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FORMULATION OF LINSEED HYDROGEL-BASED FLOATING DRUG DELIVERY SYSTEM FOR GATIFLOXACIN

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ABSTRACT:

A novel gastroretentive drug delivery system based on a polysaccharide substance from linseeds (Linum usitatissimum L.) has been developed as floating matrix tablets for Gatifloxacin. To achieve a desirable prolonged release profile of gatifloxacin, a number of formulations were created using a combination of linseed hydrogel (LSH) and various excipients. The drug release test was carried out mostly at pH 1.2. However, due to specific factors, the tablet may pass through the stomach and into the intestine, where it provided sustained drug release at intestinal pH 7.4. The results showed that sustained gatifloxacin release was related to LSH concentration and that drug release followed a non-Fickian diffusion pattern. The porous character of LSH with elongated channels was revealed by SEM of the tablets, which contributed to the swelling of the tablet and later promoted the release of gatifloxacin from the core of the tablet. An in vivo X-ray investigation was conducted to examine tablet disintegration and real-time floating, which proved the tablet's presence in the stomach for 6 hours. These findings suggest that LSH could be exploited to create novel gastroretentive sustained release drug delivery systems that have the added benefit of delivering drugs at all GIT pH levels.

Keywords: Oral delivery, Sustained release, Gastroretentive, Gatifloxacin, Linseed hydrogel.

I. INTRODUCTION:

To achieve a desirable prolonged release profile of gatifloxacin, a number of formulations were created using a combination of linseed hydrogel (LSH) and various excipients. The drug release test was carried out mostly at pH 1.2. However, due to specific factors, the tablet may pass through the stomach and into the intestine, where it provided sustained drug release at

intestinal pH 7.4. Increasing the retention period in the upper part of the GIT is one way to improve drug absorption and bioavailability (Goole et al., 2007). To keep the dose forms in the stomach, many strategies are used. For example, floating or low-density dosage forms, mucoadhesive, high-density dosage forms, dosage form expansion by swelling or unfolding of excipients, and modified shape systems. Naturally occurring polysaccharides showed high swelling indices at varied physiological pH and stimuli-responsive swelling/deswelling against diverse solvent systems, piqued the researcher's interest in using these polysaccharides in a variety of biomedical sectors (Pawar et al., 2011).
Flax is an ancient crop, and its seeds (flaxseeds/linseeds) provide a high-carbohydrate source (15–20%). Linseeds emitted mucilage made up primarily of rhamnogalacturonans (upper molecular weight fraction (1510 kDa) and arabinoxylan after being soaked in hot water (Kajla et a., 2015). LSH (hot water extracted linseed hydrogel/mucilage) is a safe excipient with a wide range of biomedical applications, including reducing and capping agent for the synthesis of silver nanoparticles and incorporation in wound healing dressings, stimuli-responsive oral sustained release drug delivery system, development of nanoparticle carrier system for anticancer drug, and mucoadhesive beads, nasal gel and microspheres (Goyal et al., 2014).

II. MATERIALS AND METHODS

Materials:

Linseeds were purchased from a trusted local dealer in Nashik, India. Linseeds were dusted and cleaned of physical contaminants before being stored at room temperature in an airtight container. Merck, Germany, provided microcrystalline cellulose (Avicel® PH 102) and HPMC K100M. The gatifloxacin utilised in this study was manufactured according to the United States Pharmacopoeia's specifications (USP). Riedel-de Han, Germany, provided the KCl, NaOH, n-hexane, potassium dihydrogen phosphate, and HCl. Sigma-Aldrich in the United States provided magnesium stearate, polyvinylpyrrolidone K30 (PVP K30), talcum, sodium bicarbonate, and -cyclodextrin. A nylon mesh was used to separate linseed hydrogel (LSH) from linseeds. The entire experiment was conducted with deionized water.

Isolation of LSH:

LSH was isolated using a method that has previously been published. Linseeds (200 g) were properly cleansed with deionized water before being soaked in 1000 mL deionized water. Soaked seeds were heated for 30 minutes at 80°C after 48 hours. Mucilage extruded from seeds was separated using nylon mesh and extensively cleaned with n-hexane to eliminate lipophilic components before being rinsed with deionized water. Mucilage was centrifuged at 4000 rpm for 30 minutes and dried at 60 °C in a vacuum oven for 24 hours to isolate LSH. Finally, dried LSH was milled, passed through mesh no. 40, and stored in an airtight container at room temperature (Haseeb et al., 2017; Haseeb MT et al., 2017).

Drug-excipient compatibility study:

Fourier transform infrared (FT-IR) spectroscopy was utilised to evaluate LSH and look for any potential incompatibilities with other tablet constituents. For FTIR analysis, the KBr pellet technique was used, and spectra were acquired from 4000 to 400 cm1 using an IR Prestige-21 Shimadzu, Japan (Ergin et al., 2013).

Preparation of tablets:

All materials, except talcum and magnesium stearate, were sieved no. 40 and well combined before kneading with a 5% (w/v) solution of PVP K30 in isopropyl alcohol for each tablet

formulation (Table 1). Wet mass was granulated through sieve no. 10 and dried for 8 hours at 40 °C. The dried granules were then greased with talcum and magnesium stearate and passed through sieve no. 20. Pre-compression parameters were used to assess lubricated grains (Njega et al., 2018). The granules were then compacted with a 15 mm flat surface punch with a hardness of 7.5–9.0 kg/cm2 and a hardness of 7.5–9.0 kg/cm2. Post-compression characteristics were used to evaluate the prepared tablets.

Table 1: Composition of formulations to study the effect of ingredients on the release of gatifloxacin from LSH based tablets

Ingredient (mg)	F0	F1	F2	F3	F4	F5	F6	F7	F8	F9
Gatifloxacin	200	200	200	200	200	200	200	200	200	200
Linseed hydrogel (LSH)	–	20	40	30	30	30	30	30	30	30
β-cyclodextrin	130	130	130	100	160	130	130	130	130	130
Sodium bicarbonate	100	100	100	100	100	70	130	100	100	100
HPMC K100M	20	20	20	20	20	20	20	10	30	20
Avicel® PH 102	105	85	65	105	45	105	45	85	65	75
PVP K30	10	10	10	10	10	10	10	10	10	10
Magnesium stearate	20	20	20	20	20	20	20	20	20	20
Talcum	15	15	15	15	15	15	15	15	15	15
Weight of each tablet	600	600	600	600	600	600	600	600	600	600

Pre-compression evaluation:

The angle of repose, bulk and tapped density, Hausner's ratio, and compressibility index of lubricated granules of each formulation were determined before feeding into a tablet compression machine to determine flow characteristics and compressibility (Shah et al., 2008; Patel and Pingale, 2014).

Angle of repose: The funnel method was used to determine the angle of repose of API powder. The maximum angle that can be reached between the surface of a pile of powder and the horizontal plane is called the angle of repose. The powder combination was weighed and placed into the funnel with precision. The height of the funnel has been reduced to 2.5 cm above ground level. Allow for free flow of the powder mixture through the funnel and onto the surface. The diameter of the powder cone is measured three times to provide an average value.

The equation is used to calculate the angle of repose:

$$\text{Angle of Repose } (\theta) = \tan^{-1}\left[\frac{h}{r}\right]$$

Where, h = height of pile, r = radius of the base of the pile, θ = angle of repose.

Bulk density determination: The mass to volume ratio of an untapped powder sample determines a substance's bulk density (including inter particulate void volume). The powder (W) is weighed and placed in a graduated measuring cylinder to calculate the volume (V0). The formula used to compute bulk density is given below:

$$\text{Bulk density (BD)} = \left[\frac{W}{V_0}\right]$$

Where, W=Weight of powder, V_O=Volume of powder.

Tapped density determination:The tapped density is obtained by mechanically tapping a graduated cylinder containing the sample until only a minor volume change is seen. The

powder sample weighing 25 gm was screened using sieve No.18, and the weight of the sample was placed in a 100 mL graduated cylinder. A tapped density tester was used to mechanically tap the cylinder 500 times at a nominal rate, and the tapped volume Vo was recorded. When the difference between two tapping volumes is less than 2%, Vf is tapped volume. The blend volume was used to compute the tapped density, Hausner's ratio, and Carr's Index. The unit of bulk density and tapped density is g/ml.
The formula used to calculate tapped density is given below:

$$\text{Tapped density (TD)} = \left[\frac{W}{V_f}\right]$$

Where, W=Weight of powder, Vf=Volume of powder.
Carr's index: Carr's index is described by the term compressibility. It's a metric for how compressible a powder is. It is linked to relative flow rate, cohesion, and particle size in an indirect way.
The formula for calculating Carr's index was:

$$\text{Carr's Index (\%)} = \frac{(\text{Tapped Density} - \text{Bulk Density}) \times 100}{\text{Tapped Density}}$$

Hausner's ratio: Hausner's ratio, which indicates the flow properties of the powder, is calculated using the ratio of tapped density to bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post-compression evaluation of LSH tablets

The diameter, thickness, hardness, friability, and weight variation of compressed tablets were all measured. Gatifloxacin uniformity in manufactured tablets was also tested (Khan et al., 2011).
Thickness of the prepared tablets were performed by Vernier calliper (Mitutoyo 500-196-30-Advanced), the thicknesses of the tablets were measured, and average values were calculated using 20 tablets from each batch.Each tablet in a batch should be the same weight, and weight deviations should be within the pharmacopeia's allowed acceptable range. A Mettler Toledo AB analytical balance, model AB104-S, was used to determine weight uniformity. The weight variation was determined using a sample of ten tablets. The tablet's hardness reflects its durability. A hardness tester (Erweka, TBH 425) was used to determine the hardness of 10 tablets from each batch. Using the friability test instrument, the friability of 10 tablets for each formulation was determined (Electrolab, EF-2W).Ten tablets from each formulation were randomly selected and crushed in a pestle and mortar to determine the amount of Gatifloxacin in the formulations. Each formulation's crushed powder (800 mg) was vigorously mixed with methanol in a volumetric flask, filtered, diluted (if necessary), and measured at 286 nm on a UV spectrophotometer (UV PharmSpec 1700, Shimadzu, Japan). The calibration curve was used to calculate the quantity of gatifloxacin. The procedures were carried out three times, with the average value being reported.

Swelling study:

The swelling study was carried out to test the swelling capacity of formulated formulation. Each prepared tablets were wrapped in a Tea bag and placed in separate beakers filled with a pH 1.2 buffer (900 mL) and kept at 37 ±0.5°C. After 12 hours, the tea bags containing swelled tablets were removed from the beakers, hung for a while to drain the excess media (Yadav et al., 2017), and the swelling capacity was determined using following equation.

$$\text{Swelling capacity (g/g)} = \frac{W_s - W_e - W_i}{W_i}$$

Where Ws, We and Wi represented the

weight of wet Tea bag having swollen tablet, weight of empty Tea bag and initial weight of the tablet, respectively. All of these formulations had their swelling capacity tested at pH 7.4 as well as in deionized water. The swelling capacity of the ideal formulation (F9) was measured at pH 1.2, 7.4, and in deionized water to investigate the swelling behaviour of the tablet at different time intervals using above equation.

In vitro dissolution test: Dissolution tests on the manufactured tablets were carried out using the Electro lab apparatus II. At 37 ±0.5°C and 100 rpm, dissolution was carried out in 900 mL of pH 7.4 phosphate buffer (Bajerski et al., 2010). An autosampler (UV spectrophotometer Shimadzu, UV1900i) linked to the dissolution apparatus was set to extract and replenish 5 ml of the dissolution media at 0, 2,4,6,8,10,12,15, 18 and 24 hours and Gatifloxacin was estimated at 286 nm in 100 mM phosphate buffer (pH 7.4) and 292 nm in 100 mM hydrochloric acid (pH 1.2).

III. RESULTS AND DISCUSSION:

Drug-excipient compatibility study:
The results of FTIR analysis of formulations revealed that each ingredient's characteristic peaks are clearly defined, with no notable shifts or losses of functional peaks, indicating that they are compatible.

Pre-compression evaluation of formulations
To evaluate whether the tablet blend is suitable for compression, a pre-compression study is required. Table 2 shows the results of the pre-compression parameters. The bulk density (1.278–1.712 g/cm3), tapped bulk density (1.812–2.179 g/cm3), compressibility index (10.009–19.987 percent), Hausner's ratio (1.119–1.312), and angle of repose (23.89–29.83) are all within the standard range, indicating good flow-ability and suitable mechanical strength of the prepared granules.

Table 2. Pre-compression parameters of different gatifloxacin formulations \ (n=10, Mean ± SD)

Formulation	Angle of repose	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Compressibility index (%)
F0	29.83 ± 0.33	1.562 ± 0.33	1.923 ± 0.18	1.231 ± 0.29	18.750 ± 0.11
F1	25.46 ± 0.21	1.650 ± 0.22	2.083 ± 0.38	1.312 ± 0.14	19.412 ± 0.14
F2	23.89 ± 0.41	1.689 ± 0.19	2.008 ± 0.15	1.153 ± 0.11	13.240 ± 0.31
F3	26.97 ± 0.57	1.695 ± 0.26	1.992 ± 0.26	1.175 ± 0.34	14.915 ± 0.27
F4	24.72 ± 0.81	1.712 ± 0.39	2.179 ± 0.16	1.245 ± 0.21	19.655 ± 0.41
F5	28.51 ± 0.92	1.661 ± 0.08	1.887 ± 0.18	1.136 ± 0.19	11.960 ± 0.35
F6	27.18 ± 0.29	1.667 ± 0.51	1.873 ± 0.18	1.119 ± 0.17	10.009 ± 0.29
F7	28.73 ± 0.42	1.278 ± 0.18	1.812 ± 0.67	1.254 ± 0.15	19.987 ± 0.18
F8	29.29 ± 0.19	1.515 ± 0.17	1.792 ± 0.19	1.183 ± 0.09	15.454 ± 0.24
F9	26.41 ± 0.41	1.613 ± 0.41	1.852 ± 0.21	1.148 ± 0.11	12.903 ± 0.31

Post-compression evaluation of formulations:
The results of analyzing compressed tablets using various post-compression parameters are shown in Table 3. The weight (597.3–602.7 mg), thickness (4.36–4.54 mm), hardness (7.47–

9.12 kg/cm2), and friability (0.60–0.90%) are all within normal ranges. Gatifloxacin concentrations in all formulations were also between 96.89 and 99.52 percent.

Table 3: Post-compression parameters of different gatifloxacin formulations (n=10, Mean ± SD)

Formulation	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F0	7.95 ± 0.01	4.53 ± 0.08	600.4 ± 1.74	0.87± 0.23	96.89 ± 1.02
F1	8.23 ± 0.05	4.47 ± 0.14	598.2 ± 0.99	0.88 ± 0.19	98.77 ± 0.79
F2	9.12 ± 0.03	4.43 ± 0.21	601.4 ± 2.56	0.90 ± 0.19	98.34 ± 0.96
F3	8.45 ± 0.02	4.49 ± 0.19	600.6 ± 2.89	0.75 ± 0.22	98.97 ± 0.88
F4	7.47 ± 0.03	4.51 ± 0.13	597.3 ± 2.52	0.83 ± 0.29	97.34 ± 0.83
F5	8.11 ± 0.05	4.48 ± 0.08	602.5 ± 2.44	0.82 ± 0.11	97.11 ± 0.82
F6	8.45 ± 0.07	4.36 ± 0.11	601.6 ± 3.22	0.91 ± 0.56	98.88 ± 0.66
F7	7.87 ± 0.09	4.49 ± 0.23	598.2 ± 1.67	0.90 ± 0.81	99.02 ± 0.75
F8	8.02 ± 0.05	4.52 ± 0.11	599.8 ± 2.29	0.82 ± 0.31	98.15 ± 0.59
F9	7.88 ± 0.05	4.54 ± 0.17	602.7 ± 1.59	0.60± 0.31	99.52 ± 0.77

Swelling study:

The swelling ability of the obtained tablet formulations was tested in buffer solutions with pH values of 1.2, 7.4 and deionized water, and the results are depicted in figure 1A-D respectively. As shown in figure 1, changes in excipient concentration have a direct impact on the swelling capability of various formulations. The swelling capacity dropped from 2.64 to 1.87 when the amount of LSH was raised from 30 mg (F9) to 40 mg per tablet (F2). Swelling capacity increases slightly from 2.64 to 3.03 when LSH is reduced from 30 mg to 20 mg per tablet (F1). This change in swelling capacity is caused by a change in LSH concentration, demonstrating an inverse link between swelling and LSH concentration, which is consistent with earlier research. Because LSH has a minor tendency to swell in acidic pH, its presence in the tablet has prevented tablet swelling. The penetration of swelling medium (pH 1.2 buffer) into the tablet is more difficult with a higher concentration of LSH (F2) than with a lower quantity of LSH (F1) (F1). As a result, in comparison to F1, F2 showed less edoema.

The ability of formulations F1 and F2 to swell is, however, dependent on HPMC (swelling agent) and -cyclodextrin (channeling agent). In the absence of LSH, the swelling capacity of formulation F0 was somewhat higher than that of formulation F9, which could be attributed to the presence of HPMC K100. By changing the concentration of HPMC K100 in formulations F7 and F8, the influence on the swelling index was found. Because HPMC K100 is a slightly swellable polymer, a little difference in swelling was noted as the concentration of HPMC K100 was changed. Changes in the concentrations of -cyclodextrin and sodium bicarbonate, as indicated in formulations F3 and F4, and F5 and F6, respectively, had less of an influence on the swelling of tablets. The swelling of the formulation increases as the concentration of -cyclodextrin rises. It diffuses out of the formulation, generating microscopic channels, because it is a very soluble polymer. As a result, media penetration into the deep region of the tablet is feasible, and there is relatively more swelling. These findings revealed that LSH is the primary component in these formulations, and that its concentration has a significant impact on tablet swelling, which affects gatifloxacin release.

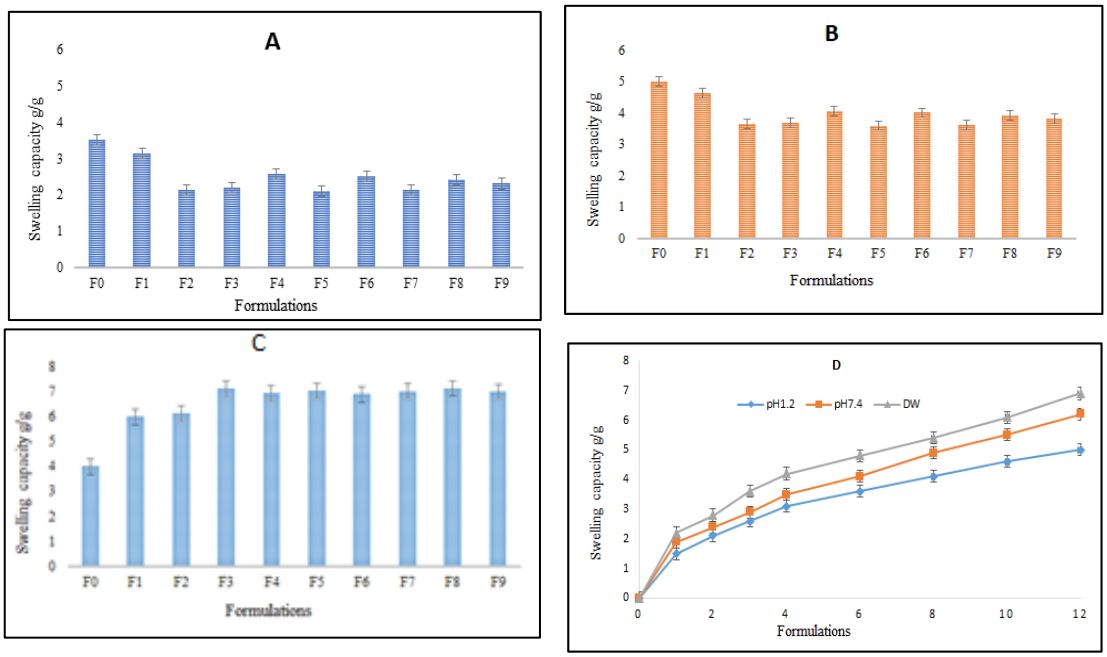

Figure 1: Swelling capacity of all formulations after 12 h study at pH 1.2 (A), pH 7.4 (B) and in deionized water (C), and optimum formulation (F9) at different time intervals (D)

Tablet density measurement:

All formulations have the same density, indicating that they will float (Table 4). As a result, all tablet formulations took a little longer to start floating (minimum 6 to 7 minutes).

In vitro buoyancy study:

When sodium bicarbonate in the formulation comes into touch with an acidic medium, CO2 is released. Because of the polymeric makeup of the formulation, the tablet absorbs and then retains the media. As a result, the produced gas became trapped within the polymeric matrix, enhancing the tablet's buoyancy. The period of buoyancy will be extended as long as this gas is caught within the tablet. Table 4 shows the buoyancy lag time for all of the formulas. The buoyancy lag time ranged from 385 s to 455 s in all formulations, with the exception of formulation F0, which had a 125 s lag time. The absence of LSH could explain why F0 has a

shorter buoyancy lag time. Without LSH, the media was easily penetrated, resulting in rapid CO2 generation and release. As a result, the buoyancy lag time was shorter than with other formulations.

Table 4: Different physical parameters of gatifloxacin tablet formulations

Formulation	Tablet density (g/cm^3)	Duration of buoyancy (h)	Buoyancy lag time (s)
F0	1.09 ± 0.01	< 1 h	125 ± 2.5
F1	1.11 ± 0.05	> 12 h	385 ± 4.5
F2	1.08 ± 0.03	> 12 h	397 ± 5.1
F3	1.10 ± 0.02	> 12 h	408 ± 3.5
F4	1.08 ± 0.03	> 12 h	421 ± 4.3
F5	1.11 ± 0.05	> 12 h	455 ± 3.5
F6	1.09 ± 0.07	> 12 h	425 ± 4.5
F7	1.10 ± 0.09	> 12 h	420 ± 3.7
F8	1.12 ± 0.05	> 12 h	415 ± 4.0
F9	1.10 ± 0.05	> 12 h	425 ± 1.2

Furthermore, keeping the CO2 within the tablet for a longer amount of time was impossible with formulation F0. As a result, the duration of buoyancy was less than 1 hour, which was extremely short in comparison to other formulations. The amount of CO2 produced within the tablet has a direct relationship with the length of buoyancy. As a result, it was discovered that as the concentration of sodium bicarbonate (F6) increased, so did the duration of buoyancy, and vice versa (F5). Figure 2 shows the length of F9 buoyancy at various time intervals.

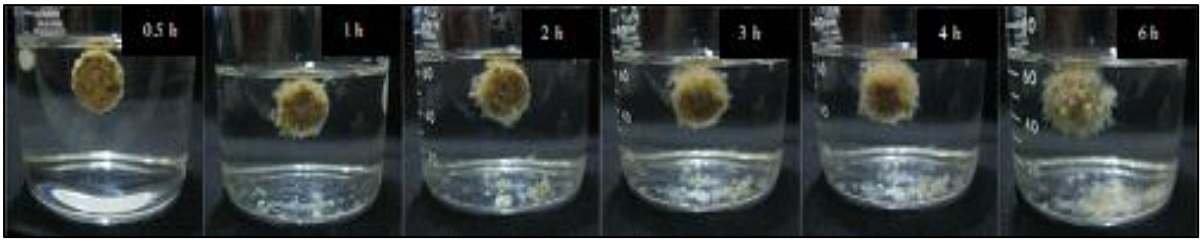

Figure 2. Photographs depicting the buoyancy of formulation F9 at pH 1.2

Drug release study:

Figure 3 shows the release of gatifloxacin from various formulations. Except for formulation F0, which is produced without the inclusion of LSH, all formulations showed prolonged and sustained drug release. As a result, it can be concluded that the presence of LSH was primarily responsible for the sustained and prolonged release of these formulations. However, because of the differences in excipient concentrations, all of these formulations had a somewhat distinct release pattern.

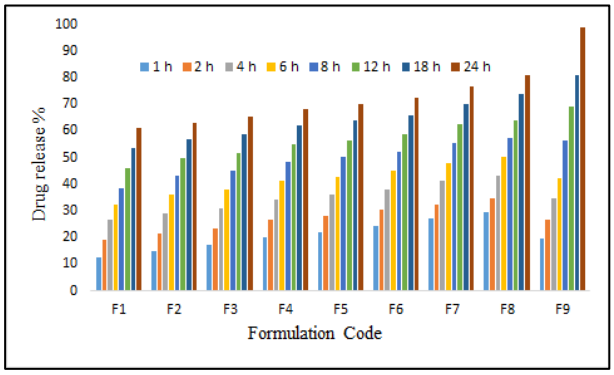

Figure 3: Gatifloxacin release profile from different formulations (F1 to F9) at pH 1.2

IV. CONCLUSION:

The development of an LSH-based gastroretentive drug delivery system that sustained the release of gatifloxacin in the stomach and allowed tablets to float for 6 hours was effective. Furthermore, sustained-release was observed at all GIT pH levels, demonstrating the value of this newly designed formulation. The results of in vitro drug release at various physiological pH of the GIT demonstrated that our newly formulated LSH-based gastro-retentive formulations provided a double benefit; even if the tablet pumps to the gut, the gatifloxacin is released continuously. The release of gatifloxacin in an acidic environment was also demonstrated in an in vitro drug release investigation.

V. REFERENCES:

1. Bajerski L, Rossi RC, Dias CL, Bergold AM, Fröehlich PE. Development and validation of a discriminating in vitro dissolution method for a poorly soluble drug, olmesartanmedoxomil: comparison between commercial tablets. AAPS Pharmscitech. 2010;1(2):637-644.
2. Ergin Ç, İlkit M, Gök Y, Özel MZ, Çon AH, Kabay N, Söyleyici S, Döğen A. Fourier transform infrared spectral evaluation for the differentiation of clinically relevant Trichophyton species. Journal of Microbiological Methods. 2013; 93(3):218-223.
3. Goole J, Vanderbist F, Amighi K. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. International Journal of Pharmaceutics. 2007; 334(1-2):35-41.
4. Goyal A, Sharma V, Upadhyay N, Gill S, Sihag M. Flax and flaxseed oil: An ancient medicine and modern functional food. Journal of Food Science and Technology. 2014; 51(9):1633-1653.
5. Haseeb MT, Hussain MA, Abbas K, Youssif BG, Bashir S, Yuk SH, Bukhari SN.Linseed hydrogel-mediated green synthesis of silver nanoparticles for antimicrobial and wound-dressing applications. International Journal of Nanomedicine. 2017; 12:2845-2852.
6. Haseeb MT, Hussain MA, Bashir S, Ashraf MU, Ahmad N.Evaluation of superabsorbent linseed-polysaccharides as a novel stimuli-responsive oral sustained release drug delivery system. Drug Development and Industrial Pharmacy. 2017; 43(3):409-420.
7. Kajla P, Sharma A, Sood DR. Flaxseed-a potential functional food source. Journal of Food Science and Technology. 2015;52(4):1857-1871.
8. Khan A, Hanif M, Yousuf RI, Ghayas S, Shoaib HM, Arshad HM. Pharmaceutical quality control studies on Gatifloxacin 200 mg tablets available in the Pakistani market. Latin American Journal of Pharmacy. 2011;30(10):1922-1926.
9. Njega EK, Maru SM, Tirop LJ. The binder effect of povidone on the mechanical properties of paracetamol containing tablets. East and Central African Journal of Pharmaceutical Sciences. 2018; 21(1-3):3-9.
10. Patel MA, Pingale PL. Comparative effect of different high functionality excipients on various characteristics of vardenafil HCl tablets (BCS II drug). International Journal of Pharmaceutical Sciences and Research. 2014; 5(12):5447-5452.
11. Pawar VK, Kansal S, Garg G, Awasthi R`, Singodia D, Kulkarni GT. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Delivery. 2011;18(2):97-110.

12. Shah RB, Tawakkul MA, Khan MA. Comparative evaluation of flow for pharmaceutical powders and granules. AAPS Pharmscitech. 2008;9(1):250-258.
13. Yadav GU, Joshi BS, Patwardhan AW, Singh G. Swelling and infusion of tea in tea bags. Journalof Food Science and Technology. 2017; 54(8):2474-2484.