

2. Floating Duration Time: The floating duration time was determined as the duration of time the tablet remained floating on the mediums' surface **[8]**.

***In vitro* dissolution studies**

Dissolution profiles of the LD were determined in triplicate at 37 ± 0.5^0 C using the USP XXIII dissolution test apparatus (LABINDIA, Disso 2000). The dissolution medium was 900 ml 0.1 N HCL and the paddle stirrer rotated at 50 rpm. Samples (5 ml) were withdrawn with replacement at fixed time intervals and filtered through a 0.45mm pre filter. The filtered samples were then diluted with dissolution medium and the absorbance measured at 280 nm **[9]**.

Fourier transforms infrared spectroscopy (FTIR)

The SHIMADZU FTIR Spectrophotometer was used to record the infrared spectrum of the pure drug, each retardant, and the physical mixture of the optimized formulation. The scanning range was 500-4000 $cm^1$and the IR spectra of samples were obtained using KBr disc method. To find any chemical interactions, any change in drugs spectrum pattern due to the presence of polymers was studied **[10].**

Drug release kinetics

To study the kinetics of drug release from formulations.

Zero order kinetics

$C=K_0t$

It refers to a system in which the rate of drug release is unaffected by its concentration. K_0 is the zero order release constant, and represents the cumulative amount of medication released in time t **[11]**.

First order kinetics

$\text{Log } C_t=\log C_0 \; K_1t/2.303$

It describes the drug release from the systems in which the release rate is concentration dependent, Where C_t is the amount of drug released in time t, Co represents the drugs initial concentration, and K_1 denotes the first order release constant **[11]**.

Higuchi kinetics

$W=K_2{}^{t1/2}$ It describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion. W represents the cumulative amount of drug released in time t and K_2 is the Higuchi dissolution constant **[12]**.

Korsmeyer Peppas equation

$K_4t^n= M_t=M\infty$ it represents drug release from a polymeric system when it deviates from Fickian diffusion, as seen in the equation below. Where K_4 is release constant, n is release exponent, indicative of the drug release mechanism and M represents the cumulative amount of drug dissolved in time t, For matrix tablets, If the release exponent n=0.45, the drug release mechanism is fickian diffusion; if it is 0.45-0.89, it is non fickian or anomalous diffusion. Case-II transport or typical zero orders release is represented by an exponent value of 0.89**[12]**.

***In -vivo* (x-ray) studies**

To perform this study 200 mg tablets prepared, x-ray opaque (BaSO4) is incorporated to make the tablet opaque, quantity of the drug and part of MCC were replaced with BaSO4 for in vivo studies **[12]**.

***In -Vivo* buoyancy by using radiographic studies**

The *in-vivo* study was carried out by administering LD floating tablets to human volunteers and monitoring them through a radiological method. Three healthy male subjects (mean age 26year: mean weight 60±10 kg) participated after giving informed consent. The study was approved by the Human Ethical Committee of St. Peters Institute of Pharmaceutical sciences, Warangal and conducted by administering to each subject one. The prepared tablets were administered orally with a glass of water, during the experiments subjects were not allowed to eat but allowed water, they remained in a sitting or upright posture. In

each subject the position of the floating tablet was monitored by X-ray photographs at different time intervals like 0.5, 1.5,3 and 4 hours **[13]**.

Stability studies

The optimized formulation(F7) is packed in silver foil for studying stability parameters at 40^0C± 2 /75 ± 5% RH, withdrawn samples at predetermined time intervals of 0 (initial), The tablet was then characterized for various physicochemical parameters such as appearance, weight variations thickness, hardness, friability and drug content after 30,60,and 90 days **[13]**.

RESULTS AND DISCUSSION

Construction of standard graph of Loratadine in 0.1 N hydrochloric Acid

Standard graph of LD in 0.1 N HCl showed linearity with R^2 value 0.9981 which suggests that it obeys the "Beer – Lambert "law in the concentration range of 5mcg/ml –40 mcg/ml.

Fourier transforms infrared spectroscopy (FTIR)

Figure 1 and 2, shown the infrared spectrum of a physical mixture of optimized formulation was evaluated, and it was determined that they have no interaction. The spectra revealed all of the drugs and polymers significant peaks, The IR spectra showed characteristic peaks that belonged to the measurement. As a result, no significant changes or behavior pattern in the physical mixture of Loratadine and Carbopal 940.

Pre compression parameters

The angle of repose values were found to be between 26.05^0 and 29.00^0 , Hausner ratio values were found to between 1.13 and 1.30, these values indicates the good flow properties and acceptable .Percentage compressibility index was found to be in the range of 11.94 to 21.53, Pre compression parameters values indicates good flow properties as per IP.

Post compression parameters

The post compression parameters are summarized in **Table 3,** the tablets showed acceptable hardness. Thickness of all formulations found to be 3.0±0.34 to 3.2±0.03mm, weight variation of tablets ranges from 199±0.02 to 201±0.05mg, the drug content was found to be 97.2±0.05 to 99.1±0.03, friability for all formulations was less than 0.5% which indicates the good mechanical strength, all the values are in within specifications as per Indian Pharmacopeia (IP).

***In-vitro* buoyancy of floating tablets in 0.1 N -HCl**

The formulations were all found to be buoyant. **(Table 3 and Figure 3)**. They floated immediately when immersion in to the media and remained floated for 12 hrs

with lag time of 30 sec to 51 sec. The use of sodium bicarbonate as gas forming agents dispersed in the matrix was found to be effective in achieving the desired buoyancy characteristics. Upon Addition of sodium bi carbonate rapid floating starts reaction immediately with the acidic dissolution media, which generates sufficient amount of CO_2 which get entrapped and protected within the gel layer formed by hydration of Carbopal 940. As a result, the tablets' density reduces (reported as 1.004 to 1.010 g/cm^3) and the tablet becomes buoyant. Buoyancy is further facilitated by relatively good acid solubility of LD as a result dissolution media penetrates the matrix more quickly. This in turn causes quicker initiation of reaction resulting in faster generation of CO_2 the tablets more buoyant **[14]**.

***In-vitro* dissolution studies**

The *in-vitro* dissolution studies revealed that formulations F1-F7(CARBOPAL 940) showed the release of 99.2%, 98.8%, 99.1.%, 99.3%, 99.1%, 99.3%, 99.6 % respectively, in 12 hrs **(Figure 4)**, The *in vitro* dissolution studies indicated that formulations F8-F14 (HPMC K100M) showed the release of 99.1%, 99.6%, 99.1%, 99.2%, 99.1%, 99.3%, 99.4% respectively, in 11 hrs, Dissolution profile of F1and F2 Formulations showed rapid burst release within 5-6 hrs, This is due to the low quantity of polymer used, From F3-F7,formulations release was retarded continuously which is because of high quantity of polymer used, as an increasing the amount of polymer decreases the release rate ,which is because of increased gel strength of formulation, which prevents the escape of entrapped generated gas from formulation leads to decreased density and increases the total floating time, Carbopal 940 shown a more sustained release profile because which remains un ionized in acidic dissolution media and leads to act as a physical barrier for sustained release.F7 was selected as optimized formulation because of sustained the drug release among the other formulations **[15]**.

Formulation F8 and F9 showed rapid burst release within 5-6 hrs, This is due to the low quantity of polymer used, From F10-F14, formulations release was retarded continuously which is because of high quantity of polymer used, with increasing the amount of polymer decreases the release rate, the optimized (F7) formulation dissolution profile was compared with marketed product and F7 was retarded the drug release over the marketed product within 12 hours.

***In-Vivo* Evaluation (X-Ray Studies)**

Figure 5, using a radiographic imaging approach, the behavior of the floating tablet in the human stomach was observed in real time. In radiographic images made 30 min after the administration, the tablets were observed in the human stomach. In the next picture taken at 90 minutes, 3 hours and 4 hours, significant changes were detected. *In vivo* x-ray studies shown that tablet had rotated around and altered it location. This provided evidence that the tablets did no adhere to the gastric mucosa, but, on the contrary, floated on the gastric fluid. In addition, the swelling of the tablet, as well as the white dry core and translucent swelling layer around it, was clearly visible. As the swelling progressed, the glassy core of the floating tablets shrank, the swelling layer eroded off the outer surface, and the size of the floating tablets shrank. The gastric residence time of floating tablets was observed for 4 hours **[16]**.

Drug release mechanism

The mechanism of release for the optimized formulations was determined by fitting dissolution data in to different kinetic models like Zero-order, First-order, Higuchi, and Korsmeyer-Peppas corresponding to the release data of formulations. The values of K, and r^2 (correlation coefficient of the regression analysis) of zero order, first order and Higuchi models of designed formulations are given in **Table 4**. The n values calculated for different formulations were found in the range of 0.46 to 0.76, Dissolution kinetic studies for most of the formulations R^2 value is very near to 1 than the R^2 values of other kinetic models, and the drug is released as per the Korsemeyer –Peppas and zero–oder and Higuchi model mechanisms. The drug release kinetics studies revealed high correlation coefficient values of zero order than first order indicating that the drug release from LD gastro retentive floating tablets followed zero order profile. The Higuchi models high regression value ensured that drug release form matrix tablets followed a diffusion mechanism, the n values indicating non fickian diffusion or anomalous diffusion.

Stability studies

Stability studies performed for optimized formulation according to ICH guidelines, studies were conducted for three months and there are negligible changes in parameters.

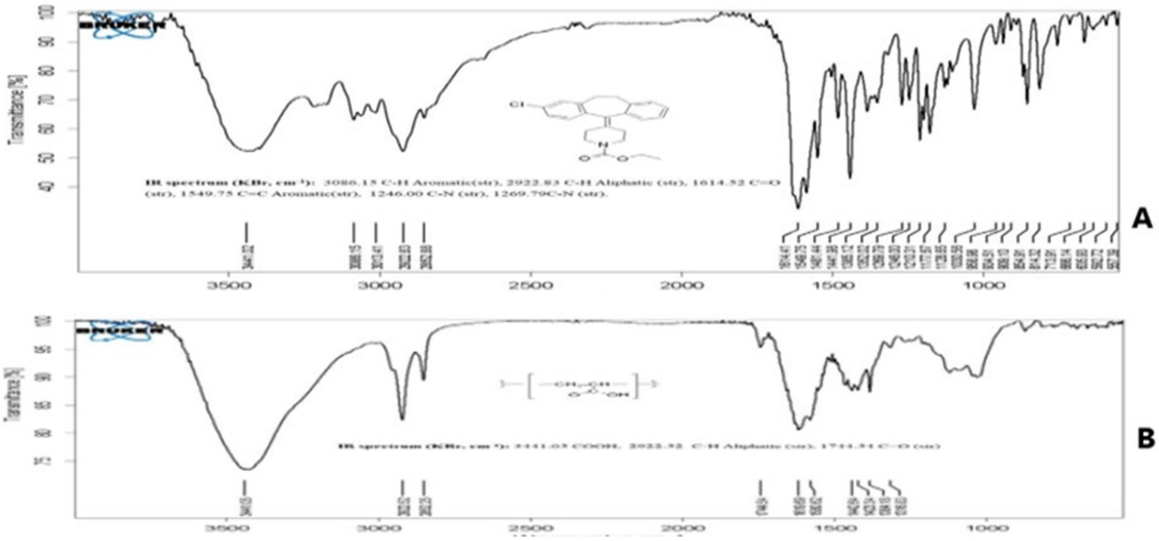

Figure 1: A) FTIR spectra of Loratadine pure drug, B) FTIR spectra of carbopal 940

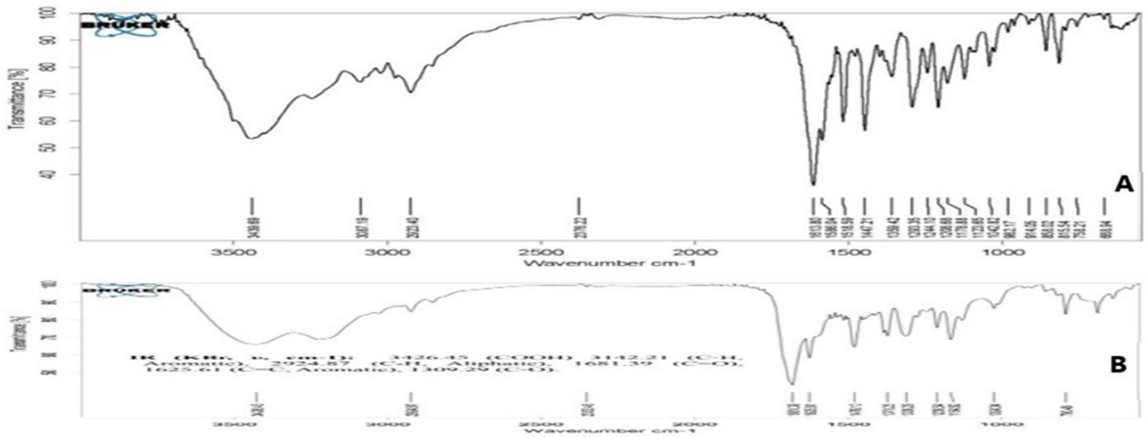

Figure 2: A) FTIR spectra of HPMC K 100M, B) FTIR spectra of Optimized formulation (F7)

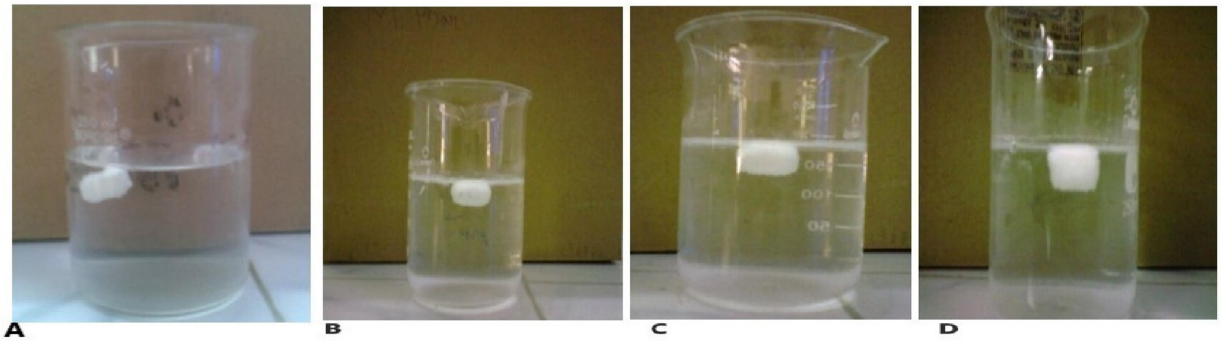

Figure 3: *In-vitro* buoyancy of floating tablets A) After 30 minutes B) After 2 hours C) After 6 hours D) After 12 hours

Formulation code	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	Total Floating Time(hrs)	Floating Lag Time(sec)	Weight Variation (%)
F1	3.8 ±0.05	0.24±0.07	3.12±0.01	97.4±0.03	6 hr	37 sec	200±0.03
F2	4.1±0.03	0.27±0.02	3.1±0.02	97.2±0.05	6.5hr	36sec	199±0.05
F3	3.9±0.01	0.29±0.03	3.4±0.04	97.6±0.02	7.0hr	40 sec	199±0.02
F4	4.0±0.06	0.64±0.08	3.1±0.03	98.4±0.05	7.0 hr	35 sec	199±0.08
F5	4.5±0.01	0.52±0.05	3.1±0.06	97.3±0.08	8.0 hr	34sec	200±0.04
F6	3.9±0.04	0.35±0.02	3.0±0.05	99.1±0.03	10 hr	32sec	201±0.01
F7	3.6±0.05	0.26±0.06	3.0±0.03	99.5±0.01	12 hr	30 sec	200±0.03
F8	4.0±0.04	0.34±0.05	3.2±0.02	96.9±0.02	5 hrs	46sec	200±0.03
F9	3.9±0.02	0.42±0.04	3.1±0.05	97.5±0.04	6 hrs	48sec	199±0.05
F10	4.1±0.01	0.41±0.06	3.2±0.06	98.4±0.03	6.5 hrs	44 sec	199±0.02
F11	4.2±0.02	0.51±0.05	3.0±0.04	98.2±0.06	7 hrs	50 sec	199±0.08
F12	3.8±0.04	0.35±0.01	3.1±0.08	97.3±0.05	8 hrs	51 sec	200±0.04
F13	4.3±0.05	0.34±0.02	3.2±0.03	99.1±0.03	10 hrs	49sec	198±0.01
F14	3.8±0.06	0.28±0.08	3.1±0.05	97.2±0.06	11 hrs	43 sec	199±0.03

Table 3: Post compression parameters
Mean± SD, n =3

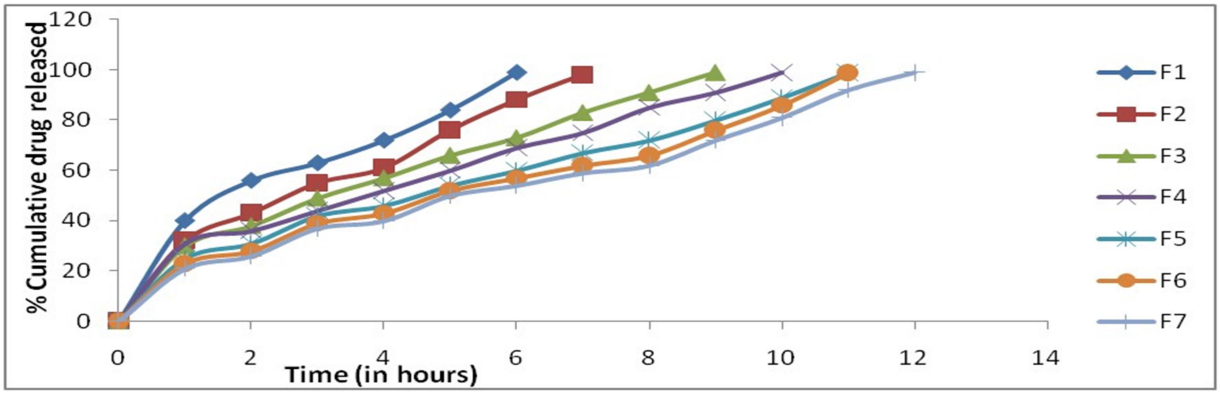

Figure 4: Dissolution release profile of F1-F7 Formulations

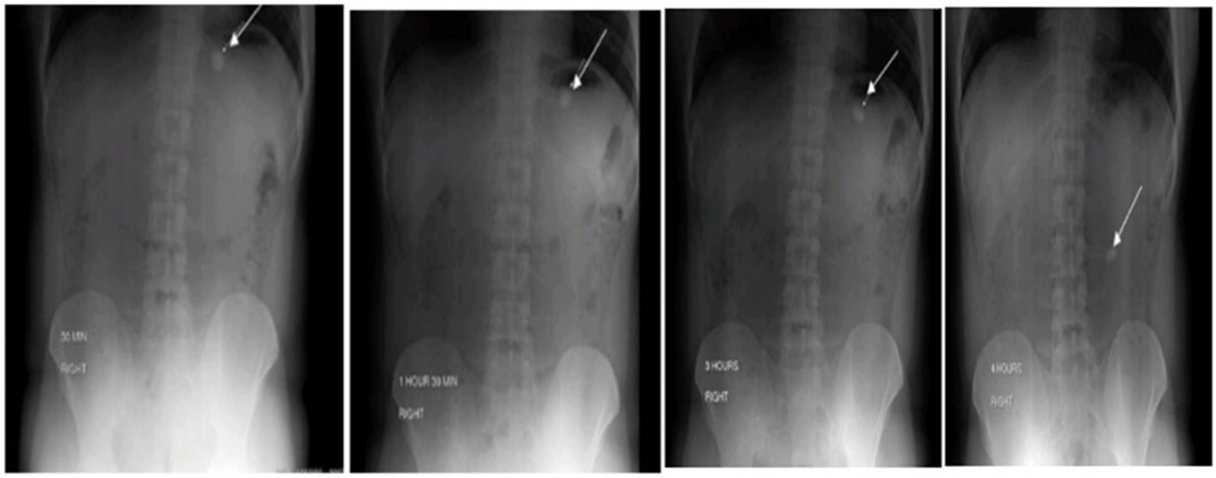

Figure 5: In-*vivo* x-ray studies, a) After 30 minutes, b) After1 hour 30 minutes) After 3 hours, d)After 4 hours

Table 4: Release kinetics of formulations

Formulation code	Zero order R^2	First order R^2	Higuchi's R^2	Korsmeyer & Peppas R^2	n
F-1	0.852	0.706	0.928	0.903	0.51
F-2	0.879	0.731	0.927	0.945	0.57
F-3	0.890	0.805	0.933	0.954	0.53
F-4	0.925	0.823	0.942	0.970	0.54
F-5	0.916	0.821	0.947	0.972	0.58
F-6	0.956	0.807	0.952	0.968	0.63
F-7	0.990	0.838	0.965	0.987	0.47
F-8	0.928	0.823	0.956	0.973	0.53
F-9	0.937	0.826	0.951	0.966	0.65
F-10	0.960	0.816	0.948	0.959	0.46
F-11	0.951	0.827	0.938	0.961	0.76
F-12	0.878	0.825	0.949	0.966	0.52
F-13	0.890	0.779	0.950	0.962	0.49
F-14	0.970	0.829	0.959	0.971	0.46

CONCLUSION

Loratadine floating tablets were prepared with two polymers (CARBOPAL 940 and HPMC K100M) in different concentration ranges, the optimized formulation (F7) showed good i*n-vitro* buoyancy lag time of 30 sec and floated continuously for 12 hrs, FTIR studies indicated that there is no interaction between dug and polymer, *in-vitro* dissolution studies of optimized formulation (F7), marketed product was compared, F7 formulation was retarded the drug release over the marketed product within 12 hours. The optimized formulation follows Zero order, Higuchi model, Korsemeyer –Peppas, and mechanism of drug release is non fickian diffusion or anomalous diffusion, and *in-vivo* x-ray studies revealed the gastric residence time of 4 hrs, stability studies indicated that there is negligible change in parameters.

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CONFLICT OF INTEREST

No conflict of interest are declared

ABBREVATIONS USED

LD: Loratadaine; HPMC: Hydroxy propyl methyl cellulose; GIT: Gastro intestinal tract; MCC:Micro crystalline cellulose; HCL: Hydrochloric acid;%: Percentage; hrs: Hours; ml:Milli liter; mg: Milli grams; nm: Nano meter; RH: Relative humidity; ^{0}C: Degree celcius.

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