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Original Article

FORMULATION DEVELOPMENT AND CHARACTERIZATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS OF LORATADINE

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ABSTRACT

Objective: The main objective of the research work is to develop a single unit non-effervescent drug delivery system of Loratadine (LTD) by direct compression process to prolong the gastric residence time (GRT).

Methods: LTD non-effervescent floating tablets were prepared with different polymers like hydroxypropyl methylcellulose (HPMC) K15M, HPMC K100M (i.e.: 1:1, 1:2, 1:3) as release retardants. Glyceryl behenate (Compritol 888 ATO) and Glyceryl palmitostearate (Precirol ATO 5) were used (1:1, 1:2, 1:3) as low-density lipids to impart buoyancy for longer period.

Results: The drug (LTD) and excipient (i.e. HPMC, low-density lipid aids, etc.,) interaction studies were carried out by Fourier Transform Infrared Spectroscopy (FTIR) and there was no likely interaction involving them. The developed LTD floating matrix tablets were characterized by pre and post-compression parameters and all results were found within the pharmacopoeial limits. The cumulative percentage of drug release ranges from 56.87±0.25 % (F12) to 99.87±0.09 % (F2). The drug release profiles of the all formulations (F1 to F12) were subjected to various pharmacokinetic parameters and the optimized formulation (F3) followed the Korsmeyer Peppas (R^2=0.996) model with non-Fickian diffusion (n>0.5). The obtained data by radiographic images of F3 formulation showed the GRT of 6±0.5 h (n=3).

Conclusion: Hence, from all evaluation studies, it was evident that F3 formulation was optimized (99.82±1.63 % drug release in 12 h).

Keywords: Buoyant, Non-effervescent, Low-density lipids, Direct compression

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INTRODUCTION

Oral directions of drug administration have broad recognition of up to 50-60% of whole dosage forms [1]. Oral drug delivery (i.e.: tablets, capsule, powders, emulsions, suspensions, etc.,) is considered as the most common, most popular, convenient and safe (when compared to parental route) [2]. Solid dosage forms are more popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance [3-5]. The majority accepted solid dosage forms are tablets and capsules; one of the important drawbacks of solid dosage forms; especially solids are not recommended to pediatrics, geriatrics and unconscious patients [6-8]. Gastrointestinal physiology offers additional flexibility in dosage form design than the popularity of other routes [9, 10].

The term extended-release (i.e. controlled release, sustained release, etc,) formulations are used to categorize drug delivery systems (DDS) that are considered to accomplish or extend phase of time subsequent for administration of a single dose and as an alternative to multiple dosage, having a benefit that the drug release was long-standing and it has been noticeable to pharmaceutical manufacturing [11-15]. LTD is a lipophilic, non-sedating H_1 blocker and used to treat seasonal allergic rhinitis having low bioavailability (40%), and biological half-life (8 h). So, patients can avoid frequent administrations in a day [16-20]. Such frequent drug administration may reduce patient obedience and therapeutic effectiveness [21-25]. To overcome the above-mentioned problems it is required to convey the single dose for an extended period. Besides, LTD shows the greatest solubility at acidic pH and it is an appropriate candidate for the expansion of gastroretentive drug delivery systems (GRDDS). The aim of extended release (ER) DDS is to be customized in such a method with the intention; extra residence time in the stomach to release the drug before the absorption window. The goal of GRDDS is to provide a beneficial quantity of the drug to the appropriate location in the body and sustain the required drug concentration. To avoid the problems associated with the delivery of LTD, we planned to formulate LTD in an extended-release floating matrix formulation. This will allow us to reduce the frequency of administration and enhances patient compliance. To achieve the goal we have used low-density lipids or floating aids like compritol and precirol that can allow the formulation to stay on top of the gastric contents. It will avoid the first-pass metabolism and will improve the bio-availability of the formulation.

MATERIALS AND METHODS

Materials

Loratadine received as a gift sample from Hetero Labs Ltd, Hyderabad, India. HPMC K15 M and HPMC K100 M procured from B and K Technologies, China. Compritol and precirol were purchased from Gattefosse, Germany. MCC–(Avicel PH 200), Aerosil and Magnesium stearate from SD Fine Chemicals Ltd., Mumbai. Hydrochloric acid from Merck specialities Pvt. Ltd. Mumbai, India

Methods

Pre-compression characterization

Drug excipient compatibility studies

Fourier transform infrared spectroscopy (FTIR)

The drug excipient compatibility study was carried out by FTIR with in the frequency range of 4000–400 cm^{-1} and 4 cm^{-1} resolution. The IR spectra for the test samples were obtained using the KBr disk method using an FTIR (Star Tech Labs Pvt. Ltd., Hyderabad) [26].

Differential scanning calorimetry (DSC)

The differential thermal analyzer was used to find out the presence of any interaction among drug and excipients. About 5-15 mg of the sample was taken in pierced DSC aluminium pan and scanned in the temperature range of 50-300 °C and the heating rate was 10 °C/min.; nitrogen served as purged gas and the system was cooled down by liquid nitrogen [27].

Flow properties of the powder blend

The powder mixtures of different formulations were evaluated for angle of repose (ɵ), bulk density (gm/cm^3), tapped density (gm/cm^3), Carr's index or compressibility index (%) and Hausner's ratio. [28] And the evaluation test results are shown in table 2.

Angle of repose (ɵ)

The fixed funnel method was employed to measure the 'ɵ' and it was determined by below formula

$$\theta = \tan^{-1}(h/r)$$

Here 'ɵ' is the angle of repose, 'h' is the height of the pile and 'r' is the radius of the base.

Carr's index or compressibility index (%)

Bulk density (BD) and tapped densities (TD) were determined by the following formulas.

$$BD = \frac{\text{Weight of the sample}}{\text{Volume of the sample}}$$

$$TD = \frac{\text{Weight of the sample}}{\text{Tapped volume of the sample}}$$

The carr's index was calculated by the following formula

$$\text{Carr's index} = \frac{TD - BD}{BD} \times 100$$

Hausner's ratio

Hausner's ratio was calculated by the following formula

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

Construction of loratadine calibration curve

The study started with the construction of a standard calibration curve of Loratadine. The standard graph of LTD with 0.1N hydrochloric acid (HCl) was plotted by taking concentration ranging from 5µg/ml to 45µg/ml on X-axis and absorbance values on Y-axis [29-30].

Preparation of LTD non-effervescent floating matrix tablets

Floating tablets containing LTD were prepared by a direct compression technique [31]. Polymers and floating aids ratios were taken as 1:1, 1:2, and 1:3 (table 1). LTD and all other additives are precisely weighed and sieved through 44 mesh.

The LTD was well mixed with a magnitude of necessary polymers (HPMC K15M, HPMC K100M), floating aids (Compritol 888 ATO and Precirol ATO 5), MCC (Avicel PH 200) in geometric proportions. After that the blend was lubricated with previously weighed, sieved magnesium stearate and aerosil. Finally, about 100 mg of the lubricated blend was subjected to compression by using a 6 mm circular standard flat-faced punch on 10 stations rotary tablet punching machine (i.e. Karnavathi, Gujarat, India) [32].

Table 1: Composition of LTD floating matrix tablets

*Formulation (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Drug (LTD)	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K15M	10	20	30	-	-	-	10	20	30	-	-	-
HPMC K100M	-	-	-	10	20	30	-	-	-	10	20	30
Compritol 888 ATO	10	20	30	-	-	-	5	10	15	5	10	15
Precirol ATO 5	-	-	-	10	20	30	5	10	15	5	10	15
Avicel PH 200	65	45	25	65	45	25	65	45	25	65	45	25
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100	100	100	100	100

*Each value represents mean±SD (n=30)

Post-compression characterization

The above-compressed LTD floating tablets should be characterized by several specifications, which include weight variation, thickness, friability; hardness and drug content uniformity, etc., were shown in table 3.

Weight variation (mg)

The weight of the prepared LTD floating tablets (i.e. n=20; randomly from every batch, then average weight should be well-thought-out) determined by using an electronic balance (Shimadzu, AUX220, Japan) [33].

Thickness (mm)

The thickness of the prepared LTD floating tablets (i.e. n=20) measured by, vernier calipers, tablet thickness is reliable from batch to batch or within a batch only if the tablet granulation or dust mix is satisfactorily dependable on particle size and size distribution, if the punch tooling is of regular length, and the tablet press is clean and in good working order. Thickness must be controlled for consumer acceptance of the product, and to facilitate packaging [34].

Friability (%)

The friability test was performed with prepared LTD floating tablets (i.e. n=20; unintentionally from the entire batches) by placing in Roche friabilator and allowed to make 100 revolutions (i.e. 25 rpm for 4 min).

$$\% \text{ Friability} = \frac{W_1 - W_2}{W_1} \times 100$$

Where W_1 is the initial weight of tablets; W_2 is the final weight of de-dusted tablets; and the values<1% is usually good [35].

Hardness (Kg/cm^2)

The hardness (i.e. n=6; erratically from every grouping after that middling should be deliberate) of the prepared LTD floating tablets were measured by using Pfizer type hardness tester (Dolphin Pharmacy Instruments, Pvt. Ltd., Mumbai). By this test, the tablet mechanical potency or crushing strength will be determined and the average hardness with standard deviation was reported [36].

Content uniformity (%)

The prepared LTD floating tablets (n=6) were collected at random and pulverized. Several fine particles corresponding to the weight of 1 tablet was transferred into 100 ml volumetric flask (VF), to this 100 ml of methanol was added, then the solution was subjected to sonication for about 2 h. The solution was up to the mark with an equivalent concentration of the standard solution (i.e. 0.1N HCl) [37].

***In vitro* buoyancy studies (h)**

The *in vitro* floating (n=3) was determined by the reported method. Here, the prepared LTD was placed in a 100 ml beaker containing 0.1N HCl. The time required to float the tablet or rise from the bottom of the beaker to the surface of the liqid called floating lag

time (FLT) and the total duration of tablet float on the surface is called as total floating time (TFT) [38].

***In vitro* dissolution (%)**

The drug release or *in vitro* dissolution studies (i.e. n=6) of LTD non-effervescent floating tablets were carried out with USP dissolution type–II (i.e. paddle) method at 50 rpm in 900 ml of 0.1N HCl as dissolution medium, maintained at 37 °C±0.5 °C. About to 5 ml of aliquot (i.e. sample) was withdrawn at predetermined time intervals for every 1 hour up to 12 h and replaced with 5 ml of fresh medium (i.e. 0.1N HCl) each time. The samples were analyzed by using a double beam UV visible spectrophotometer (Elico, SL210, Hyderabad) at 280 nm. By using a standard calibration curve, calculate the cumulative percentage of drug release [39-40].

***In vivo* buoyancy studies (h)**

In vivo gastric retention time (GRT) was determined by X-ray procedure in healthy human volunteers (n=3). The procedure of the radiographic studies was approved by the institutional human ethical committee (IHEC). For *in vivo* study (i.e.: Proposal no. IRB-AGI/2018-19/11), Barium sulphate ($BaSO_4$) containing LTD floating tablets were prepared by a similar method as described in the formulation. In this revision, part of the LTD was replaced using $BaSO_4$ each one of the ingredients remained equivalent [41].

Mechanism of drug release kinetics

The drug release data of LTD prepared floating matrix tablets were fitted into different kinetic models representing Zero order, First order, Higuchi and Peppas model to know the release mechanism [42-45].

RESULTS AND DISCUSSION

Construction of loratadine calibration curve

The maximum concentration (λ_{max}) of LTD in 0.1N HCl was scanned and found to have the maximum absorbance at 280 nm. The standard graph of LTD in 0.1 N HCl was shown in fig. 1 by taking concentration ranging from 5µg/ml to 45µg/ml and a good correlation was obtained with a regression coefficient (R^2) value of 0.998.

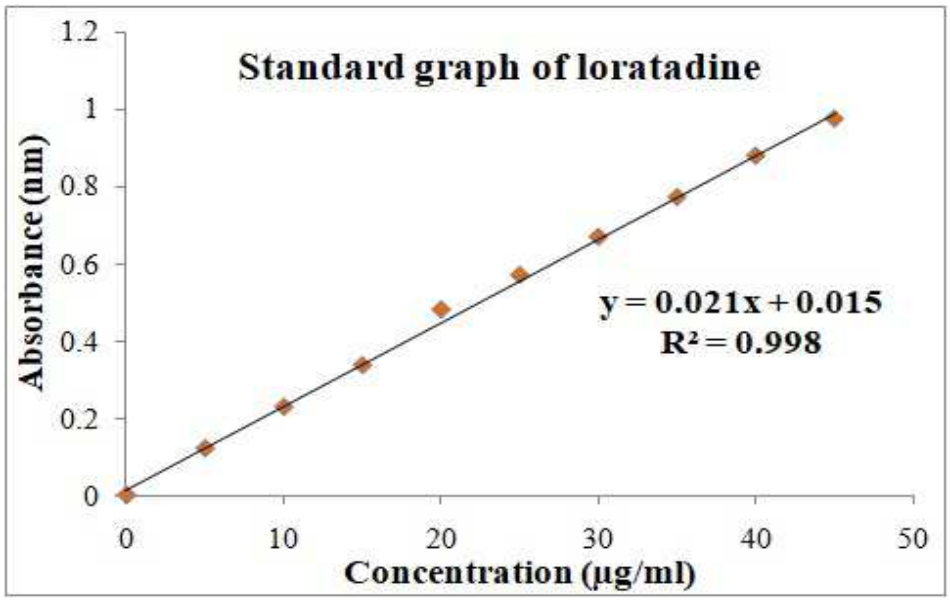

Fig. 1: Standard graph of LTD; (n=1)

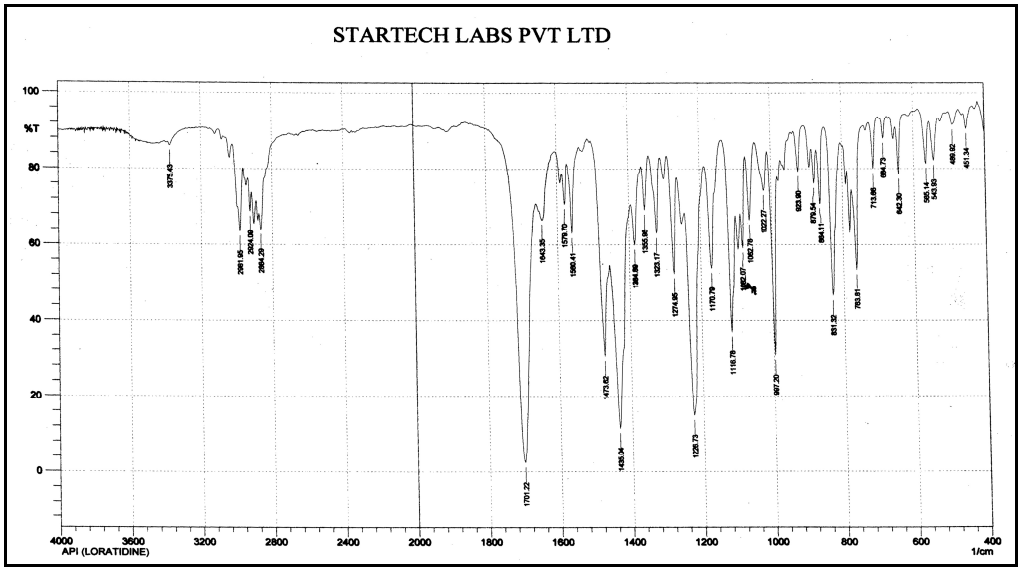

Fig. 2: FTIR spectrum of the pure drug; (n=1)

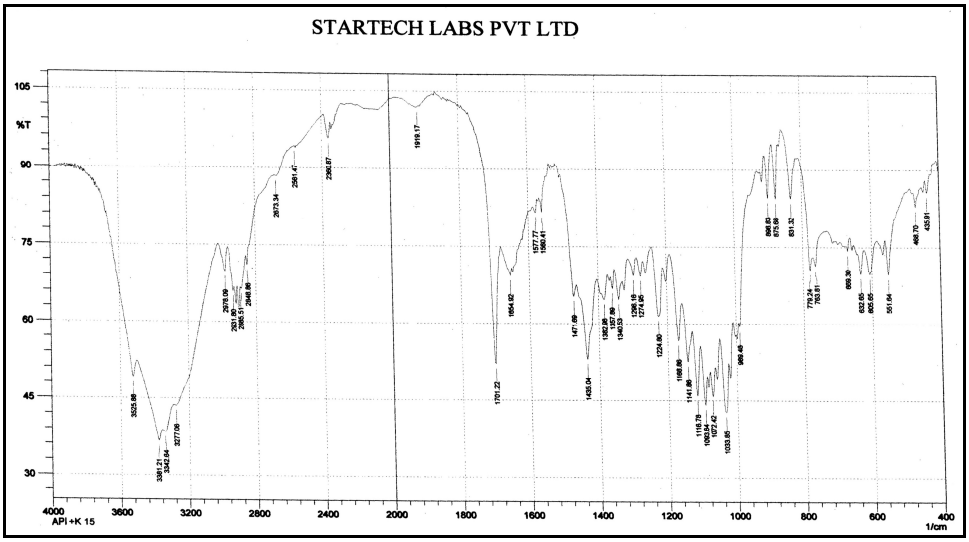

Fig. 3: FTIR spectrum of optimized formulation (F3); (n=1)

Pre-compression characterization

Drug excipient compatibility studies

The drug excipient compatibility study was carried out by using DSC and FTIR. FTIR is one of the most powerful analytical techniques when it comes to the determination of the presence of various functional groups and DSC is a thermo analytical method in which the differentiation in the sum of heat required to raise the temperature of the sample and reference is precisely the same.

Fourier transform infrared spectroscopy (FTIR)

The spectral laboratory analysis of pure drug (LTD) and optimized formulation (F3) as shown in fig. 2 and fig. 3 correspondingly; principle peaks at similar wave-numbers and in an optimized formulation (F3) some different wave numbers observed.

However, these additional peaks were observed with physical mixtures, which could be due to the occurrence of polymers. The results advise that there is no reaction connecting the drug and polymers used in the current study.

Differential scanning calorimetry (DSC)

The thermal properties of the drug and the mixture of drugs and excipients are of important interest since this can help to assess the interaction among different components of the formulations (i.e., drug and other additives). Pure drug (LTD) and optimized formulation (F3) were subjected to DSC analysis.

The DSC curve of a pure drug (i.e. fig. 4) showed a sharp endothermic peak at 136.11 °C. The optimized formulation (F3) drug and Compritol 888 ATO showed a sharp endothermic peak at 135.10 °C (i.e. fig. 5). From the results, it was concluded that the drug was compatible with excipients used in formulations.

Flow properties of the powder blend

All prepared LTD powder blends are subjected to various parameters. The angle of repose ranges from 21.23±1.08 (F2) to 31.40±1.05 (F8); Carr's index ranges from 10.12±0.36 (F11) to15.36±0.47 (F4); Hausner's ratio values ranges from 1.06±1.01 (F9) to 1.26±0.55 (F7). From the above results, the powder blends (i.e. F1 to F12) showed well to excellent flow properties [46].

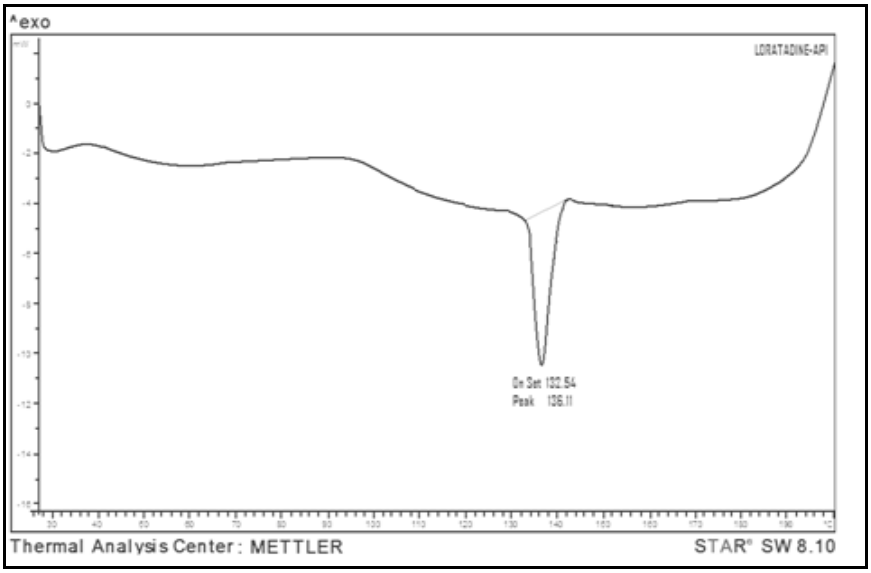

Fig. 4: DSC thermogram of pure drug (LTD); (n=1)

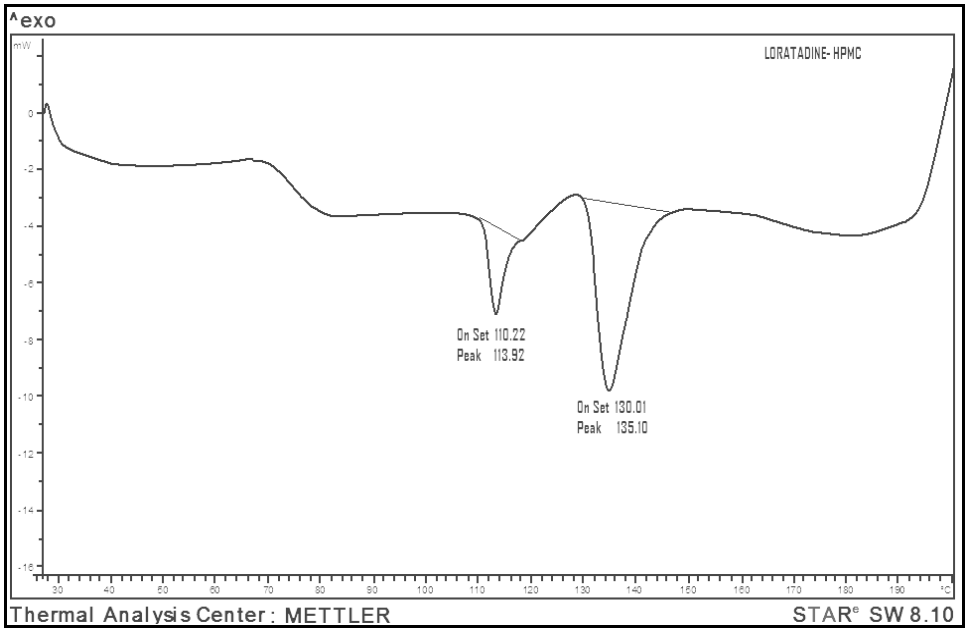

Fig. 5: DSC thermogram of optimized formulation (F3); (n=1)

Table 2: Pre-compression characterization of LTD floating matrix tablets

Formulation code	Angle of repose[a] (Θ)	Carr's index[a] (%)	Hausner's ratio[a]	Flowability
F1	26.51±1.26	12.38±1.04	1.12±0.44	Very good
F2	21.23±1.08	10.54±0.89	1.10±0.38	Excellent
F3	25.34±0.54	14.79±0.63	1.12±1.06	Very good
F4	23.71±0.82	15.36±0.47	1.14±0.89	Very good
F5	27.34±0.09	13.79±1.02	1.08±0.61	Good
F6	23.23±0.06	14.54±0.68	1.17±0.74	Very good
F7	21.34±0.84	12.79±1.09	1.26±0.55	Good
F8	31.40±1.05	12.08±0.53	1.23±1.08	Good
F9	28.52±1.02	15.32±1.27	1.06±1.01	Excellent
F10	25.26±0.93	14.36±0.84	1.17±0.82	Very good
F11	25.78±0.64	10.12±0.36	1.14±0.64	Very good
F12	24.61±0.14	12.09±0.52	1.19±0.76	Very good

[a]Each value represents mean±SD (n=3)

Post-compression characterization

Weight variation (n=20)

The above-prepared formulations, 20 tablets from each batch (i.e. F1 to F12) were individually weighed in milligrams (mg) on electronic balance (Shimadzu, AUX 220, Japan) and results in ranges from 96.86±1.61 mg (F10) to 100.08±0.01 mg (F4).

Thickness (n=20)

Thickness is the only dimensional variable related to the compression process and is measured for all formulations (i.e. F1 to F12) by Vernier calipers and results range from 2.75±0.76 mm (F11) to 3.05±0.48 mm (F4).

Friability (n=20)

Initially, weigh the tablets (i.e. total weight of the tablets is W_1) and after 100 revolutions, de-dusted and reweighed (i.e. total weight of the tablets is W_2) then worked at percentage weight loss and found the range from 0.12±0.65 % (F10) to 0.49±0.07 % (F4). Friability test of each one formulation (F1 to F12) was found satisfactory (i.e.<1%) and viewing sufficient struggle to the mechanical shock and abrasion.

Hardness (n=6)

The hardness of the tablet was maintained for every batch, was instructed to play downwards on drug release because the effect of polymer concentration is the only area of interest and it was found between 4.27±1.08 kg/cm^2 (F5) to 6.09±1.10 kg/cm^2

Drug content uniformity (n=6)

The drug content was estimated by using UV visible spectrophotometer and the drug released from the entire prepared non-effervescent floating matrix tablets ranges from 96.16±1.15 % (F8) to 99.81±1.54 % (F7).

***In vitro* buoyancy studies (n=3)**

All prepared LTD floating matrix tablet formulations (F1 to F12) were evaluated for buoyancy; 0.1N HCl used as medium and lipid aids used to float the tablet without using any gas generating agents such as sodium bicarbonate, citric acid, and tartaric acid etc,. To develop the desired non-effervescent floating matrix tablets of LTD, it was needed to optimize the buoyant properties and release rates. The floating aids (Compritol 888 ATO and Precirol ATO 5), slow down the water diffusion and results in the buoyancy of dosage form over an encoded time. There was no FLT, (i.e. all prepared LTD non-effervescent floating matrix tablets buoyant was zero seconds) which means by floating aids the prepared tablets directly float on the surface of the medium (i.e. 0.1N HCl) and the TFT of all prepared LTD formulations (i.e. F1 to F12) showed ≥12 h [47, 48]. The *in vitro* buoyancy was shown in fig. 6 and fig. 7.

Table 3: Post-compression characterization of LTD floating matrix tablets

Formulation code	Weight variation[a] (mg)	Thickness[a] (mm)	Friability[a] (%)	Hardness[b] (Kg/cm²)	Drug content[b] (%)	Matrix integrity
F1	98.88±1.01	2.97±0.61	0.22±1.25	4.95±0.71	97.25±0.87	Good
F2	98.55±1.09	2.95±0.52	0.29±0.87	5.07±0.85	96.93±1.07	Very Good
F3	99.06±1.03	2.85±0.63	0.41±0.35	5.12±0.59	99.86±1.54	Very Good
F4	100.08±0.01	3.05±0.48	0.49±0.07	6.01±1.63	98.33±0.15	Excellent
F5	99.55±1.25	2.89±0.31	0.21±1.15	4.27±1.08	97.90±1.09	Very Good
F6	98.75±1.91	2.95±0.74	0.14±0.98	5.37±0.58	97.40±0.54	Excellent
F7	98.88±1.02	3.04±0.79	0.21±0.56	5.32±1.53	99.81±1.54	Good
F8	99.88±0.95	2.85±0.93	0.23±1.05	4.96±1.43	96.16±1.15	Very Good
F9	98.01±1.06	3.01±0.67	015±1.54	5.61±1.12	98.31±0.76	Excellent
F10	96.86±1.61	2.79±0.31	0.12±0.65	4.35±1.56	98.16±0.65	Good
F11	98.98±0.75	2.75±0.76	0.24±1.34	6.09±1.10	98.83±0.20	Excellent
F12	98.99±1.36	2.96±0.27	0.20±1.14	4.38±1.12	96.31±1.85	Excellent

[a]Each value represents mean±SD (n=20); [b]Each value represents mean±SD (n=6)

Fig. 6: Top views of *in vitro* buoyancy studies of optimized formulation (F3), a) at zero time b) at 3 h c) at 6 h d) at 12 h; (n=3, mean±SD)

Fig. 7: Front view of *in vitro* buoyancy studies of optimized formulation (F3), a) at zero time b) at 3 h c) at 6 h d) at 12 h; (n=3, mean±SD)

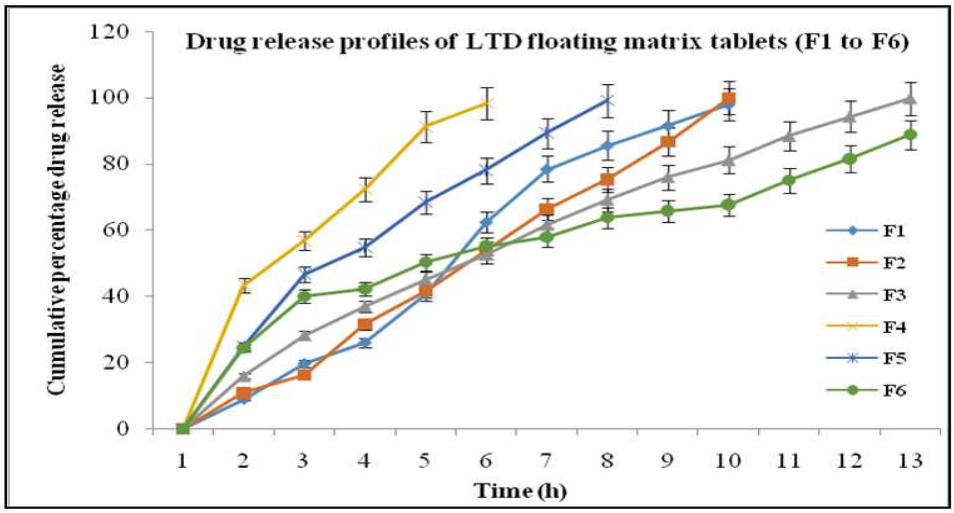

Fig. 8: Cumulative percentage drug release profiles of LTD prepared floating matrix tablets (F1 to F6); (n=6, mean±SD)

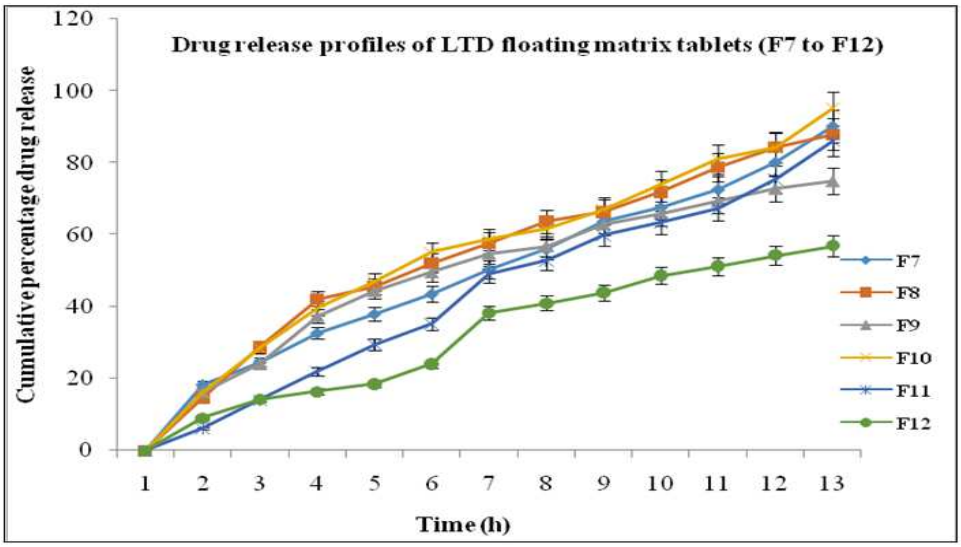

Fig. 9: Cumulative percentage drug release profiles of LTD prepared floating matrix tablets (F7 to F12); (n=6, mean±SD)

***In vitro* dissolution (n=6)**

The prepared LTD floating tablets were exposed to dissolution medium (i.e. 0.1N HCl), the medium penetrates the free spaces, hydrating the polymer and lipid aid. Finally, it forms a gel-like consistency, from which the drug releases slowly for a prolonged time [49]. The cumulative percentage of drug releases was shown in fig. 8 and fig. 9. The most promising formulation was F3 because it cumulative percent of drug release was about 99.82±0.29 % in 12 h.

***In vivo* buoyancy studies (n=3)**

The optimized formulation (F3) was prepared with the same compression force as $BaSO_4$. All the physicochemical properties were within the pharmacopoeial limits [50]. *In vivo,* radiographic studies were conducted on 3 healthy male human volunteers with a glass of water and a standard diet was provided to find out the GRT of the tablets. X-ray pictures were taken at different time intervals such as 1, 3 and 6 h.

The X-ray image shows that tablets remain in the stomach for about 6 h and which indicate the good floating property (shown in fig. 10). These studies revealed that the mean GRT was found to be 6±0.5 h.

Mechanism of drug release kinetics

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release, the dissolution data were fitted into zero-order, First order, and Higuchi and Korsmeyer Peppas models. In all formulations (F1 to F12), the diffusion exponent value was>5. The correlation coefficient (R^2) and diffusion exponent (n) of release data of all prepared LTD non-effervescent floating tablets (i.e. F1 to F12 formulations) were calculated. The optimized formulation F3 followed the Peppas model (R^2 =0.996) with the non-Fickian mechanism and it was shown in table 4.

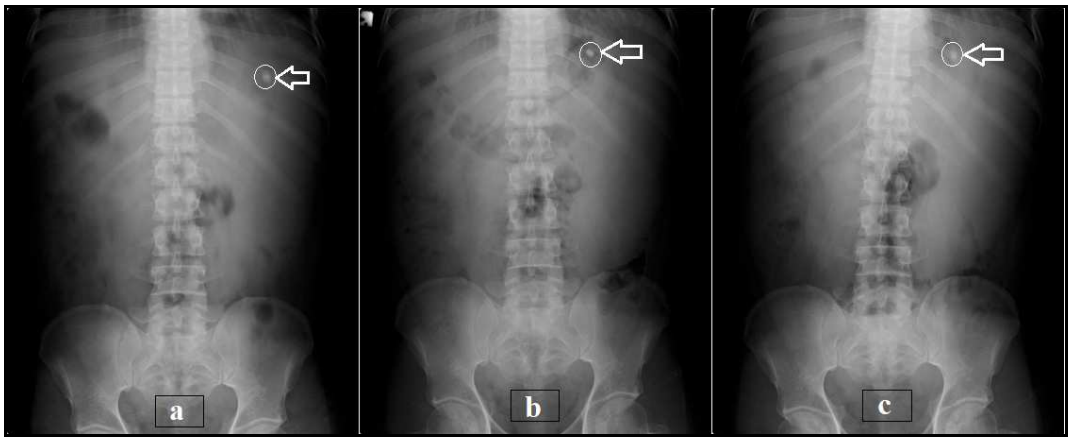

Fig. 10: X-ray images of optimized formulation (F3); a) at 30 min; b) at 3 h; c) at 6 h (tablet position was indicated with the circle and arrow mark); (n=3, mean±SD)

Table 4: Compilation of the results from all the mathematical models applied to the optimized formulation (F3)

Formulation code	Zero-order	First-order	Higuchi	Hixon crowell	Korsmeyer peppas	
			R^2		R^2	n
*F3	0.978	0.869	0.914	0.862	0.996	0.57

*Each value represents mean±SD (n=6)

CONCLUSION

The LTD non-effervescent floating tablets were developed by using HPMC K15, HPMC K 100 as release retardants and Compritol 888 ATO, Precirol ATO 5 were used as floating aids. From the above DSC and FTIR results, there was no drug and excipient interaction found in the formulations. All the formulations showed good physicochemical characteristics and F3 formulation was optimized based on all parameters. The radio-graphical studies revealed a mean GRT of 6±0.5 h. From the above results, it was concluded that the formulations retained in the stomach for a longer period and extended the drug release. Hence, this dosage form helped to improve the absorption of LTD.

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest

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