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RESEARCH ARTICLE
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DESIGN, DEVELOPMENT AND CHARACTERIZATION OF CIPROFLOXACIN BASED FLOATING DRUG DELIVERY SYSTEM

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Abstract

Ciprofloxacin is associated with reduced bioavailability due to dissolution and absorption from upper part of GIT. Controlled release technology covers frequency of administration, but reduced bioavailability demands increased gastric residence time. So, floating drug delivery systems represent an ideal drug delivery mode to increase gastric residence time leading to improved bioavailability. This study aimed to formulate polymeric floating tablets of ciprofloxacin for oral drug delivery. Direct compression method was employed for the preparation of tablets using different polymers like HPMC, alginate and chitosan. Physicochemical evaluation tests were performed on all the prepared tablets. 0.1 N HCl solution was used for floating, swelling and *in-vitro* release studies. The drug, polymers and excipients had no incompatibilities as confirmed by FTIR results. Total floating time of all the formulated tablets was higher than 12 h with maximum swelling index exhibited by F6. *In-vitro* studies depicted that combination of polymers can sustain the release of drug in better way and followed anomalous non-Fickian diffusion mechanism. Similarly, the optimized ciprofloxacin floating tablets were investigated for effect of pH, agitational intensity and osmotic pressure. The results confirmed that ciprofloxacin loaded floating drug delivery system produced promising results to enhance bioavailability.

Key words: Ciprofloxacin, swelling index, direct compression, floating lag time, in-vitro drug release.

1. Introduction

Oral route is regarded as the most commonly used route, employed to achieve both systemic as well as local actions for variety of infections. Patients mainly select oral route due to suitability for self-administration, high patient compliance and ease of use (1). Different physiological factors such as solubility, stability, ionization, and lipophilicity control the absorption of drug including gastric intestinal transient time. Fluid and food intake gastric and intestinal secretion, absorption mechanism, pH and metabolism process (2). Since oral route is patient friendly, so high percentage of patient compliance is achieved. But variability in gastric emptying time is a major drawback of oral drug administration (3). Sometimes, prior to drug release from the delivery system, the drug may be ejected in the stomach, necessitating the drug delivery system that cannot only produce sustaining action but also provide prolonged gastric residence time. The combined outcome of such interventions is better drug bioavailability with minimal drug wastage resulting in improved drug solubility which is vital for pharmacological action (4).

Ciprofloxacin belongs to the group fluoroquinolone. The dose of ciprofloxacin is usually 500 mg and has 70% bioavailability. The drug peak plasma concentration of ciprofloxacin is usually 2.5 µg/ml and the reaching time is 1 to 2 h (5). But conventional ciprofloxacin administration produces poor response due to poor bioavailability and penetration, thus the clinical efficacy of ciprofloxacin can be increased by increasing the half-life of this drug. When the drug reaches the GIT then it affects the absorption value of the drug and this problem is overcome in floating drug delivery system (6).

Conventionally, ciprofloxacin dissolves and absorbs from upper part of GIT, leading to increased frequency of administration and reduced bioavailability (7). Although controlled release technology covers frequency of administration parameter, but reduced bioavailability demands increased gastric residence time. So, floating drug delivery systems represent an ideal drug delivery mode to increase gastric residence time leading to improved bioavailability while use of natural polymers also offer controlled drug delivery (8).

Among gastro-retentive drug delivery systems, the floating dosage forms represent potential candidates to achieve prolonged gastric residence time thus helping to achieve improved bioavailability and therapeutic outcomes (9). Floating drug delivery system offers drug floating on gastric fluid. This can effectively slow the release of drug as well as enhance the gastric residence time providing sufficient drug plasma level to achieve outcome indicators (10). Site specific drug delivery to the stomach offers numerous therapeutic outcomes such as limiting the drug systemic exposure. The dosing frequency of the drug may also be reduced by achieving sustained and elevated gastric availability (11).

The present study aimed to design and formulate floating tablets of ciprofloxacin using rate controlling polymers like HPMC, chitosan and alginates to enhance bioavailability caused by increased gastric residence time.

2. Materials and Methods

2.1. Materials

Ciprofloxacin was generously gifted by Ferozson Laboratory, Nowshera, Pakistan . Chitosan, alginate and HPMC (Sigma-Aldrich, P.O. Box 14508, St. Louis, MO, USA, +1-314-771-5765, Sigma-AldrichChemie GmbH, Riedstr, 2, 89555 Steinheim, Germany, +49-7329-970) were used as rate controlling polymers. Citric acid, sodium bicarbonate, magnesium stearate and talc (The Dow Chemical Company., 693 Washington St. #627, Midland, MI 48640, USA) were also used in the preparation of polymeric floating tablets. All the materials in this project were of analytical grades and used without any further purification.

2.2. Compatibility Studies

ATR-FTIR was used to evaluate the drug and excipient compatibility investigations. PerkinElmer ATR-FTIR (USA) has been used to analyze the FTIR spectra of ciprofloxacin, polymers and other excipients.

2.3. Preparation of Tablets

Direct compression method was used to fabricate ciprofloxacin loaded floating tablets (12). Accurately weighed portions of the drug, polymers and excipients were taken followed by adequate mixing of all the ingredients. However, polymers used in the formulations such as chitosan, alginate, and HPMC were incorporated either alone (160 mg) representing 22.31 % of total formulation weight and 1:0.32 drug to polymer ratio or their physical admixture with other polymers in the concentration of 80 mg each representing 11.15 % of total formulation weight and 1:0.16 drug to polymer ratio. Pilot batches were created, each containing 50 tablets of a different formulation type. A computerized electronic balance (AX 120, SHIMADZU, Kyoto, Japan) was used to weigh each element in the mixture, including ciprofloxacin. A mortar and pestle were used to geometrically mix hydrophilic and gel-forming polymers. The amount of ciprofloxacin that had been previously measured was added to this mixture and well-mixed. The resulting mixture was passed through a mesh size 40, collected in a plastic bag, and blended for an additional 5 minutes. After adding the necessary amounts of citric acid and $NaHCO_3$, the mixture was mixed for an additional 5 minutes. Finally, adequate amounts of talc and magnesium stearate were added. The resulting mixture was thoroughly mixed for 10 minutes, then again passed through sieve number 40 before being compacted into tablets using a single punch tablet machine (Erweka Apparatebau compression machine type T B-24). Table 1 shows the composition of various formulations:

Table 1. Composition of ciprofloxacin loaded floating tablets

Materials (mg)	F1	F2	F3	F4	F5	F6
Ciprofloxacin	500	500	500	500	500	500
Chitosan	160	----	----	80	80	----
HPMC	----	160	----	80	----	80
Alginate	----	----	160	----	80	80
Citric Acid	5	5	5	5	5	5
Sodium Bicarbonate	20	20	20	20	20	20
Magnesium Stearate	12	12	12	12	12	12
Talc	10	10	10	10	10	10

2.4. Characterization of Ciprofloxacin Floating Tablets

2.4.1. Physical Appearance & Thickness

Floating tablets thickness were noted with the help of vernier caliper (Erweka GmbH, Langen, Germany) whereas shape and physical form of compressed tablets were observed under microscope. A random selection of at least 5 tablets from each batch was made to subject them individually for dimensional specifications assessment. The results were expressed as mean ± SD (13).

2.4.2. Hardness

A hardness tester (Erweka Model TB 24 Apparatus, Langen, Germany) was used to determine tablet crushing strength. Randomly, 10 tablets from each batch were selected for checking their hardness and results expressed in kg/cm^2 (14).

2.4.3. Friability

To calculate floating tablets friability, Roche friabilator was employed. For this purpose, 20 tablets were taken randomly, and friability was measured after 100 rpm (4 minutes treatment at 25 rpm). Friability was measured using following equation (15):

$\% F = w_1\text{-}w_2/w_1 \times 100$ (1)

where w_1 indicates tablet weight before it becomes friable and w_2 represents weight of tablet after friability. % friability of < 1 % is considered acceptable.

2.4.4. Weight uniformity

20 tablets were picked at random and were weighed accurately using analytical weighing balance (AX 120, SHIMADZU, Kyoto, Japan). The average weights (mean ± SD) of tablets were calculated (16).

2.4.5. Drug content uniformity

10 tablets were selected randomly for the identification of drug content uniformity. The selected tablets were weighed accurately using analytical weighing balance and then crushed in pestle and mortar. The specified quantity of powder was taken and dissolved in 0.1 N HCl solution. The filtrate was obtained by passing through a cellulose member filter (0.45 μ) and then analyzed spectrophotometrically using UV Visible spectrophotometer (UV1800, SHIMADZU, Kyoto, Japan) at the wavelength of 276 nm wavelength. Drug content of the formulated tablets was identified with the help of already prepared standard curve of ciprofloxacin. An average of three readings was taken and recorded (17).

2.5. Tablet floating capacity

Paddle method (USP type 2 apparatus) was utilized to investigate tablet floating capacity. The tablets were put into glass jars with 0.1 N HCl up to a capacity of 900 mL, and the jars were rotated at a speed of 50 rpm. The equipment's temperature was kept at constant temperature of 37 ± 0.5 ºC for 24 h. Both the amount of time that it took for the tablets to rise to the top of the dissolution medium and the amount of time that they remained floated on the medium were recorded. These were referred to as floating lag time and total floating time, respectively. To generate an average result, triplicates were used. The result is displayed as mean ± SD (18).

2.6. Swelling and erosion

For the determination of swelling index and erosion, USP Dissolution Apparatus-II (Erweka GmbH, Germany) and 0.1 N HCl solution was used. For this purpose randomly 3 tablets were selected for the test and were weighed individually and accurately using analytical weighing balance. These formulated tablets were subjected into dissolution apparatus for further analysis. At certain intervals, tablets were carefully taken from the medium with a spoon (at 0.5h, 1h, 2h, 4h, 6h, 8h, 12h, and 24h respectively). The tablets were cleaned using filter paper and were again weighed. Then the tablets were placed at 60 ºC in oven. After achieving complete drying the tablets were again weighed to achieve final weight (19).

Following equation was used for calculation of erosion and percentage of swelling:

$$\text{Swelling (\%)} = Ww\text{-}Wi/Wi \times 100 \quad (2)$$

$$\text{Erosion (\%)} = Wi\text{-}Wd/Wi \times 100 \quad (3)$$

Where Wi is Initial weight tablet, Ww is Wet weight of tablet, and Wd is the tablet's dry weight.

2.7. *In-Vitro* Release Study

In-vitro release study was carried out for the formulated tablets using USP dissolution apparatus II (Erweka GmbH, Germany). The temperature maintained was 37 ± 0.5 °C and experiment was run at 100 rpm. As a simulated gastric fluid, the formulated tablets were subjected into 0.1 N HCl (pH 1.2) in a total volume of 900 ml. At predetermined intervals (0.5h, 1h, 2h, 4h, 6h, 8h, 12h, & 24h), 5 ml samples were removed and replaced with fresh prepared medium. The drug content as well as the percent cumulative drug release were calculated and results averaged (20).

2.8. Effect of Agitational Intensity on Drug Release

The dissolution apparatus was set at various rotational speeds to ascertain the drug release pattern of the optimized formulation, taking into consideration the impact of the agitational intensity of 0.1 N HCl and other release media like acetate buffer having pH 4.5 and simulated intestinal fluid having pH 6.8. The dissolution apparatus was used with rotating basket (USP technique 1) at 50 and 100 rpm.

Similar to this, samples were collected at a predetermined period and examined at 276 nm after passing through a 0.4 μ membrane filter (10).

2.9. Effect of pH on Drug Release

The pH change approach was used to examine the impact of pH and produce optimum formulation performance reliability that was independent of the pH effect. According to the protocol of the pH change approach, the release behavior of optimized formulations was observed using this method. The drug release was monitored using this pH change technique in an effort to replicate the GIT transit duration and pH. The pH change strategy included using simulated gastric fluid having pH 1.2 as release medium for the first two h, followed by acetate buffer having pH 4.5 for the next two hours, and finally replacing with simulated intestinal fluid having pH 6.8 for the last 24 h. It is preferable to detect the drug release at pH 1.2 for a maximum of 24 h since it is impossible to investigate the mechanism and kinetics of drug release by pH change technique and transit time (21). According to USP guidelines, 900 mL of each of the required dissolution media i.e. acetate buffer (pH 4.5), 0.1 N HCl (pH 1.2) and simulated intestinal fluid (pH 6.8) were produced and maintained at 37 ± 1 °C. At 100 rpm, the dissolution apparatus was in operation. An aliquot of 5 mL was obtained at certain intervals, put through a 0.45 μ membrane filter, and then subjected to a UV spectrophotometer to be analyzed at 276 nm (UV-1800, SHIMADZU, Kyoto, Japan) (22).

2.10. Effect of Osmotic Pressure on Drug Release

In order to corroborate the drug release mechanism, release behavior studies of optimized formulations were carried out using media with various osmotic pressures. To raise the osmotic pressure of the medium, an osmotically active solute such as NaCl was added to simulated stomach fluid (0.1 N HCl kept at 37 ± 1 °C). With sodium chloride concentrations of 0.5 % and 0.9 %, this experiment was started at 100 rpm. 5 mL samples were taken out of the vessel at regular intervals and replaced with an equivalent amount of new solvent kept at the same temperature to maintain the vessel's volume. The absorbance of samples that had been withheld was measured using a UV spectrophotometer (UV-1800, SHIMADZU, Kyoto, Japan) at a wavelength of 276 nm in order to investigate drug concentration (23).

2.11. Release Kinetics

In order to investigate the drug release mechanism, the release data obtained from ciprofloxacin loaded floating tablets were fitted into different kinetics models such as Korsmeyer-Peppas equation, Higuchi, Hixson Crowell, first-order and zero-order (24).

2.12. Statistical Analysis

The averages from each experiment were run in triplicates and shown as mean ± SD. The statistical analysis used paired t-test and one-way ANOVA. A p-value of 0.05 or less was regarded as significant.

3. Results and Discussion

3.1. Drug Compatibility Studies

ATR-FTIR spectra of pure ciprofloxacin and its physical admixtures with various polymers (HPMC, sodium alginate and chitosan) are shown in Figure 1. Major infrared (IR) bands in the functional group area between 2700 and 3500 cm^{-1} (representing N-H stretch, O-H stretch, and C-H stretch) and 1600 to 1800 cm^{-1} (representing C=C, C=O, and C=N stretches) were visible in the spectra of pure ciprofloxacin (25). The primary bands visible in the spectra of ciprofloxacin were also visible in the spectrum of physical admixtures, but with less intensity. Since no new peak appeared or the original drug or excipient peak vanished, which would indicate a drug-excipient interaction, the spectrum of the formulated tablet demonstrated that there were no interactions between the excipients utilized in the formulation and the ciprofloxacin (26).

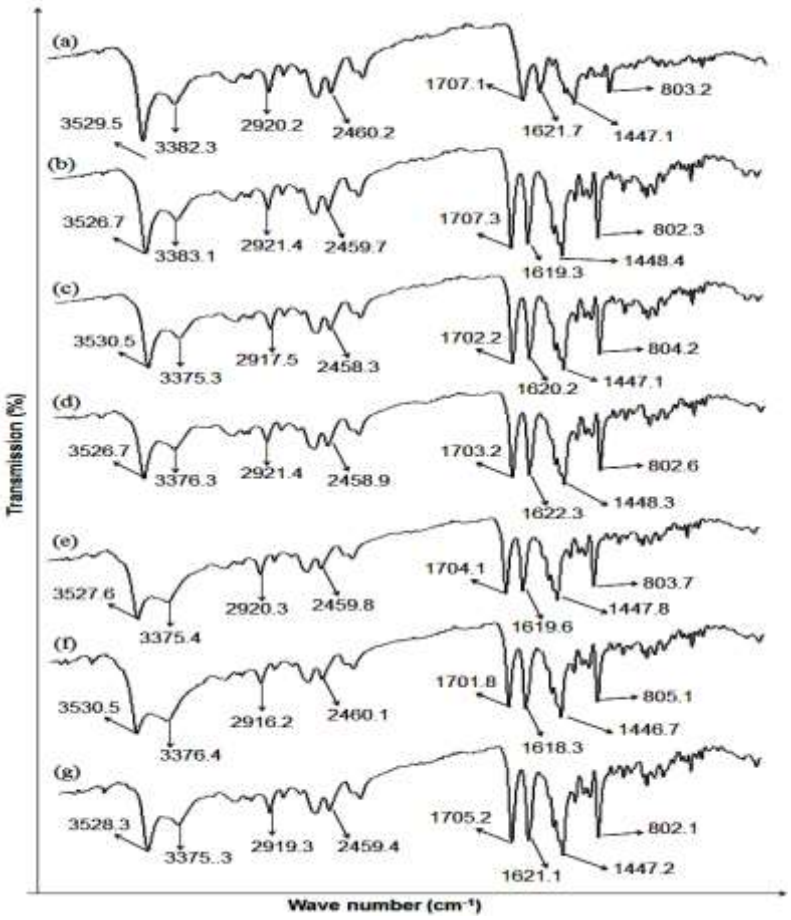


Figure 1. ATR-FTIR spectra of (a) ciprofloxacin (b) F1 (c) F2 (d) F3 (e) F4 (f) F5 (g) F6

3.2. Characterization of Tablets

3.2.1. Thickness of Tablets & Physical Appearance

Tablets seemed round and uncracked under the microscope. Vernier calipers were used to measure the thickness of floating tablets. As indicated in Table 2, the floating tablets' dimensional requirement (thickness) was determined to be within the permitted range. Thickness values of the formulated tablets ranged in between 3.4 ± 0.3 mm to 3.6 ± 0.4 mm, and all batches were determined to be uniform.

A significant part of the floating tablet's performance is its thickness, as changing this factor directly affect the density of the tablet. An increase in tablet thickness may change the floating behavior of the tablets, whilst a decrease in tablet thickness may affect the floating lag time. Thus, average of these two parameters should be lesser than density of stomach contents i.e. 1.004 g/cm^3 (27).

3.2.2. Hardness

Tablet hardness or crushing strength is an essential factor in tablet formulation. The hardness values for all formulated tablets ranged in between 67.5 ± 0.6 N to 71.5 ± 1.3 N, as shown in Table 2. Increased hardness of formulated tablets causes alterations in floating lag time while decreased values directly affect dissolution profile (28). In addition, the hardness of tablet increases when two polymers are used in combination, as shown in Table 2. It has been reported that tablet manufactured from two or more polymers, exhibits greater hardness values as compared to tablets manufactured from single polymer (29).

3.2.3. Friability

The friability of the ciprofloxacin loaded floating tablets formulations (F1-F6) was displayed in Table 2. After the friability test, no broken, split, or cracked tablets were seen. The friability results were within BP limits i.e. < 1 %. Thus, the mechanical stability of formulated tablets was guaranteed. In

general, as tablet hardness increases, the formulation's friability or % mass loss drops accordingly. Thus, by maintaining a higher compression force, the friability test results tend to adhere to USP guidelines (30).

3.2.4. Weight uniformity

The weight uniformities of all of the formulated tablets were shown in the Table 2. Since no individual tablet weight deviated from its corresponding mean value by more than ± 5%, all formulations (F1–F6) properly passed the weight uniformity test. The results of weight uniformity of prepared tablets ranged from 706 ± 1.6 mg to 713.5 ± 3.2 mg, indicating that all the tablets were found uniform in weight (31).

3.2.5. Drug Content

Results of content uniformity test are shown in Table 2. Because the individual contents of every formulation batch came within the permitted official range of 85-115 %, the findings for content uniformity of all the formulations were fitted in the official compendial criteria and determined to be within the allowed range. For ciprofloxacin loaded tablets, the findings were in the range of 86.5 ± 1.3 % to 91.6 ± 2.0 %.

In this case, the active ingredient ciprofloxacin makes up a large portion of the tablet, as opposed to formulations that contain potent drugs that are only available in low doses and where the excipients make up the majority of the tablet. Thus, the content uniformity test was able to help ensure the achievement of dosage form uniformity (32).

Table 2. Physico-chemical parameters of ciprofloxacin loaded floating tablets

F. Code	Thickness (mm)	Hardness (N)	Weight Uniformity (mg)	Friability (%)	Drug Content (%)
F1	3.5 ± 0.1	67.5 ± 0.6	708.5 ± 2.4	0.88 ± 0.3	86.5 ± 1.3
F2	3.4 ± 0.3	67.9 ± 0.4	708 ± 3.1	0.90 ± 0.5	87.9 ± 1.1
F3	3.5 ± 0.1	68.2 ± 1.1	713.5 ± 3.2	0.86 ± 0.2	90.4 ± 2.4
F4	3.6 ± 0.2	70.1 ± 0.9	706 ± 1.6	0.94 ± 0.6	91.6 ± 2.0
F5	3.4 ± 0.5	71.5 ± 1.3	711.5 ± 1.9	0.82 ± 0.5	91.1 ± 1.8
F6	3.6 ± 0.4	70.8 ± 1.2	707.3 ± 1.1	0.78 ± 0.4	89.3 ± 1.5

Data are expressed as mean ± SD (n = 3)

3.3. Tablet Floating Capacity

According to the tablet floating study findings, which are presented in Table 3, all formulations exhibited good buoyancy (total floating time greater than 12 h). Due to an increase or reduction in the concentration of incorporated polymers, the floating behavior of the tablets may alter dramatically. The tablet is kept buoyant by gas trapping in the gel network due to polymers' low density and limited gelling ability. The floating lag time in the formulations was reduced by the use of $NaHCO_3$ as an effervescent agent, and ranged from 0.86 ± 0.15 min to 1.14 ± 0.17 min. Floating lag time decreases and tablet floating capacity increases when a combination of polymers is employed instead of single polymer (33).

Table 3. Floating lag time and total floating time of ciprofloxacin loaded floating tablets

F. Code	Floating Lag Time (min)	Total Duration of Floating (h)
F1	1.14 ± 0.17	> 12
F2	0.96 ± 0.13	> 12
F3	0.92 ± 0.1	> 12
F4	0.94 ± 0.12	> 20
F5	0.86 ± 0.15	> 20
F6	0.89 ± 0.14	> 20

Data are expressed as mean ± SD (n = 3)

3.4. Erosion & Swelling Studies

The polymers' water intake was measured by their swelling ratio or water uptake. As the designed floating tablets are composed of gel-forming polymers like chitosan, HPMC, and alginate thus erosion and swelling studies are also necessary. Erosion and swelling studies were conducted using 0.1 N HCl solution. The percent swelling or dissolution medium uptake for all floating tablets was publicized in Figure 2. The results showed that % swelling of all tablets increases until 12 h. The formulations using combination of polymers, such as F5 which contained chitosan and alginate, showed maximum dissolution medium uptake. Functional network structure and group ionization both seemed to have contributed to the swelling. The swelling index rose proportionately with the passage of time. Incorporating hydrophilic polymers may have contributed to this result (HPMC, sodium alginate, chitosan). A gel layer may form as a barrier when polymer swelling first happens in the topmost layer. The expansion of the new gel layer was caused by water absorption as the outermost gel layer barrier gradually disintegrated. Towards newly exposed surfaces, this process is continuously repeated. As a result, the decreased swelling rate of F1, F2 and F3 formulation batches compared to F4, F5, and F6 may be attributed to the surface area accessible for water uptake and the floating time. Swelling of the polymers and development of a gelatin layer takes place after contact with liquid, limiting the penetration of the test medium into the porous structure of the floating tablet. In addition to facilitating the controlled drug release profile, this phenomenon is in charge of maintaining dosage form integrity (34).

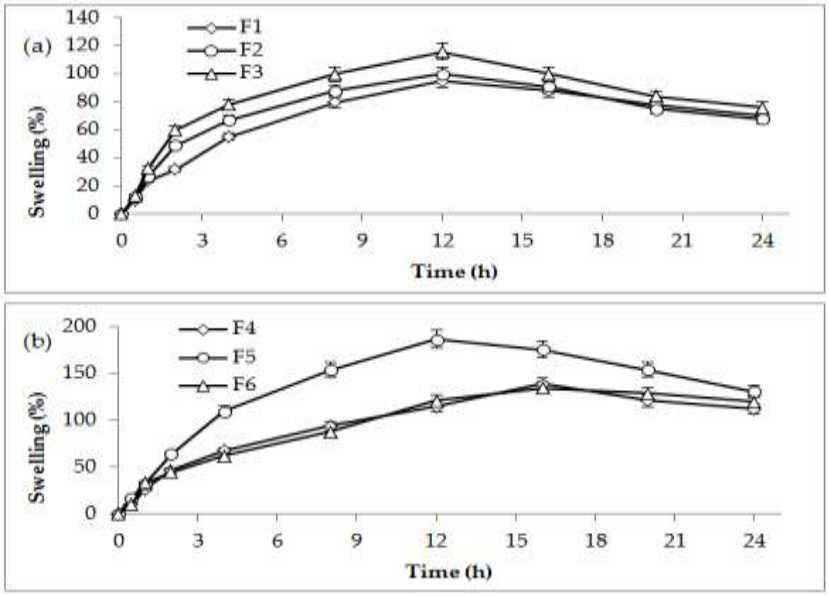


Figure 2. Swelling (%) of formulations (A) F1, F2 and F3 and (B) F4, F5 and F6

3.5. *In-vitro* Release Studies

In-vitro drug release is an essential analytical approach to examine drug release from the delivery system. Furthermore, the resulting release profile can disclose key facts about the kinetics and release mechanism, allowing for a more scientific and rational approach towards drug development. Release profile of all the prepared floating tablets was shown in Figure 3. It was found that initially abrupt drug release occurs followed by sustained drug release up to 24 h. Furthermore, it was found that chitosan, HPMC and alginate used alone has faster release as compared to tablets prepared from combination of polymers. The combination of polymers resulted in slowdown of ciprofloxacin release from the tablets; 100% of ciprofloxacin was released after 24 h. It was found that the concentration of retardant polymers included in the formulation had a substantial impact on the drug release from all floating tablets. When more retardant polymer was present, floating tablets showed evidence of lower drug release. Due to its low molecular weight and reduced viscosity, HPMC was found to be insufficient on its own to preserve matrix integrity and needed to be combined with sodium alginate to regulate drug release. The matrix integrity of the floating tablets has to be studied since a lack of

physical integrity might enable the tablets to break down into smaller fragments and escape from GIT (35). The formulation F5 showed sustained/controlled release up to 24 h. It was hypothesized that the drug release mechanism might be controlled by both the gels layers formation in the region of a matrix tablets and the porosities of the gel layer (36).

In-vitro dissolution was carried out for all formulation batches and convincingly better drug release profile was exhibited by formulation F2 and F6 compared to other formulation batches, as illustrated in Figure 3.

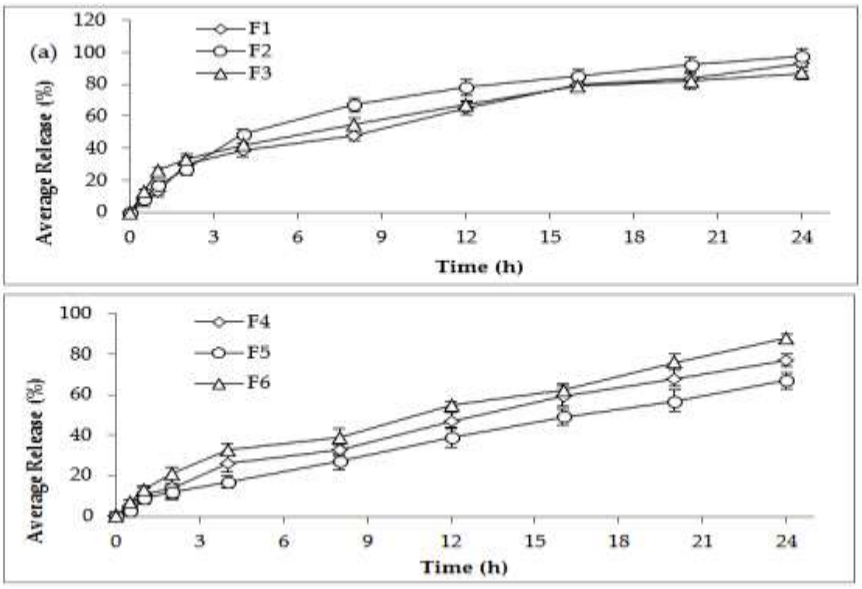
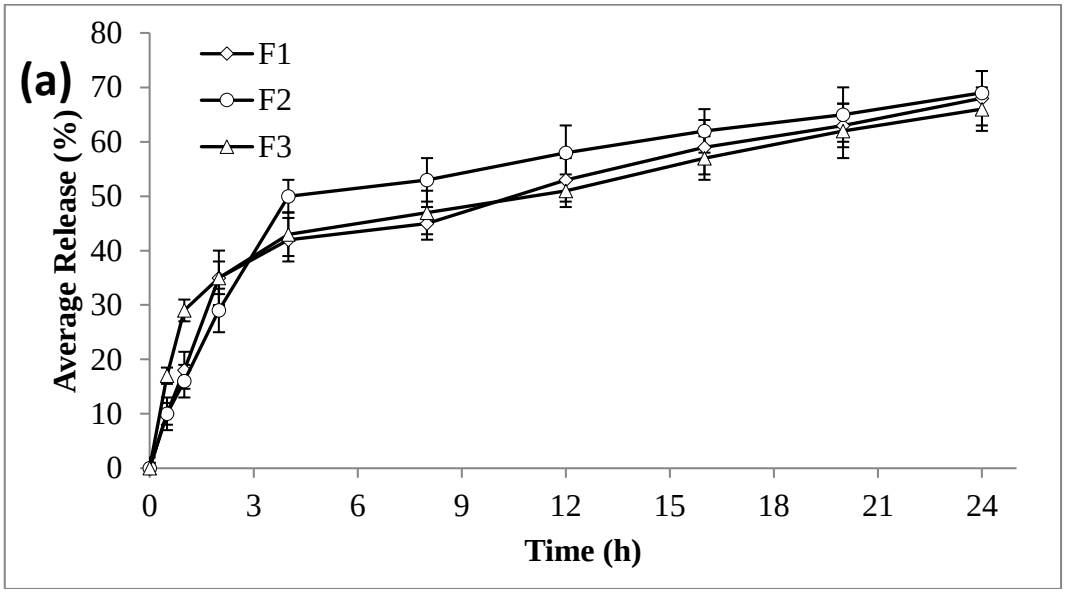


Figure 3. Release profile of formulations (a) F1, F2 and F3 and (b) F4, F5 and F6 at 100 rpm

3.6. Effect of Agitational Intensity

To determine the behavior of agitational intensity on drug release, USP type 1 dissolution apparatus was used at various rotational speeds i.e. 50 and 100 rpm. Ciprofloxacin floating tablet did not show any noticeable change in drug release, as evident in Figure 4. Therefore, it is reasonable to believe and anticipate that the ciprofloxacin formulations will continue to be independent of the hydrodynamic circumstances that naturally emerge at the absorption site (37).



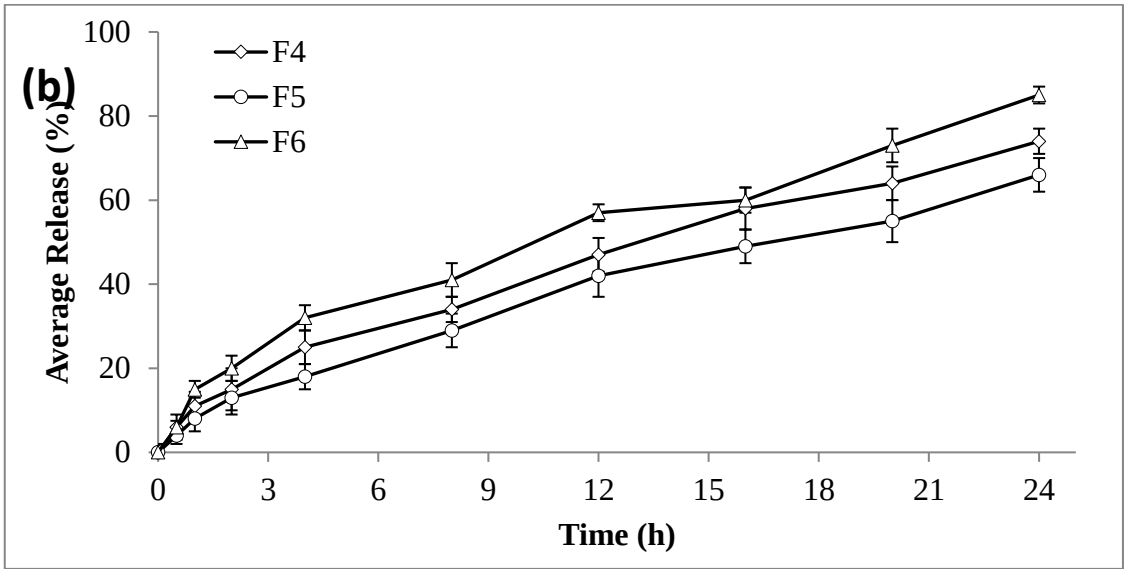


Figure 4. Release profile of formulations (a) F1, F2 and F3 and (b) F4, F5 and F6 at 50 rpm

3.7. Effect of pH

USP type 1 method set at 100 rpm was employed by using 0.1 N HCl (pH 1.2 for first 2 h), followed by acetate buffer (pH 4.5 for next 2 h), and finally simulated intestinal fluid (pH 6.8) for the final 8 h to investigate the effect of pH on drug release from ciprofloxacin loaded floating tablets. The experiment was conducted at a constant temperature of 37 ± 1 ºC. At predetermined intervals (0.5, 1, 2, 3, 4, 6, 8, and 12 h), samples were obtained, replaced with an equivalent amount of fresh dissolution media maintained at the same temperature. The samples were examined spectrophotometrically at 276 nm. Figure 5 displays the cumulative percent drug release statistics.

As seen in rare circumstances, floating tablets might occasionally travel to the gut (10). Therefore, a study that considers the physiological pH of various GIT regions should be carried out. The pH and transit time characteristics of the GIT were taken into consideration while studying the drug release from optimized formulations. This was carried out at pH 1.2 for two h, pH 4.5 for the following two h, and pH 6.8 for the remaining time. At pH 1.2 and 4.5, ciprofloxacin showed controlled release behavior, as could be seen. This was mostly caused by the presence of hydrophilic polymers, either alone or in combination. Our results are in close agreement with previously reported study (38). The observed drug release was unexpected at pH 6.8 because the floating tablets' swelling had been significantly decreased. This may be because ciprofloxacin, a drug with weak basic properties, remained unionized at higher pH levels, resulting in noticeable decreased solubility and erratic drug release (39).

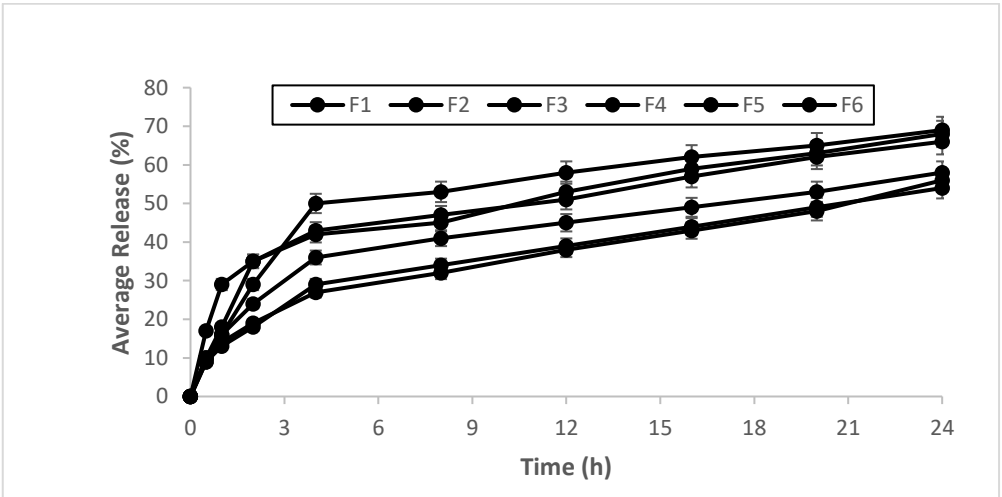


Figure 5. Release behavior of ciprofloxacin floating tablets at different pH values (n=3)

3.8. Effect of Osmotic Pressure

Figures 6 and 7 revealed that ciprofloxacin release increased in release media having NaCl concentrations of 0.5 % and 0.9 %. Since ciprofloxacin is a water-soluble drug moiety, the pace of matrix swelling was a key factor in determining how quickly it was released.

The formulations were subjected to mediums with various osmotic pressures to observe the impact of osmotic pressure on release studies. Ciprofloxacin loaded formulations were examined for drug release patterns in release media with various NaCl concentrations (0.5 % and 0.9 %). There was direct relationship found between drug release and concentration of NaCl whereas an inverse relationship was exhibited by the formulations in swelling rates upon exposure to increased concentration of NaCl. Ciprofloxacin release from the formulations was attributed to diffusion path length and resistance. However, when the NaCl content in the medium increased, both the swelling index and the barrier gelled layer correspondingly reduced leading to higher diffusion rate. In media containing 0.1 N HCl, the gel barrier layer was thicker than in media containing NaCl. This showed a decreased rate of drug release in 0.1 N HCl and an enhanced rate in fluids containing NaCl (40).

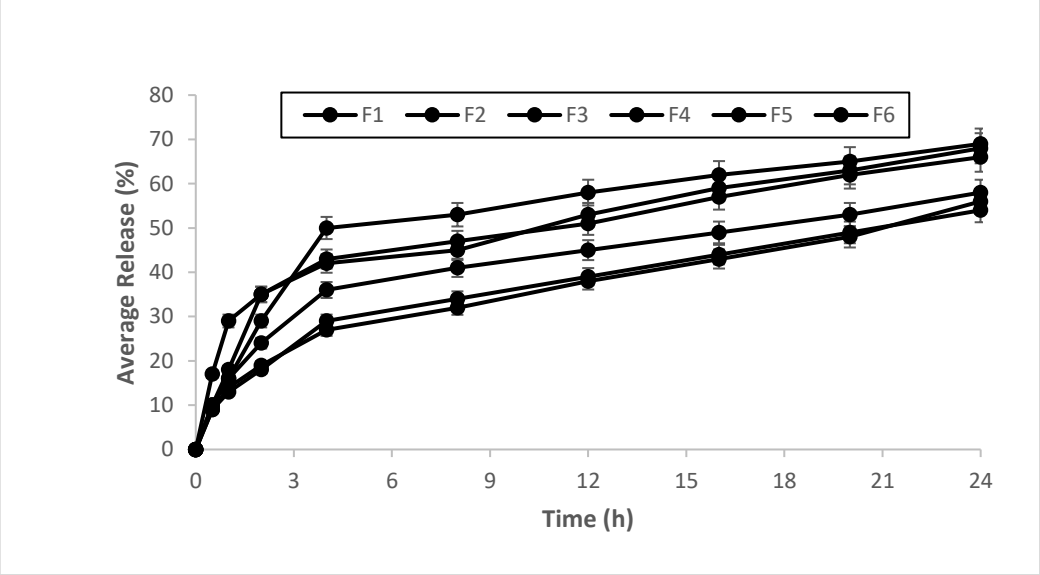


Figure 6. Effect of osmotic pressure on drug release (0.5% NaCl) at 100 rpm in 0.1 N HCl (n=3)

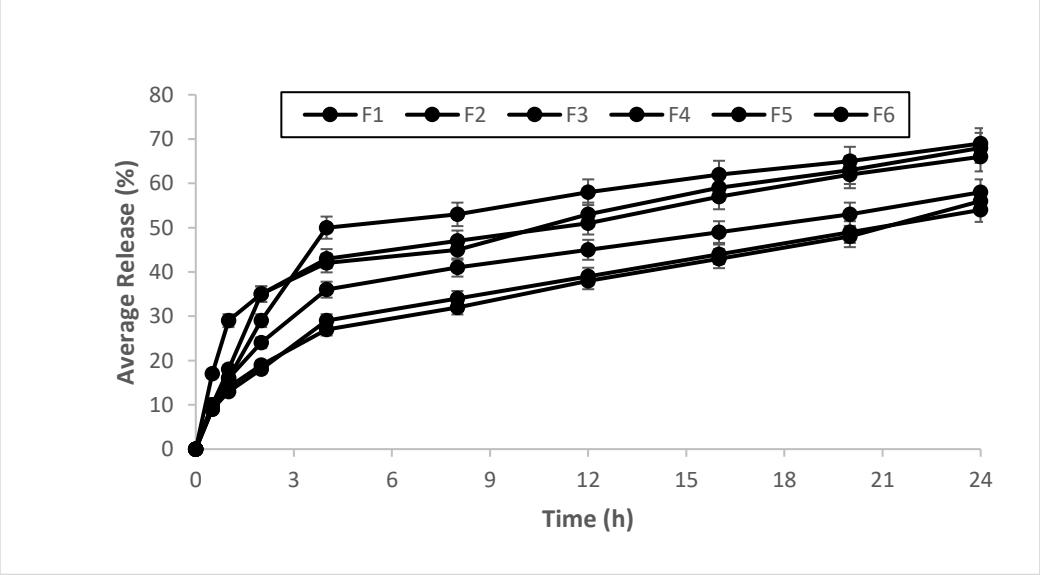


Figure 7. Effect of osmotic pressure on drug release (0.9% NaCl) at 100 rpm in 0.1 N HCl (n=3)

3.9. Release Kinetics

Data of *in-vitro* drug release of all formulation batches were fitted into various kinetic models such as Korsemeyer Peppas, Higuchi, first order and zero order. Both the Higuchi and first order models showed the best match findings, followed by zero order, showing drug release via diffusion process. Erosion, swelling and diffusion are the three most crucial factors that are responsible for controlling drug release. Diffusion is the most common way for polymeric systems to release drugs, and it is best characterized by Fickian diffusion (41). Formulations containing swellable polymers, on the other hand, cause additional processes such as polymer chain relaxation and water imbibition into polymers, enabling polymers to swell (42). Swelling of the polymers results in considerable expansion of the delivery systems. As a result, drug release data was fitted into the Korsemeyer Peppas equation, which describes the transport process. Mechanism of release is indicated with the value of "n" where n = 1 exhibited zero order case II transport, n = 0.5 showed Fickian diffusion, and n value 0.5 to 1.0 showed non-Fickian transport. Super case II transport is shown when n > 1 (43). Regression coefficient lines for all formulated tablets were shown in Table 4. Controlled drug release was observed with anomalous or non-Fickian diffusion mechanism. Thus, it was concluded that Higuchi and Korsemeyer Peppas models were effective in explaining drug release mechanism (44).

Table 4. *In-vitro* release kinetics of ciprofloxacin loaded floating tablets

F. Code	Zero Order	First Order	Higuchi	Peppas Equation	
	R^2	R^2	R^2	n	R^2
F1	0.8771	0.8566	0.9122	0.5210	0.9283
F2	0.7873	0.9214	0.9401	0.4612	0.9532
F3	0.8043	0.8731	0.9563	0.4907	0.9701
F4	0.8359	0.8413	0.9497	0.5191	0.9452
F5	0.8013	0.8524	0.9624	0.5082	0.9662
F6	0.8782	0.8318	0.9513	0.5625	0.9541

4. Conclusion

This study focused on the development and assessment of ciprofloxacin floating tablets for improving bioavailability of model drug. The achievement of *in-vitro* buoyancy was made possible by the inclusion of different rate controlling polymers such as HPMC, sodium alginate, chitosan and gas-generating agents like citric acid and sodium bicarbonate. All formulation batches remained buoyant for more than 12 h. Swelling index of prepared formulations was higher when a blend of polymers was employed. Following anomalous non-Fickian diffusion, formulations F2 and F6 demonstrated a preferable drug release profile for up to 24 hours. The addition of NaCl to release media was observed to boost drug release when compared to media without NaCl. The findings of this study clearly demonstrate the potential of ciprofloxacin loaded floating drug delivery system to augment bioavailability via enhanced gastric residence time.

5. References

1. Asghar AA, Akhlaq M, Jalil A, Azad AK, Asghar J, Adeel M. Formulation of ciprofloxacin-loaded oral self-emulsifying drug delivery system to improve the pharmacokinetics and antibacterial activity. Front Pharmacol. 2022 Oct 4;13:967106.
2. Alam A, Hasan Khan M, Kumar H, Ranjan Swain S. DESIGN AND IN VITRO AND IN VIVO EVALUATION OF FLOATING MICROSPHERES OF METFORMIN HYDROCHLORIDE FOR ORAL CONTROLLED RELEASE. World J Pharm Res [Internet]. 2021 [cited 2023 Feb 3];10(5):1499–510. Available from: www.wjpr.net
3. Vinarov Z, Abdallah M, Agundez JAG, Allegaert K, Basit AW, Braeckmans M. Impact of gastrointestinal tract variability on oral drug absorption and pharmacokinetics: An UNGAP review. Eur J Pharm Sci. 2021 Jul 1;162:105812.
4. Hua S. Advances in Oral Drug Delivery for Regional Targeting in the Gastrointestinal Tract - Influence of Physiological, Pathophysiological and Pharmaceutical Factors. Front Pharmacol.

2020 Apr 28;11:1–22.
5. Almeleebia TM, Akhter MH, Khalilullah H, Rahman MA, Ahmad S, Alam N, et al. Co-Delivery of Naringin and Ciprofloxacin by Oleic Acid Lipid Core Encapsulated in Carboxymethyl Chitosan/Alginate Nanoparticle Composite for Enhanced Antimicrobial Activity. ACS Omega [Internet]. 2024 [cited 2024 Feb 23];9(6):6845–60. Available from: https://pubs.acs.org/doi/full/10.1021/acsomega.3c08200
6. Alalor CA, Uhumwangho MU, Iwuagwu MA. Evaluation of Ciprofloxacin Floating-Bioadhesive Tablet Formulated with Okra Gum as Multifunctional Polymer. UK J Pharm Biosci. 2018;6(2):1–11.
7. Arshad R, Tabish TA, Kiani MH, Ibrahim IM, Shahnaz G, Rahdar A, et al. A hyaluronic acid functionalized self-nano-emulsifying drug delivery system (Snedds) for enhancement in ciprofloxacin targeted delivery against intracellular infection. Nanomaterials [Internet]. 2021 May 1 [cited 2024 Feb 20];11(5):1086. Available from: https://www.mdpi.com/2079-4991/11/5/1086/htm
8. Ahirrao S, Bhambere D, Todkar K, Patil M, Khairnar P, Udavan P, et al. Formulation Development and Evaluation of Floating Tablets of Zolmitriptan. Biosci Biotechnol Res Asia. 2022 Jun 30;19(2):395–405.
9. Rahamathulla M, Hani U, Pharm Sci PJ, Alam N, Ibrahim Q, Alhamhoom Y. Development and in vitro evaluation of effervescent floating matrix tablet of neritinib: An anticancer drug. Pak J Pharm Sci [Internet]. 2021 [cited 2023 Feb 3];34(4):1297–303. Available from: https://www.researchgate.net/publication/356422761
10. Naseem F, Shah SU, Rashid SA, Farid A, Almehmadi M, Alghamdi S. Metronidazole Based Floating Bioadhesive Drug Delivery System for Potential Eradication of H. pylori: Preparation and In Vitro Characterization. Polymers (Basel) [Internet]. 2022 Jan 27 [cited 2022 Jan 28];14(3):519. Available from: https://www.mdpi.com/2073-4360/14/3/519/htm
11. Maddiboyina B, Hanumanaik M, Nakkala RK, Jhawat V, Rawat P, Alam A, et al. Formulation and evaluation of gastro-retentive floating bilayer tablet for the treatment of hypertension. Heliyon. 2020 Nov 1;6(11):e05459.
12. Eswaraiah M, Jaya S. Design and in Vitro Characterization of Floating Tablets of Metronidazole. Asian J Pharm Clin Res. 2019;12(3):539–44.
13. Khan J, Kusmahani SH, Ruhi S, Al-Dhalli S, Kaleemullah M, Saad R, et al. Design and evaluation of sustained release matrix tablet of flurbiprofen by using hydrophilic polymer and natural gum. Int J Med Toxicol Leg Med. 2020 Jan 1;23(1–2):149–59.
14. Rashid R, Zaman M, Ahmad M, Khan MA, Butt MH, Salawi A, et al. Press-Coated Aceclofenac Tablets for Pulsatile Drug Delivery: Formulation and In Vitro Evaluations. Pharmaceuticals [Internet]. 2022 Mar 8 [cited 2023 Mar 12];15(3):326. Available from: https://www.mdpi.com/1424-8247/15/3/326/htm
15. Balkrishana VY, Ajinath SH, Singh KH, Gokul TS, Govindrao JA, Balkrishana VY. Formulation and evaluation of gastro retentive extended release formulation of metformin hydrochloride. GSC Adv Res Rev [Internet]. 2020 Feb 28 [cited 2023 Feb 3];2(2):008–17. Available from: https://gsconlinepress.com/journals/gscarr/content/formulation-and-evaluation-gastro-retentive-extended-release-formulation-metformin
16. Gawai N, Zaheer Z. Formulation and evaluation of 5-fluorouracil buccal mucoadhesive buccal tablet. J Pharmacogn Phytochem [Internet]. 2018 Sep 1 [cited 2023 Jun 21];7(6S):19–23. Available from: https://www.phytojournal.com/special-issue/2018.v7.i6S.6616/formulation-and-evaluation-of-5-fluorouracil-buccal-mucoadhesive-buccal-tablet
17. Koirala S, Nepal P, Ghimire G, Basnet R, Rawat I, Dahal A. Formulation and evaluation of mucoadhesive buccal tablets of aceclofenac. Heliyon [Internet]. 2021 Mar 1 [cited 2023 Apr 11];7(3):e06439. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2405844021005442
18. Pandey NK, Ghatuary SK, Dubey A, Jain PK. Formulation and In Vitro Evaluation of Sustained Release Floating Matrix Tablet of Levofloxacin by Direct Compression Method. J Drug Deliv

Ther [Internet]. 2019 Aug 15 [cited 2023 Aug 10];9(4-s):398–403. Available from: https://jddtonline.info/index.php/jddt/article/view/3345
19. Djebbar M, Chaffai N, Bouchal F. Development of Floating Tablets of Metformin HCl by Thermoplastic Granulation. Part II: In Vitro Evaluation of the Combined Effect of Acacia Gum/HPMC on Biopharmaceutical Performances. Adv Pharm Bull [Internet]. 2020 [cited 2023 Feb 3];10(3):399. Available from: /pmc/articles/PMC7335996/
20. López KJS, Vásquez SLG, Vásquez YAG, Suárez AIT, Barranco PG, Gutiérrez MLY, et al. Formulation and evaluation of gastroretentive floating tablets of metformin hydrochloride based on effervescence and swelling. Farma J. 2019;4(1):305.
21. Sheikh FA, Hussain MA, Ashraf MU, Haseeb MT, Farid-ul-Haq M. Linseed hydrogel based floating drug delivery system for fluoroquinolone antibiotics: Design, in vitro drug release and in vivo real-time floating detection. Saudi Pharm J. 2020 May 1;28(5):538–49.
22. Teaima M, Hamid MMA, Shoman NA, Jasti BR, El-Nabarawi MA. Promising swellable floating bupropion tablets: Formulation, in vitro/in vivo evaluation and comparative pharmacokinetic study in human volunteers. Drug Des Devel Ther [Internet]. 2020 Jul 1 [cited 2023 Feb 3];14:2741–57. Available from: http://doi.org/10.2147/DDDT.S258571
23. Gundu R, Pekamwar S, Shelke S, Shep S, Kulkarni D. Sustained release formulation of Ondansetron HCl using osmotic drug delivery approach. Drug Dev Ind Pharm [Internet]. 2020 Mar 3 [cited 2024 Jun 23];46(3):343–55. Available from: https://www.tandfonline.com/doi/abs/10.1080/03639045.2020.1716372
24. Labot JM, Manzo RH, Allemandi DA. Double-layered mucoadhesive tablets containing nystatin. AAPS PharmSciTech [Internet]. 2002 [cited 2021 Apr 7];3(3):1–6. Available from: https://pubmed.ncbi.nlm.nih.gov/12916937/
25. Singh K, Mishra A, Singh A. Synthesis Characterization and In Vitro Release Study of Ciprofloxacin-Loaded Chitosan Nanoparticle. Bionanoscience [Internet]. 2018 Mar 1 [cited 2024 Jun 23];8(1):229–36. Available from: https://link.springer.com/article/10.1007/s12668-017-0470-7
26. Jatav R, Singh D, Rathore P, Prakash Jain N, Goswami RB, Jatav Students of MPharm R. FORMULATION AND EVALUATION OF FLOATING PELLETS OF AMOXICILLIN TRIHYDRATE FOR ERADICATION OF H.PYLORI. World J Pharm Res [Internet]. 2021 [cited 2023 Feb 14];10(9):1024–47. Available from: www.wjpr.net
27. Dumpa NR, Bandari S, Repka MA. Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing. Pharmaceutics [Internet]. 2020 Jan 8 [cited 2021 Apr 6];12(1). Available from: /pmc/articles/PMC7023033/
28. Raza A, Bukhari NI, Karim S, Hafiz MA, Hayat U. Floating tablets of minocycline hydrochloride: Formulation, in-vitro evaluation and optimization. Futur J Pharm Sci. 2017 Dec 1;3(2):131–9.
29. Iglesias N, Galbis E, Romero-Azogil L, Benito E, Lucas R, García-Martín MG, et al. In-Depth Study into Polymeric Materials in Low-Density Gastroretentive Formulations. Pharmaceutics [Internet]. 2020 Jul 7 [cited 2023 Feb 10];12(7):636. Available from: https://www.mdpi.com/1999-4923/12/7/636/htm
30. Noreen M, Farooq MA, Ghayas S, Bushra R, Yaqoob N, Abrar MA. Formulation and in vitro characterization of sustained release tablets of lornoxicam. Lat Am J Pharm. 2019;38(4):701–11.
31. Manogna K, Nagaveni P, Thyagaraju K. A Review On Mucoadhesive Bilayer Buccal Tablets. Am J PharmTech Res. 2018;8(1):101–15.
32. Patel MB, Shaikh F, Patel V, Surti NI. Application of simplex centroid design in formulation and optimization of floating matrix tablets of metformin. J Appl Pharm Sci [Internet]. 2017 [cited 2023 Feb 3];7(04):23–030. Available from: http://www.japsonline.com
33. Huh HW, Na YG, Kang HC, Kim M, Han M, Pham TMA, et al. Novel self-floating tablet for enhanced oral bioavailability of metformin based on cellulose. Int J Pharm. 2021 Jan 5;592:120113.
34. Kumar SA, Debnath M, Anusha K, Manna K, Rao JS. Studies on Formulation Development and

Evaluations on Losartan Floating and Bioadhesive Drug Delivery System. Pakistan J Pharm Res. 2017;3(2):84–98.
35. Nigusse B, Gebre-Mariam T, Belete A. Design, development and optimization of sustained release floating, bioadhesive and swellable matrix tablet of ranitidine hydrochloride. PLoS One [Internet]. 2021 Jun 1 [cited 2023 Feb 14];16(6):e0253391. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0253391
36. Varshi R, Jain V, Pal P. A review on Advanced approaches and polymers used in gastroretentive drug delivery systems. J Drug Deliv Ther [Internet]. 2022 Jul 15 [cited 2023 Feb 10];12(4):181–5. Available from: http://www.jddtonline.info/index.php/jddt/article/view/5422/4793
37. Bhatt P, Patel D, Patel A, Patel A, Nagarsheth A. Oral Controlled Release Systems: Current Strategies and Challenges. In: Novel Drug Delivery Technologies: Innovative Strategies for Drug Re-positioning [Internet]. Springer, Singapore; 2019 [cited 2024 Jun 23]. p. 73–120. Available from: https://link.springer.com/chapter/10.1007/978-981-13-3642-3_4
38. Iqbal DN, Tariq M, Khan SM, Gull N, Sagar Iqbal S, Aziz A, et al. Synthesis and characterization of chitosan and guar gum based ternary blends with polyvinyl alcohol. Int J Biol Macromol. 2020 Jan 15;143:546–54.
39. Vega MAC, Deng M, Pinal R. Modular solid dosage form design – Application to pH-independent release of a weak-base API. Int J Pharm. 2021 May 15;601:120518.
40. Gull N, Khan SM, Zahid Butt MT, Khalid S, Shafiq M, Islam A, et al. In vitro study of chitosan-based multi-responsive hydrogels as drug release vehicles: a preclinical study. RSC Adv [Internet]. 2019 Oct 1 [cited 2024 Jun 23];9(53):31078–91. Available from: https://pubs.rsc.org/en/content/articlehtml/2019/ra/c9ra05025f
41. Huang J, Lin H, Peng B, Huang Q, Shuai F, Xie Y. Design and Evaluation of Hydrophilic Matrix System for pH-Independent Sustained Release of Weakly Acidic Poorly Soluble Drug. AAPS PharmSciTech [Internet]. 2018 Jul 1 [cited 2023 Mar 12];19(5):2144–54. Available from: https://link.springer.com/article/10.1208/s12249-018-1008-1
42. Swain RP, Nagamani A, Shankar PU. Formulation and Evaluation of Gastro-bilayer Floating Tablets of Ezetimibe as Immediate Release Layer and Atenolol as Sustained Release Layer. Indian J Pharm Educ Res | [Internet]. 2019 [cited 2023 Jun 21];53(2):S93–103. Available from: www.ijper.org
43. Kumari B, Pandey P, Dureja H. Formulation and Characterization of Gastroretentive Floating Tablets of Atorvastatin Calcium Using Central Composite Design. J Pharm Res [Internet]. 2017 Sep 1 [cited 2021 Apr 4];16(3):247. Available from: http://www.journalofpharmaceuticalresearch.org/index.php/kpc/article/view/118782
44. Ovenseri AC, Uhumwangho UM, Obarisiagbon AJ, Umechukwu CP. Formulation of non-effervescent floating matrix tablets of metronidazole using Abelmoschus esculentus gum as binder and 2-camphanone as sublimating agent. J Phytomedicine Ther. 2020;19(1).