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FORMULATION AND EVALUATION OF SUSTAINED RELEASE FLOATING TABLETS OF LORATADINE

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Keywords:

Gastro retentive floating tablets, HPMC K15 M, Sodium alginate, Direct compression, Total buoyancy, *In-vitro* release

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ABSTRACT: Loratadine a long-acting tricyclic antihistamine with selective peripheral histamine H1-receptor antagonistic activity, is used for the symptomatic relief of allergic conditions like runny nose, itchy or watery eyes, sneezing and nasal or throat itching and chronic urticaria. It is stable in acidic pH, has a narrow therapeutic absorption window in the GI tract and found to be absorbed in the proximal part of the small intestine. Thus, it is decided to prolong the gastric residence time in terms of making floating gastro retentive drug delivery system to increase drug absorption and hence bioavailability. In this study, Loratadine floating tablets were prepared by using HPMC K15 M and Sodium Alginate as polymers and gas generating agents like sodium bicarbonate and calcium carbonate at varying polymer concentrations and combinations. The tablets prepared by direct compression technique were evaluated in terms of their pre-compression parameters and post-compression characteristics such as physical characteristics, total buoyancy, buoyancy lag time, swelling index, and *in-vitro* release. The best formulation showed no significant change in physical appearance, drug content, total buoyancy time, buoyancy lag time, or *in-vitro* release after storage at 40 ºC/75% RH for three months. The *in-vitro* release studies confirmed that the formulation (F10) containing 3:4 % w/w of HPMC K15 M and sodium alginate showed sustained drug release (78.51%) for 12 h and remained buoyant for more than 12 h. Loratadine floating tablets prepared using HPMC and Sodium Alginate polymers adopting direct compression technology found to be very economical mean of improving bioavailability.

INTRODUCTION: The oral route represents the predominant and most preferable route for drug delivery unlike the majority of parenteral dosage forms it allows ease of administration by the patient and highly convenient way for substances to be introduced into the human body.

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Oral drug delivery systems are divided into immediate release and modified release systems [1]. Modified release systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients and patient compliance as well as reducing side effects.

Oral modified-release delivery systems commonly include delayed-release, extended-release programmed release and site-specific or timed release. Oral extended-release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period following administration.

Extended-release drug delivery systems offer several advantages compared to conventional drug delivery system including avoiding drug level fluctuations by maintenance of optimum therapeutic plasma and tissue concentrations over prolonged time periods, avoiding subtherapeutic as well as toxic concentrations, thus minimizing the risk of failure of the medical treatment and undesirable side effects, reducing the administered dose and reduced frequency of administered dose while achieving comparable results, Targeting or timing of the drug action. Hence, it is highly desirable to develop a sustained drug delivery system releasing the drug at predetermined rates to achieve optimal plasma drug levels and at the site of action [2, 3]. Majority of drugs are preferentially absorbed in the upper part of the small intestine. So, Gastro retentive drug delivery systems are preferred. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with GI mucosa leading to higher bioavailability and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance [4-6].

There are various approaches to extend gastrointestinal transit time by prolonging the residence time of drug delivery system in the stomach such as hydrodynamically balanced intragastric delivery system, Intragastric floating gastrointestinal drug delivery system, Inflatable gastrointestinal drug delivery system, Intragastric osmotically controlled drug delivery system, Intra rumen controlled release drug delivery device, Bioadhesive gastrointestinal drug delivery system [7].

The concept of floating drug delivery systems (FDDS) was first described in the literature in 1968 when Davis developed a method for overcoming the difficulty experienced by persons of gagging and choking while swallowing medicinal pills. He suggested that such difficulty could be overcome by providing pills with a density of less than 1g/cm^3 such that the pill will float on the surface of water [8]. FDDS are low-density systems that have sufficient buoyancy float over the gastric contents and remain in the stomach for a prolonged period.

FDDS are preferred as they are economic and has improved patient compliance and they are advantageous for drugs absorbed from the stomach, *e.g.*, ferrous salts and for drugs meant for local action in the stomach, *e.g.*: antacids, drugs with narrow absorption window in the small intestine region, *e.g.*: L-Dopa. When there is a vigorous intestinal movement, and a short transit time as might occur in a certain type of diarrhea, poor absorption is expected. Under such circumstances also it may be advantageous to keep the drug in the floating condition in the stomach to get a relatively better response [9, 10].

The present work is an attempt to develop FDDS in the form of tablets taking loratadine as the model drug. Loratadine is a long-acting tricyclic second-generation antihistamine. It is an antagonist at peripheral histamine (H1) receptors. Desloratadine (decarboethoxy loratadine) is the active metabolite of loratadine and produces the same pharmacological effect as the parent compound. An oral dose of loratadine or desloratadine typically begins to inhibit the wheal and flare reaction after intradermal histamine injection within 1-3 h reaches a peak effect within 8-12 and lasts for approximately 24 h. Some of the common adverse effects are sleepiness, headache, nausea, stomach ache, or rash. But the adverse effects were generally not so bad that people would stop taking the drugs. The main safety concern with antihistamines is possible adverse effects on the heart; this did not happen in these trials. But loratadine has short absorption window, preferentially absorbs at the proximal part of small intestine [11].

In this regard, loratadine gastro retentive effervescence floating tablets were prepared by using polymers such as HPMC K15 M and sodium alginate in different combinations and concentrations using direct compression technology to enhance gastric retention and to increase its bioavailability and duration of action.

MATERIALS AND METHODS: Loratadine was obtained as a gift sample from Strides Arco Laboratories, Bangalore. Hypromellose K15M, magnesium stearate, talc were purchased from S.D Fine Chemicals Ltd, Mumbai.

Sodium bicarbonate, Calcium carbonate were obtained from Central Drug House Private Ltd,

New Delhi, Microcrystalline cellulose was obtained from Emco Industries Ltd Hyderabad, India.

Preparation of Floating Tablets: All ingredients were collected and weighed accurately. Loratadine with polymers was sifted and passed through sieve #60, and then the remaining excipients were rinsed over after pre-blending all ingredients in mortar for 15 min. The entire mixture was blended for 5 min. Then magnesium stearate was added and blended again for 5-6 min; lubricated powder was compressed under 8mm punch of Remake tablet punching machine, Minipress - I 12 station D tooling. The composition of different formulations is shown in **Table 1**.

TABLE 1: COMPOSITION OF DIFFERENT FORMULATIONS

Ingredients mg/tablet	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Loratadine	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
HPMC (K15M)	_	18	30	60	90	90	120	120	120	120	120	105	90	75	60
Sodium alginate	90	60	30	18	_	30	_	21	30	60	90	60	60	60	60
$CaCO_3$	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
$NaHCO_3$	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
MCC	137	149	167	149	137	107	107	86	77	47	17	62	77	82	107

All the quantities are in mg. Total weight of each tablet is 300 mg

Evaluation of Floating Sustained-Release Tablets: The powder was evaluated for bulk density, tapped density, Carr's index, Hausner's ratio, and angle of repose. The prepared tablets were evaluated for thickness, hardness, friability, weight variation test, drug content, *in-vitro* buoyancy, swelling index, and *in-vitro* release studies [12].

Precompression Parameters: The following tests were performed for polymers as well as for drug substances.

A. Bulk Density: The powder sample under test was screened through sieve #18, and the sample equivalent to 10g was accurately weighed and filled in a 50ml graduated cylinder, and the powder was leveled, and the unsettled volume (V_0) was noted. The bulk density was calculated in g/cm^3 by the formula.

$$\text{Bulk density } (\rho o) = M/V_o$$

Where, M=Mass of powder taken, V_o=Apparent unstirred volume

B. Tapped Density: The powder sample under test was screened through sieve #18 and the weight of sample equivalent to 10g was filled in 50ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as tapped volume (V_f). The tapped density was calculated in g/cm^3 by the formula

$$\text{Tapped density } (\rho t) = M/V_f$$

Where, M = Weight of sample powder taken, V_f = Tapped volume

C. Percentage Compressibility or Carr's Index: Based on the poured density and tapped density, the percentage compressibility of the granules was computed using the Carr's compressibility index by the formula,

Carr's index (%) = Tapped density – poured density × 100 / Tapped density

Hausner's ratio: Hausner's ratio was calculated using the formula,

Hausner's ratio = Tapped density / poured density

D. Angle of Repose: Angle of repose of the granules was determined by the height cone method. A funnel was fixed to a desired height, and granules were filled in it. They were allowed to flow down on a graph paper fixed on a horizontal surface, and angle of repose was calculated using the formula,

$$\tan \theta = 2h / D$$

Where h and D are the height and diameter of the pile, respectively.

Post Compression Parameters: All the prepared matrix tablets were evaluated for the following parameters.

Hardness: The hardness of ten tablets was measured using Monsanto hardness tester. The mean and standard deviation were computed and reported. It is expressed in kg/cm^2.

Friability: The friability of the tablets was determined using electrolab friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into the friability. The friabilator was operated at 25 rpm for 4 min. After 4 min, the tablets were weighed again. The friability was then calculated using the formula,

Friability (%) = initial weight – final weight × 100 / initial weight

Weight Variation Test: Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 10 tablets were calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weights deviate from the average weight.

Drug Content: Ten tablets were weighed, and the average weight was calculated. All the 10 tablets were crushed in a mortar. The powder equivalent to 100mg of Loratadine was dissolved in 100ml of 0.1N HCl and shaken for 20min. The solution was filtered, and 5ml of the filtrate was diluted to 100ml using 0.1N HCl. The absorbance of the resultant solution was measured at 280nm using 0.1N HCl as a blank. The amount of drug present in one tablet was calculated.

Swelling Index: The swelling of the floating tablet were determined by swelling the tablets in 0.1 N HCl (pH 1.2) at the room temperature. Swollen weight of the tablet determined then swelling index was calculated by the following equation [13].

Swelling index = final weight – initial weight × 100 / initial weight

***In-vitro* Buoyancy Study:** The time taken by the tablet to emerge onto the surface of the medium after adding to the dissolution medium is called Buoyancy lag time (BLT). Duration of time by which the dosage form constantly emerges on the surface of a medium called Total floating time (TFT) Both BLT & TFT were determined by placing the tablet in 900ml of simulated gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5 ºC, USP type II apparatus [14].

Dissolution Study: Dissolution of the tablets of each batch was carried out using USP type-II apparatus using the paddle. The dissolution medium consisted of 900 ml of 0.1N HCl (pH 1.2) for 8h, maintained at 37 ± 0.5 ºC. One tablet was placed dissolution vessel, and the paddle rotation speed was set at 50 rpm. 5 ml of the sample was withdrawn every hour for 8 h and every 1 h to 8 h the same volume of the fresh medium was replaced every time [15]. The samples were analyzed for drug content at a wavelength of 280 nm using double beam UV-Visible spectrophotometer.

The content of the drug was calculated using the equation generated from the standard curve. The cumulative percentage drug released was calculated.

Treatment of Dissolution Data with Different Release Kinetics: The dosage forms that do not disaggregate and release the drug slowly (assuming that the area does not change and no equilibrium conditions are obtained) could be represented by zero order kinetics equation. It suggested that the quantity of drug released from the matrix tablets is often analyzed as a function of the square root of time, which is typical for systems where drug release is governed by pure diffusion. However, the use of this relationship in swellable systems is not justified completely as such systems can be erodible. Therefore, analysis of drug release from swellable matrices must be performed with a flexible model that can identify the contribution to overall kinetics; an equation proposed by Ritger and Peppas. To analyze the mechanism of drug release from the matrix tablets, the data obtained from the drug release studies were analyzed according to the following equations,

1. Zero-order model: [$Q = K_0 t$]
2. Higuchi model: [$Q = K_H t^{½}$]
3. Korsmeyer -Peppa's model: $F = (M_t/M) = K_m t^n$
4. First-order model: $Q=Q_O e^{-kt}$
5. Hixson- crowell model: $Q_O^{1/3}-Q^{1/3}=kt$

In all mathematical equations, Q is the amount of drug released at time t, M_t is the drug released at time t, M is the total amount of drug in the dosage form, F is the fraction of the drug released at time t, K_0 is the zero-order release rate constant, K_H is the Higuchi square root of time-release rate constant, K_m is constant which depends on the geometry of the dosage form and n is the diffusion exponent indicating the mechanism of drug release. The value n = <0.45 indicates Fickian diffusion, the value of n between 0.45 and 0.89 indicates non-fickian diffusion and the value n = 0.89 indicates case-II transport [17].

Stability Studies: A study of the stability of the pharmaceutical product is essential. These studies were designed to increase the rate of chemical or physical degradation of the drug substance or product by using exaggerated storage conditions. Stability studies are important to prevent economic repercussions may lead to considerable financial loss. From safety to the patient, it is important that the patient receives a uniform dose of the drug throughout the shelf life of the product. The formulation stored at elevated temperatures such as 40 ºC ± / 2 ºC / 75% ± / 5% RH for 3 months [20]. The samples were withdrawn at end of 3 months checked for BLT and drug content.

RESULTS AND DISCUSSIONS: The FTIR spectra of the drug and the physical mixture confirmed the absence of interaction between drug and the polymeric mixtures. The significant peaks of pure drug and drug with excipients peaks were interpreted and shown in **Table 2** and **Fig. 1-4**.

Drug-Excipients Compatibility Studies:

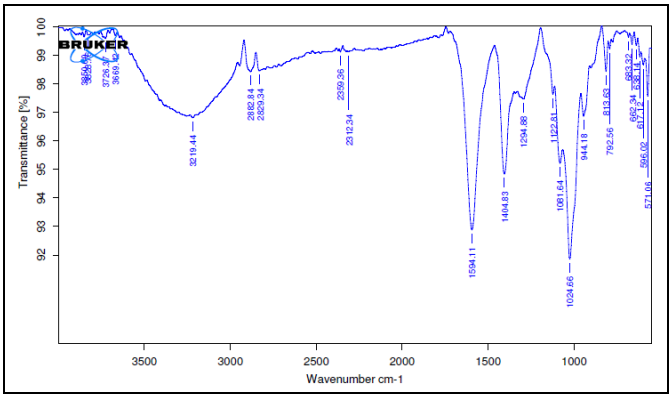

FIG. 1: FTIR SPECTRA OF LORATADINE

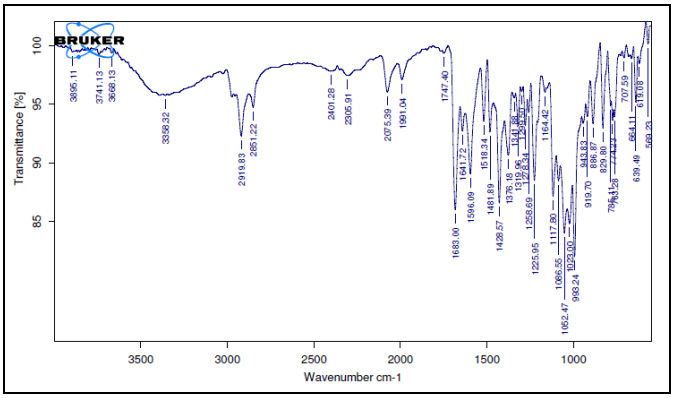

FIG. 2: FTIR SPECTRA OF SODIUM ALGINATE

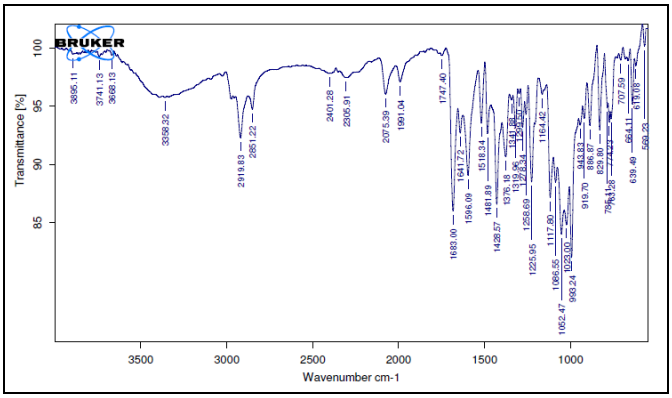

FIG. 3: FTIR SPECTRA OF LORATADINE + EXCIPIENTS

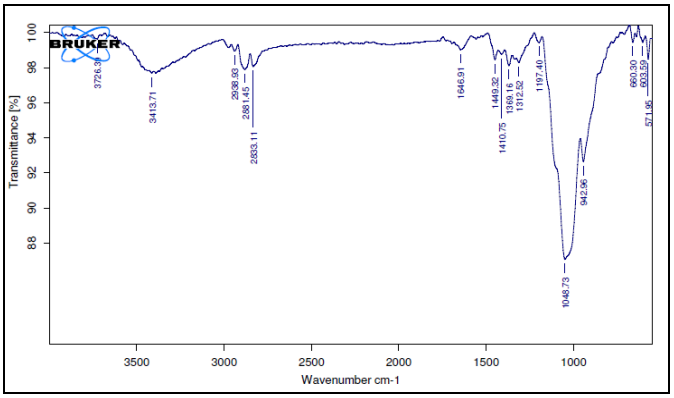

FIG. 4: FTIR SPECTRA OF HPMC15M

TABLE 2: FTIR COMPATIBILITY STUDIES

Functional groups	Stretching/ Deformation	FTIR Significant peaks	
		Pure drug (cm^{-1})	Drug+ Polymers (cm^{-1})
N=N	Stretching	1595.84	1596.09
C=C	Stretching	1683.99	1683.00
CH_3	Stretching	2974.29	2919.83
CH_3	Deformation	1429.01	1428.57
O-H	Stretching	3644.62	3668.13

Evaluation of Floating Sustained Release Matrix Tablets:

Pre-Compression Parameters: The parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose, were determined, and the results were reported, as shown in Table. The bulk density and tapped density were tabulated and was found to be 0.48 ± 0.01 to 0.57 ± 0.04 and 0.58 ± 0.03 to 0.73 ± 0.03, respectively. Carr's index or compressibility index and Hausner's ratio was found to be in between 16.1 ± 0.02 to 26.5 ± 0.03 and 0.88 ± 0.01 to 1.95 ± 0.05. The angle of repose for different formulations was less than 30, which indicates good flow properties of the powder. The values were found to be in between 25.1 ± 0.016 to 27.5 ± 0.014. All these results indicate that the powder possessed satisfactory flow properties. The results were found to be within the limits and satisfactory. The pre-compression parameters of the powder blend (F1-F15) were shown in **Table 3**.

TABLE 3: PRE-COMPRESSION PARAMETERS FOR THE POWDER BLEND F1-F15

Formulation code	Angle of repose	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Carr's index (%)	Hausner's ratio (H_R)
F1	27.5±0.02	0.57±0.02	0.67±0.02	20.8±0.03	1.26±0.04
F2	25.1±0.03	0.52±0.04	0.68±0.01	16.1±0.03	1.29±0.04
F3	27.5±0.04	0.57±0.03	0.67±0.01	21.6±0.02	1.30±0.02
F4	26.1±0.01	0.58±0.01	0.73±0.01	21.1±0.02	1.32±0.01
F5	28.0±0.01	0.57±0.01	0.69±0.01	17.6±0.05	1.24±0.04
F6	29.7±0.02	0.55±0.02	0.73±0.02	24.7±0.04	1.22±0.05
F7	25.1±0.03	0.56±0.03	0.71±0.02	21.1±0.04	1.27±0.04
F8	26.1±0.02	0.53±0.02	0.72±0.02	25.8±0.04	1.95 ±0.05
F9	26.0±0.01	0.55±0.03	0.73±0.03	17.6±0.01	1.24±0.01
F10	25.1±0.02	0.51±0.03	0.61±0.03	21.3±0.04	1.12±0.02
F11	25.4±0.01	0.48±0.01	0.58±0.03	26.5±0.01	0.88±0.01
F12	24.5±0.020	0.51±0.01	0.61±0.01	21.3±0.03	1.12±0.02
F13	27.5±0.03	0.57±0.02	0.67±0.02	20.8±0.03	1.26±0.04
F14	25.1±0.04	0.52±0.04	0.68±0.02	16.1±0.03	1.29 ±0.04
F15	27.5±0.01	0.57±0.03	0.67±0.01	21.6±0.02	1.30±0.02

Post Compression Parameters: The properties of tablets such as thickness, hardness, friability, weight variation, BLT, TBT, swelling index and drug content for the formulations F1 to F15 were determined, and the results were reported, as shown in **Table 4-7** and **Fig. 5** and **6**.

TABLE 4: POST COMPRESSION PARAMETERS (F1-F15)

Formulation code	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight variation (mg)
F1	11.0 ± 0.01	4.0 ± 0.02	4.5 ± 0.01	0.78 ± 0.02	99.45 ± 0.02	297 ± 0.02
F2	11.3 ± 0.02	4.2 ± 0.01	4.4 ± 0.01	0.92 ± 0.04	99.94 ± 0.03	302 ± 0.02
F3	10.9 ± 0.01	4.3 ± 0.02	4.5 ± 0.03	0.98 ± 0.05	99.63 ± 0.02	299 ± 0.03
F4	11.1 ± 0.02	4.0 ± 0.01	4.4 ± 0.02	0.82 ± 0.02	99.56 ± 0.02	300 ± 0.01
F5	11.2 ± 0.01	4.3 ± 0.02	4.2 ± 0.01	0.94 ± 0.04	97.98 ± 0.03	301 ± 0.02
F6	10.8 ± 0.03	4.2 ± 0.01	4.0 ± 0.02	0.86 ± 0.03	98.85 ± 0.02	297 ± 0.03
F7	11.0 ± 0.02	4.1 ± 0.02	3.8 ± 0.02	0.81 ± 0.03	99.12 ± 0.03	299 ± 0.01
F8	11.0 ± 0.03	4.3 ± 0.01	3.9 ± 0.01	0.84 ± 0.03	99.46 ± 0.02	304 ± 0.03
F9	11.4 ± 0.01	4.3 ± 0.02	4.2 ± 0.02	0.92 ± 0.04	97.92 ± 0.03	299 ± 0.02
F10	11.0 ± 0.01	4.2 ± 0.01	3.9 ± 0.02	0.74 ± 0.02	99.97 ± 0.02	301 ± 0.03
F11	11.2 ± 0.02	4.3 ± 0.02	4.5 ± 0.01	0.80 ± 0.03	99.62 ± 0.03	299 ± 0.02
F12	11.1 ± 0.01	4.2 ± 0.01	4.2 ± 0.03	0.91 ± 0.04	98.98 ± 0.02	298 ± 0.03
F13	10.9 ± 0.02	4.2 ± 0.02	4.5 ± 0.02	0.94 ± 0.04	97.98 ± 0.03	303 ± 0.01
F14	11.2 ± 0.02	4.3 ± 0.01	4.4 ± 0.02	0.93 ± 0.05	99.83 ± 0.03	301 ± 0.02
F15	11.0 ± 0.01	4.3 ± 0.02	4.4 ± 0.01	0.97 ± 0.05	99.55 ± 0.02	299 ± 0.03

The thickness of the tablets was found to be in the range of 4.0 ± 0.02 mm to 4.35 ± 0.03. According to the weight variation test in U.S.P, the percentage deviation of the tablets weighing in the range of 130-324 mg is ± 7.5%. The weight of all tablet formulations was as per the official requirements.

Good uniformity in drug content was found among different formulations, and the drug content was more than 97%. The hardness of the tablets was found to be in the range of 3.8-4.5kg/cm^2. Tablet hardness is not an absolute indicator of strength. Another measure of tablet's strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the friability for all the formulations was below 1%, indicating that the friability was within the prescribed limit.

TABLE 5: FLOATING PROPERTY OF LORATADINE TABLETS

S. no.	Formulation code	Buoyancy lag time (sec)	Total floating time (sec)	Matrix integrity	Buoyancy
1	F1	3s	>24 hrs	+	+
2	F2	70s	>8 hrs	-	+
3	F3	50s	>8 hrs	-	+
4	F4	31s	>12 hrs	-	+
5	F5	16s	>12 hrs	+	+
6	F6	15s	>12 hrs	+	+
7	F7	6s	>24 hrs	+	+
8	F8	16s	>24 hrs	+	+
9	F9	17s	>24 hrs	+	+
10	F10	45s	>24 hrs	++	+
11	F11	83s	>24 hrs	+	+
12	F12	43s	>24 hrs	+	+
13	F13	69s	>12 hrs	+	+
14	F14	43s	>12 hrs	+	+
15	F15	130s	>12 hrs	+	+

'-' poor matrix integrity, '+' good matrix integrity, '++' very good matrix integrity

All batches of tablets were found to exhibit short BLT due to the presence of sodium bicarbonate and calcium carbonate. The tablets with high viscosity grade HPMC K15M had less BLT, but after adding sodium alginate in increased concentration lag time was reduced with good sustained. Concerning buoyancy studies, it can be concluded that F10 formulation showed good BLT and TBT.

The first four formulations containing a high concentration of sodium alginate compared to HPMC K15M, which shows rapid swelling but poor matrix integrity. But after optimizing the concentration of HPMC K15M the matrix integrity is increased, and by increasing the concentration of sodium alginate, the swelling is controlled.

TABLE 6: SWELLING INDEX OF LORATADINE (F1-F7)

Time (h)	F1	F2	F3	F4	F5	F6	F7
1	33.4	85.8	35.6	95.8	104	96	97.4
2	66.4	135.5	40.8	153.2	141.6	115.6	109.2
3	97.4	186.7	47.6	168.4	166	137.7	145.4
4	116.5	200.4	NC	203.2	196.4	153.0	156.3
5	NC	202.0	NC	224.4	256.8	182.2	192.8
6	NC	206.0	NC	238	268.8	209.2	225.8
7	NC	NC	NC	NC	316	NC	298.2

NC-No change in weight

TABLE 7: SWELLING INDEX OF LORATADINE (F8-F15)

Time (h)	F8	F9	F10	F11	F12	F13	F14	F15
1	98.8	98.5	101.2	102.3	106.2	105.2	104.2	106.8
2	111.3	110.6	121.6	125.3	156.3	158.3	149.2	156.2
3	142.2	145.9	151.6	156.1	185.2	190.5	191.2	195.3
4	158.2	160.2	174.2	173.0	253.5	265.2	270.6	280.3
5	195.6	206.5	210.3	215.6	312.2	320.8	325.6	330.5
6	226.4	259.2	279.6	285.6	330.2	NC	NC	NC
7	306.3	310.3	333.4	321.6	NC	NC		NC
8	NC	NC	NC	NC	NC	NC	NC	NC

NC-No change in weight

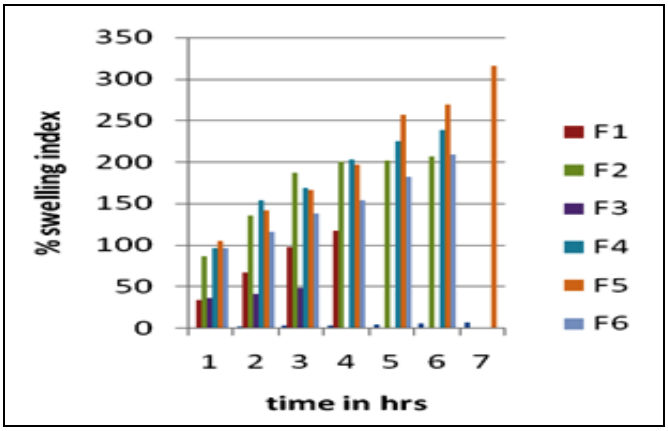

FIG. 5: SWELLING INDEX OF LORATADINE (F1-F7)

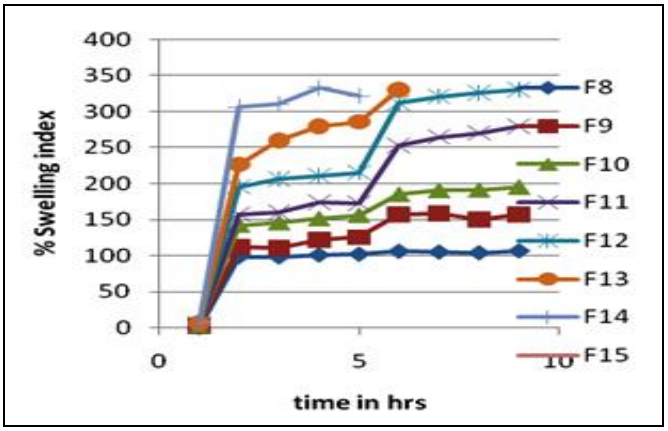

FIG. 5: SWELLING INDEX OF LORATADINE (F8-F15)

The Dissolution Profile of Loratadine Floating Tablets: Primarily first six formulations were formulated by varying the concentration of both the polymers (HPMC K15M), and they are treated as trial formulations as they show burst release and relatively less sustained. But all the formulations showed good floating lag time and log time. In F1 formulation, only sodium alginate was used as a polymer, which showed burst release because of rapid swelling.

From F2-F4 formulations, sodium alginate was gradually decreased by increasing the concentration of HPMC K15M, which also resulted in burst release. In F5 formulation, only HPMC K15M was used as a polymer, which also showed burst release but had good matrix integrity when compared to F1.

By increasing the concentration of HPMC K15M in F7, the burst release is controlled very much compared to other formulations. For decreasing the burst release and for improving the sustainability, sodium alginate concentration is increased gradually and finally optimized at F10 formulation. All the remaining formulations F12-F15 the concentration of HPMC K15M by keeping sodium alginate concentration constant, which gives burst release. Thus, formulation F10 containing a combination of sodium bicarbonate (30mg) and calcium carbonate (30mg) with HPMC K15M (120mg) and sodium alginate (60mg) was found to achieve optimum *in-vitro* buoyancy and flotability of more than 24 h. The *in-vitro* dissolution study of formulations is shown in **Table 8** and **9** and **Fig. 7** and **8**.

TABLE 8: *IN-VITRO* DISSOLUTION STUDY OF FORMULATIONS FROM F1-F7

Time (h)	% cumulative drug release						
	F1	F2	F3	F4	F5	F6	F7
1	58.6	83.94	62.22	75.25	35.43	61.86	24.57
2	64.7	90.6	87.20	96.97	52.09	85.03	37.97
3	68.01	-	99.51	107.83	78.87	96.97	50.64
4	72	-	-	108.56	86.84	-	63.31
5	83.94	-	-	112.90	90.82	-	64.39
6	85.39	-	-	126.66	97.70	-	65.84
7	86.11	-	-	134.62	105.6	-	73.08
8	90.46	-	-	145.48	114.3	-	78.51

TABLE 9: *IN-VITRO* DISSOLUTION STUDY OF F8-F15

Time (h)	%cumulative drug release							
	F8	F9	F10	F11	F12	F13	F14	F15
1	35.21	29.81	20.51	23.98	22.62	25.96	44.25	47.12
2	53.63	40.32	29.82	29.16	36.32	47.15	60.4	59.01
3	58.64	49.98	37.45	38.52	39.95	49.65	61.52	60.81
4	64.44	65.83	46.81	41.12	47.85	56.89	62.63	63.33
5	75.22	67.36	47.52	47.16	51.85	61.94	64.89	65.85
6	88.96	73.01	48.63	51.84	53.98	77.12	73.06	76.36
7	88.98	79.5	59.1	54.72	58.33	80.25	81.98	80.25
8	91.44	83.82	53.66	58.31	62.22	82.02	91.08	92.88

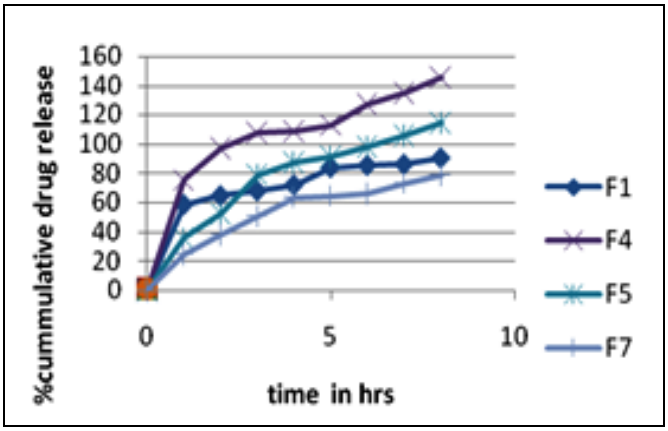

FIG. 7: *IN-VITRO* DISSOLUTION PROFILE OF LORATADINE (F1-F7)

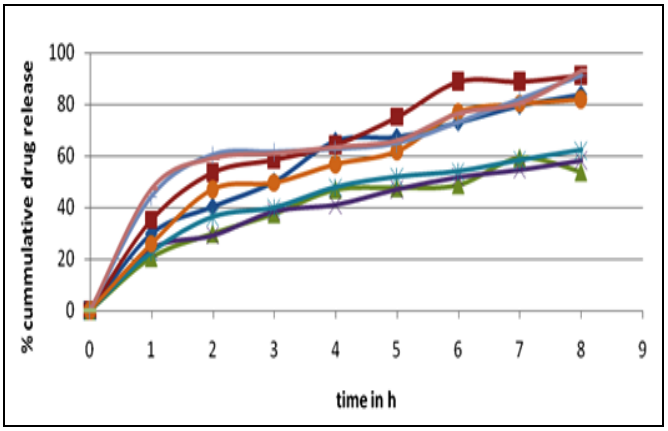

FIG. 8: *IN-VITRO* DISSOLUTION PROFILE OF LORATADINE (F8-F15)

TABLE10: RELEASE KINETICS (F7-F15)

Formulation	Zero-order		First-order		Higuchi	
	r^2	K	r^2	K	r^2	K
F7	0.8928	10.799	0.9444	-0.007	0.9790	29.064
F8	0.9131	11.437	0.9749	-0.008	0.9895	30.600
F9	0.9022	12.795	0.9267	-0.010	0.9865	34.385
F10	0.9135	6.476	0.9511	-0.006	0.9790	17.233
F11	0.8987	7.699	0.9538	-0.006	0.9956	20.826
F12	0.8760	8.386	0.9366	-0.008	0.9897	22.910
F13	0.9053	11.191	0.9434	-0.008	0.9770	29.881
F14	0.6754	9.373	0.8077	-0.007	0.9009	27.822
F15	0.6980	9.675	0.8387	-0.008	0.9117	28.415

r^2 = regression coefficient, K = release rate constant, n = diffusional exponent.

TABLE 11: RELEASE KINETICS (F7-F15)

Formulation	Korsmeyer- Peppas		Hixson Crowell	
	R^2	n	R^2	n
F7	0.9873	0.632	0.9947	0.319
F8	0.9770	0.539	0.9742	0.324
F9	0.9704	0.445	0.9067	0.326
F10	0.8779	0.407	0.8802	0.133
F11	0.9822	0.454	0.9147	0.180
F12	0.9794	0.522	0.9377	0.215
F13	0.9276	0.524	0.91690	0.277
F14	0.8379	0.225	0.7601	0.304
F15	0.9339	0.200	0.7571	0.300S

r^2 = regression coefficient, K = release rate constant, n = diffusional exponent

To know the mechanism of drug release from these formulations, the data was treated according to first-order approximation (log cumulative % drug remaining to be diffused *vs.* time) Higuchi's approximation (cumulative % drug diffused *vs.* square root of time) and Korsmeyer-Peppas approximation (log cumulative %drug diffused *vs.* log time) pattern **Table 10** and **11**. The release of the drug from matrix tablet containing hydrophilic polymers generally involves a factor of diffusion. Diffusion is related to the transport of the drug from the dosage matrix into the *in-vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. The *in-vitro* release profile of the drug from the formulations can be expressed by Higuchi's Kinetics and it indicated by Korsmeyer Peppas kinetics, as the "n" value which is less than 0.45, the drug release mechanism could be Fickian type of diffusion.

Stability Studies: The stability studies conducted as per ICH guidelines revealed that there is no change in physical appearance, hardness, drug content, and BLT. The results were shown in **Table 12**.

TABLE 12: STABILITY STUDIES OF F10 at 40 ºC ± /2 ºC /75% ± /5% RH

Formulation F10	0 Month	1st month	2nd month	3rd month
Hardness (kg/cm^2)	3.86 ± 0.08	3.86 ± 0.08	3.85 ± 0.02	3.85 ± 0.05
Drug content (%)	98.71	98.68	98.68	98.67
Buoyancy lag time	43 sec	43 sec	50 sec	55 sec
In-vitro floating time	>12 hrs	>12 hrs	>12 hrs	>12 hrs

CONCLUSION: The present investigation was carried out to develop gastro-retentive sustained release formulation of Loratadine for an effective and safe therapy by using a natural polymer and a synthetic polymer, *i.e.* sodium alginate and HPMC K15M respectively. Floating sustained tablets prepared by direct compression method were found to be good without chipping, capping, and sticking. It was found that floating log time of all formulations was found to be >12 to 24 h except F2 & F3 having >8h. Floating tablets prepared with the combination of HPMC K15M and sodium alginate in the ratio of 2:1 was found to provide healthy sustained throughout 12 h.

In-vitro release studies confirmed that the F10 formulation showed the drug release of 78.51 in 12 h. The formulation F10 was found to follow first-order kinetics, and the mechanism of drug release was diffusion, which was of Fickian type. Stability studies indicated no appreciable changes in the drug content, hardness, and BLT and TBT during the study period. Based upon the results obtained, F10 was found to be suitable for the gastro-retentive drug delivery system.

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CONFLICT OF INTEREST: Nil

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