Journal of Pharmaceutical Research International

Volume 36, Issue 3, Page 47-62, 2024; Article no.JPRI.114661
ISSN: 2456-9119, NLM ID: 101716968
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Development and Assessment of Hydroxypropyl Methylcellulose-Based Floating Tablets for Ciprofloxacin HCL Using Direct Compression Technique

K. Venkata Gopaiah [a*], J N Suresh Kumar [a], M. Ramya Teja [a], T. Lokesh [a], D. Sai Sruthi [a], M. Roja [a], N. Rushitha [a] and SK. Vahedunnisa [a]

[a] Narasaraopeta Institute of Pharmaceutical Sciences, Narasaraopeta, Palnadu, Andhra Pradesh, 522 601, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2024/v36i37506

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/114661

Original Research Article

Received: 12/01/2024
Accepted: 18/03/2024
Published: 26/03/2024

ABSTRACT

The key findings and conclusions include: such as formulation approaches as aim and objective Development of floating tablets using sodium bicarbonate and HPMC aimed at enhancing gastric residence time for improved drug bioavailability. Physicochemical Compliances The formulated tablets met compliance standards for various physicochemical parameters, including dimensions, floating time, tablet density, and drug content. Method of Formulations F2, F5, and F6 displayed favorable drug release profiles, with the F7 formulation exhibiting excellent release characteristics. in the evaluation the drug release kinetics studies show Kinetic analysis revealed that F2, F5, F6, and F7 formulations followed the Korsmeyer–Peppas model, indicating non-Fickian diffusion with

**Corresponding author: E-mail: venkatkurra88@gmail.com;*

'n' values ranging from 0.521 to 0.633 and the stability indicates the Optimal storage conditions for stability were determined as 2-8°C for 60 days. Formulations F2, F5, F6, and F7 demonstrated stability at room temperature, 40°C, and 2-8°C for 30 days, with refrigerated storage maintaining stability throughout the 60 days. In conclusion, the developed hydrodynamically balanced tablets of Ciprofloxacin HCl exhibit promising physicochemical characteristics, dissolution profiles, and stability. These tablets hold the potential for enhancing drug bioavailability, making them a viable option for localized drug delivery in the upper gastrointestinal tract.

Keywords: Ciprofloxacin; HPMC; hydrodynamically.

1. INTRODUCTION

Oral drug delivery stands as the preferred method due to its simplicity, patient adherence, and formulation versatility. However, conventional oral dosage forms lack control over drug release, leading to fluctuations in systemic drug levels when administered multiple times a day. This article explores the imperative shift towards developing an ideal drug delivery system (DDS) to address these challenges.

Current oral dosage forms maintain therapeutic drug concentrations but fail to provide sustained and controlled drug release over an extended period. The focus of contemporary pharmaceutical research is on creating DDS that consistently deliver precise drug amounts to target sites. This pursuit aims to mitigate fluctuations in drug levels, ensuring optimal therapeutic efficacy.

Pharmaceutical scientists are dedicated to the development of an ideal oral drug delivery system capable of achieving sustained, measurable, and reproducible drug release over an extended duration. This article discusses the motivation behind this research endeavor and the characteristics that define an ideal DDS.

The limitations of conventional oral drug delivery systems, such as the lack of control over drug release and resulting fluctuations in drug levels, underscore the need for innovative approaches. The article explores recent advancements in DDS to overcome these challenges, providing insights into the future of oral drug delivery for enhanced therapeutic outcomes [1].

1.1 Controlled Release Drug Delivery Systems (CRDDS)

These are designed to release drugs at a predetermined and predictable rate, enhancing the therapeutic effect with lower and less frequent dosing [2-4]. The primary objectives of controlled delivery include:

a) Sustaining drug action at a predetermined rate to maintain a constant and effective drug level in the body, thereby minimizing undesirable side effects associated with a fluctuating kinetic pattern.
b) Localizing drug action through the spatial placement of controlled release systems, typically rate-controlled, adjacent to or within the diseased tissue or organ.
c) Targeting drug action by utilizing carriers or chemical derivatization to deliver drugs to specific cell types.

In practice, few systems incorporate all these actions. Most release systems aim to create a constant drug concentration within the body over an extended period. To maintain a consistent drug level in plasma or target tissue, the release rate from the controlled release system should match the elimination rate from plasma or target tissue. While intravenous infusion is a conventional method for achieving a constant plasma level, it is often impractical for routine therapeutic situations. Therefore, non-invasive routes such as oral or transdermal administration are preferred.

In conventional drug delivery systems, the rate-limiting step for drug availability typically involves absorption across biological membranes, such as the gastrointestinal wall. In contrast, sustained/controlled release products focus on making drug release from the dosage form the rate-limiting step. Consequently, drug availability is controlled by the kinetics of drug release rather than absorption [5].

1.2 Advantages of Controlled Release Dosage Forms [6]: Controlled Release (CR) Dosage Forms (DFs) Offer Several Benefits, Including

1. Reduction in dosing frequency.
2. Minimized fluctuations in circulating drug levels.
3. Enhanced patient compliance.

4. Elimination of night-time dosing.
5. More uniform and sustained therapeutic effects.
6. Decreased gastrointestinal (GI) irritation.
7. Lower incidence of dose-related side effects.

1.3 Disadvantages of Controlled Release Dosage Forms: Despite their Advantages, controlled Release Dosage Forms (CR-DFs) Come with Potential Drawbacks

1. Higher cost and unpredictable in vitro-in vivo correlation.
2. Risk of dose dumping, limiting the potential for dosage adjustment.
3. Increased likelihood of first-pass clearance, leading to poor systemic availability.
4. The effective drug release period is often influenced and limited by gastrointestinal residence time [6].

A significant challenge in oral controlled drug delivery is the non-uniform absorption of drug candidates throughout the gastrointestinal tract (GIT). Various factors, such as physiological, physicochemical, or biochemical aspects, create an absorption window, influencing the solubility, stability, and pH-dependent characteristics of drugs. Since many drugs are absorbed through passive diffusion of the unionized form, the degree of ionization at different pH levels can result in non-uniform absorption or the creation of an absorption window. Additionally, the presence of specific enzymes in certain GIT regions can contribute to regional variability in drug absorption for enzyme substrate drugs [2].

Designing oral controlled release drug delivery systems (CRDDS) for drugs with site-specific absorption poses challenges. The drug released in the region preceding and near the absorption window is available for absorption, but once it crosses the absorption window, the released drug may go to waste with minimal or no absorption. This limitation reduces the time available for drug absorption after release, impacting the success of the delivery system [2].

The primary goal of designing oral controlled drug delivery systems (DDS) is to achieve more predictable and increased bioavailability. However, these systems face physiological challenges, including the inability to control and localize the DDS within desired regions of the GI tract and the highly variable nature of the gastric emptying process.

In humans, gastric emptying time, typically 2-3 hours in the main absorption area (stomach or upper part of the intestine), can lead to incomplete drug release from DDS, diminishing the efficacy of the administered dose. Ensuring intimate contact of the DDS with the absorbing membrane can maximize drug absorption and influence the rate of absorption, prompting the development of oral controlled gastro retentive dosage forms [4].

2. GASTRO RETENTIVE DRUG DELIVERY SYSTEMS (GRDDS)

Gastro retentive Drug Delivery Systems (GRDDS) refer to dosage forms designed to be retained in the stomach. The primary goal of GRDDS is to improve the controlled delivery and bioavailability of drugs by continuously releasing them over an extended period before reaching the absorption site [2].

Drugs with a narrow absorption window often show improved absorption in the jejunum and ileum due to enhanced properties like a larger surface area or increased solubility in the stomach compared to more distal parts of the gastrointestinal tract [7].

2.1 Types of Drugs Suitable for Gastro retentive Devices: [8]

- Drugs acting locally in the stomach (e.g., antacids).
- Drugs primarily absorbed in the stomach (e.g., albuterol).
- Drugs poorly soluble at an alkaline pH.
- Drugs with a narrow absorption window (e.g., riboflavin, levodopa).
- Drugs rapidly absorbed from the GI tract (e.g., amoxicillin).
- Drugs that degrade in the colon (e.g., metoprolol).

Longer residence time in the stomach can be advantageous for treating local ailments in the upper part of the small intestine, such as peptic ulcer disease.

2.2 Advantages of Gastro Retentive Drug Delivery Systems [9]

- Enhanced bioavailability.
- Improved first-pass biotransformation.

- Sustained drug delivery/reduced dosing frequency.
- Targeted therapy for local upper GIT ailments.
- Reduced drug concentration fluctuations.
- Improved selectivity in receptor activation.
- Minimized counteractivity of the body.
- Extended time over critical concentration.
- Reduced adverse activity at the colon.
- Site-specific drug delivery.

2.3 Ideal Drug Candidates for Gastro Retentive Drug Delivery Systems [7]:

a. Drugs stable in the gastric environment.
b. Drugs with a narrow absorption window.
c. Drugs intended for gastro-duodenal local therapy.

2.4 Drugs Incorporated into Gastro Retentive Drug Delivery Systems [7]

Various drugs have been incorporated into GRDDS in forms such as microspheres, granules, capsules, tablets, or pills.

2.5 Disadvantages of Gastro Retentive Drug Delivery Systems [9]

- Drugs that may irritate the stomach lining.
- Drugs unstable in an acidic environment should not be formulated in gastro retentive systems.
- Drugs like isosorbide dinitrate, which are equally well absorbed throughout the GI tract, do not benefit from incorporation into a gastric retention system.

2.6 Limitations of Gastro Retentive Drug Delivery Systems [2]

- High levels of fluids in the stomach are required for the delivery system to float and work efficiently.
- The presence of food is necessary to delay gastric emptying.
- Drugs with solubility or stability issues in the highly acidic gastric environment or those that irritate the gastric mucosa cannot be formulated as Gastro retentive Drug Delivery Systems.
- In bio adhesive systems, the acidic environment, thick mucus, and high mucous turnover rate prevent bond formation at the mucous-polymer interface.
- For swellable systems, the dosage form must maintain a size larger than the aperture of the resting pylorus for the required period.

2.7 Approaches to Gastric Retention

Several approaches aim to increase gastric retention time (GRT) of a dosage form in the stomach by employing various concepts:

a) Floating Systems

- Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids, remaining buoyant in the stomach for an extended period without affecting gastric emptying rate.
- Two types: non-effervescent and effervescent systems.

b) Bio/mucoadhesive Systems

- These systems bind to gastric epithelial cell surfaces or mucin, extending GRT by increasing the contact duration of the drug with the biological membrane.
- Binding categories include hydration-mediated, bonding-mediated, and receptor-mediated adhesion.

c) Swelling and Expanding Systems

- Dosage forms swell after swallowing, preventing exit from the pylorus and ensuring prolonged stomach retention (plug type system).

d) High-Density Systems

- Systems with a density of about 3 g/cm3 are retained in the stomach rugae, withstanding peristaltic movements.
- High-density formulations include coated pellets using inert materials like barium sulfate.

e) Incorporation of Passage Delaying Food Agents:

- Food excipients like fatty acids alter stomach patterns, decreasing gastric emptying rate and allowing prolonged drug release.

f) Ion Exchange Resins:

- Resins loaded with bicarbonate and negatively charged drugs are encapsulated in a semi-permeable membrane, producing a floating layer of resin beads upon contact with gastric acid.

g) Raft Systems:

- Incorporate alginate gels with a carbonate component, forming bubbles upon reaction with gastric acid and enabling floating.

Types of Floating Drug Delivery Systems (FDS):

Based on buoyancy mechanisms, two technologies are utilized: Effervescent Systems and Non-Effervescent Systems.

A. Effervescent Systems:

- Gas-generating and volatile liquid/vacuum-containing systems.
- Examples include hydrodynamically balanced systems, intragastric bilayer tablets, and multiple-unit type floating pills.

B. Non-Effervescent Systems:

- Use gel-forming or swellable polymers.
- Examples include single-layer and bilayer floating tablets, alginate beads, and hollow microspheres.

2.8 Gastric Emptying

Gastric emptying rate varies for pharmaceuticals, depending on the dosage form and the fed or fasted state of the stomach. The migrating motor complex (MMC) regulates gastric motility patterns in the fasted state, consisting of phases I, II, III, and IV. The fed state induces motor activity, churning food and emptying fine particles through the pylorus into the duodenum.

For controlled release drug delivery systems (CRDDS), the design considers resistance to gastric emptying during phase III of MMC in the fasted state and continuous gastric emptying through the pyloric sphincter in the fed state. GRDDS must be functional quickly after administration, resisting physiological events for the required duration.

Emptying of Dosage Forms (DFs) from the stomach: Non-disintegrating DFs are not typically retained in the stomach for more than 2 hours in the fasting state due to the MMC. In the fed state, GRT depends on DF size, composition, and caloric value of food. Large DFs are retropelled for further digestion or retained until the subsequent housekeeper wave. GRT is longer in the fed state for large DFs.

Gastrointestinal Transit Time: Food content remains in each GIT segment for different durations. Residence time for both liquid and solid foods varies in each segment, influenced by factors like DF size and composition.

Table 1. Various drugs incorporated into GRDDS

Acyclovir	Alendronate	Atenolol
Captopril	Cinnarizine	Ciprofloxacin
Cisapride	Furosemide	Glipizide
Ketoprofen	Levodopa	Misoprostol
Nicardipine	Riboflavin	Tetracycline
Verapamil	Diltiazem	

Table 2. Residence time

Segment	Liquid	Solid
	10 - 30 min	1 – 3 hours
Stomach	< 60 sec	< 60 sec
Duodenum	3 ± 1.5 hours	4 ± 1.5 hours
Jejunum and Ileum, Colon	-	20 – 50 hours

3. MATERIALS AND METHODS

3.1 Methodology [10]

Floating tablets of Ciprofloxacin Hcl were prepared using the direct compression technique, employing various ratios of polymers such as HPMC (K100M, K4M, and E50) with sodium bicarbonate as a gas-generating agent. The formulations (F1 to F7) had different ratios of HPMC (K100M, K4M, E50) as follows: F1 (1:2:3), F2 (1:3:2), F3 (1:1:1), F4 (2:1:3), F5 (2:3:1), F6 (3:1:2), and F7 (3:2:1).

Sifting: Ciprofloxacin Hcl was sieved through sieve no. 20 and collected in a clean bowl. HPMC K100M, HPMC K4M, HPMC E50, and sodium bicarbonate were sieved through sieve no. 40 and collected in a clean bowl. Talc was sieved through sieve no. 60 and collected in a clean bowl. Magnesium stearate was sieved through sieve no. 60 and collected in a separate clean bowl.

Mixing: Ciprofloxacin Hcl was geometrically mixed with HPMC K100M, HPMC K4M, HPMC E50, and sodium bicarbonate for 10 minutes. Talc was then added and further mixed for 5 minutes.

Lubrication: After sufficient mixing of the drug and other components, magnesium stearate was added and further mixed for an additional 2 minutes.

Compression: The lubricated granules were compressed using a Rotary tableting machine. The weight of the tablet was kept constant for all formulations.

Table 3. Composition of ciprofloxacin floating tablets

	Batch Code						
Ingredients(mg/tablet)	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
Ciprofloxacin Hcl	270	270	270	270	270	270	270
HPMC K100M	20	20	40	40	40	60	60
HPMC K4M	40	60	40	20	60	20	40
HPMC E50	60	40	40	60	20	40	20
Sodium bicarbonate	100	100	100	100	100	100	100
Talc	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5
Total	500	500	500	500	500	500	500

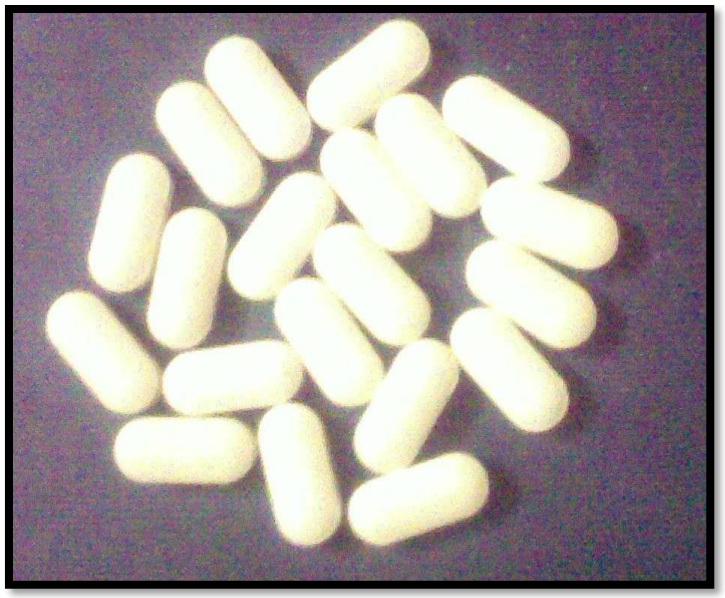


Fig. 1. Formulated tablets of ciprofloxacin floating tablets

Table 4. Scale of flow property

Flow property	Angle of Repose (θ in degrees)	Compressibility Index (CI in %)	Hausner Ratio
Excellent	25 – 30	< 10	1.00 – 1.11
Good	31 – 35	11 - 15	1.12 – 1.18
Fair	36 – 40	16 – 20 1.19 – 1.25	
Possible	41 – 45	21 - 25	1.26 – 1.34
Poor	46 – 55	26 – 31	1.35 – 1.45
Very Poor	56 – 65	32 – 37	1.46 – 1.59
Very, very poor	> 66	> 38	> 1.60

3.2 Evaluation Parameters

A) Pre-Compression Parameters [11]:

i. Bulk Density:
ii. Compressibility Index:
iii. Hausner Ratio:
iv. Angle of Repose (θ):

B) Post-Compression Parameters:

The tablets were evaluated for the various parameters enlisted below:-

1. Appearance
2. Weight variation
3. Thickness
4. Hardness
5. Friability
6. Drug content
7. Tablet density
8. Floating test
9. Swelling study
10. In-vitro dissolution studies
11. Kinetics of drug release
12. Stability studies

4. RESULTS AND DISCUSSION

4.1 Preformulation Studies

Description: Ciprofloxacin Hcl is described as a faintly yellowish to light yellow crystalline substance.

Solubility: Ciprofloxacin Hcl was determined to be soluble in water and 0.1N HCl, while being practically insoluble in acetone, acetonitrile, and dichloromethane.

pH: The pH of Ciprofloxacin Hcl was measured to be 3.6.

Compatibility Studies: Compatibility studies were conducted using an FT-IR spectrophotometer. The FTIR spectrum of the obtained drug and its combination with polymers were analyzed. Characteristic absorption peaks of Ciprofloxacin at 3335.03 cm-1 and 3084.28 cm-1 were observed in the FT-IR spectrum of the drug with polymers. This indicates the compatibility of the drug with the polymer components. Refer to the FT-IR spectrum of the drug and FT-IR spectrum of drug and polymer.

4.2 Evaluation of Floating Tablets of Ciprofloxacin Hcl

A) Pre-Compression Parameters:

The bulk density of granules is utilized for determining the compressibility index and Hausner ratio.

4.3 Compressibility Index

- Formulations F1, F3, and F4 exhibit values of 16.84%, 18.19%, and 17.01%, respectively, indicating fair flow properties.
- Formulations F2, F5, F6, and F7 show values of 14.23%, 12.60%, 13.20%, and 14.23%, respectively, indicating good flow properties.

4.4 Hausner Ratio

- Formulations F1, F3, and F4 have Hausner ratio values of 1.20, 1.22, and 1.21, respectively, indicating fair flow properties.
- Formulations F2, F5, F6, and F7 exhibit Hausner ratio values of 1.16, 1.14, 1.15, and 1.16, respectively, indicating good flow properties.

4.5 Angle of Repose

- Formulations F1, F3, and F4 display values of 31.24, 32.65, and 31.37,

respectively, indicating good flow properties.

- Formulations F2, F5, F6, and F7 show values of 28.42, 29.14, 27.34, and 28.30, respectively, indicating excellent flow properties.

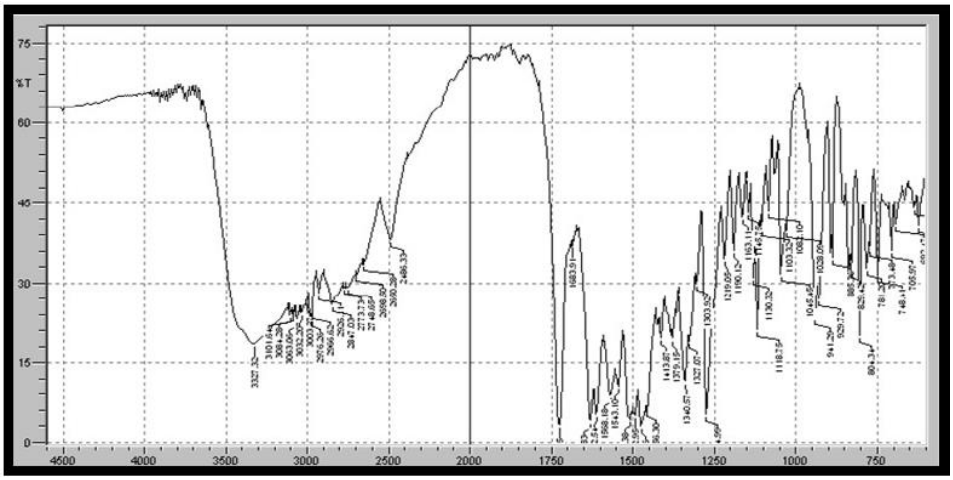


Fig. 2. FT-IR spectrum of pure drug Ciprofloxacin Hcl

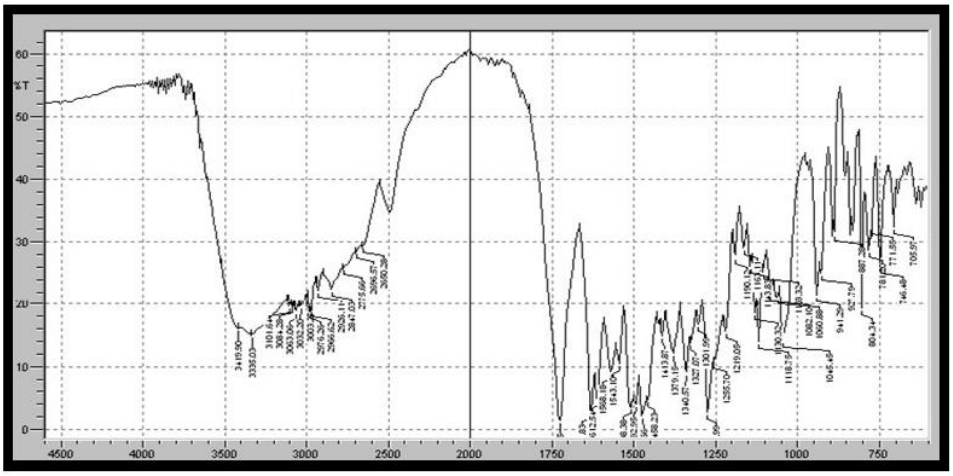


Fig. 3. FT-IR spectrum of Ciprofloxacin Hcl with HPMC (K100M, K4M and E50)

Table 5. FT-IR spectra data of pure drug Ciprofloxacin Hcl

Groups and mode ofvibrations	Frequency (in cm^{-1})	
	Drug	Expected Range
NH stretching	3327.32	3500-3300

Table 6. Pre-Compression parameters

Parameters	Formulations						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Loose Bulk Density(gm/ml)	0.454	0.476	0.454	0.400	0.416	0.434	0.476
Tapped Bulk Density(gm/ml)	0.546	0.555	0.555	0.482	0.476	0.500	0.555
Compressibility Index (%)	16.84	14.23	18.19	17.01	12.60	13.20	14.23
Angle of Repose (θ)1.20 Hausner Ratio	31.24	28.42	32.65	31.37	29.14	27.34	28.30

B) Post-Compression Parameters:

1. **Appearance:**

- Microscopic examination reveals that tablets from each batch exhibit a white, caplet shape, biconvex, and are uncoated with a plain surface on both sides.
- Weight Variation:
- Percentage weight variations for all formulations are presented in Table 12. The tablets pass the weight variation test, as the % weight variation falls within the pharmacopeial limits of ±5% of the average weight.

2. Weight variation:

- The percentage weight variations of all formulations was given tablets passed weight variation test as % weight variation was within pharmacopeial limits of ±5% of the average weight.

3. **Thickness:**

- The thickness values for all seven formulations range from 5.58 mm to 5.64 mm. Tablet thickness is crucial for consumer acceptance and maintaining tablet-to-tablet uniformity, often related to tablet hardness.

4. **Hardness:**

- The hardness of formulations varies, with F3 having the highest value of 5.6 kg/cm2. Formulations F1 and F4 share the same value of 3.5 kg/cm2. Formulations F2, F5, F6, and F7 have values ranging from 4.5 kg/cm2 to 5.0 kg/cm2. F3 has the highest hardness, while F1 and F4 have the lowest.

5. **Friability:**

- % Friability values are less than 1%, ensuring that the tablets are mechanically stable.

6. **Drug Content:**

- The percentage drug content for the seven batches ranges from 97.43% to 99.90%, falling within acceptable limits and indicating dose uniformity in each batch.

4.6 Tablet Density

To ensure good floating behavior in the stomach, the density of the system should be less than that of the gastric contents. All seven batches exhibited a density in the range of 0.92 – 0.94 g/cm³.

The study indicated that tablets from all batches demonstrated favourable floating characteristics after a buoyancy lag time. This suggests that upon contact with the test medium, the tablets expanded (due to the swellable polymer) and produced CO2 gas (due to the effervescent agent). As a result, the tablet floated as its density dropped below 1.0 due to the expansion of the polymer and the upward force of CO2 gas generation.

Table 7. Physicochemical properties of ciprofloxacin floating tablets

	Formulation						
Parameters	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
Weight Variation (gm)	0.493± 0.019	0.499± 0.016	0.498± 0.022	0.491± 0.021	0.491± 0.014	0.493± 0.015	0.492± 0.013
Thickness(mm)	5.62	5.60	5.58	5.64	5.62	5.58	5.60
Hardness(kg/cm^2)	3.5	4.5	6.5	3.5	4.5	5.0	5.0
Friability (%)	0.94	0.52	0.32	0.92	0.52	0.56	0.54
Drug Content(%)	99.90	98.67	97.43	99.63	98.12	98.82	99.09

Table 8. Tablet density of ciprofloxacin floating tablets

	Formulation						
Parameters	**F_1**	**F_2**	**F_3**	**F_4**	**F_5**	**F_6**	**F_7**
Thickness(cm)	0.562	0.560	0.558	0.564	0.562	0.558	0.560
Length (cm)	1.716	1.720	1.716	1.718	1.722	1.720	1.716
Width (cm)	0.814	0.818	0.814	0.816	0.820	0.818	0.814
Tablet Density(gm/cc)	0.93	0.93	0.94	0.93	0.92	0.93	0.94

Table 9. Floating test of ciprofloxacin Hcl tablets

Parameters	Formulation						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
Floating Lag Time or Buoyancy Lag Time (sec)	12	30	50	10	35	15	20
Total FloatingTime (hrs)	>6	>10	>10	>6	>10	>10	>10

Table 10. Swelling index of ciprofloxacin floating tablets

Time (hrs.)	Swelling Index (%)						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	51.38	30.14	24.54	49.27	30.06	32.55	34.68
2	61.77	47.33	32.51	60.51	44.18	49.92	51.33
3	79.56	54.83	39.83	76.81	51.34	67.37	74.92
4	89.92	65.44	46.41	88.56	64.29	77.11	81.29
5	88.21	78.33	50.10	88.17	76.14	82.54	87.16
6	63.11	55.42	48.23	63.43	57.55	79.13	76.44
7	32.15	39.22	41.11	32.98	42.18	59.15	54.24
8	17.18	27.93	39.87	17.26	29.46	30.29	29.35

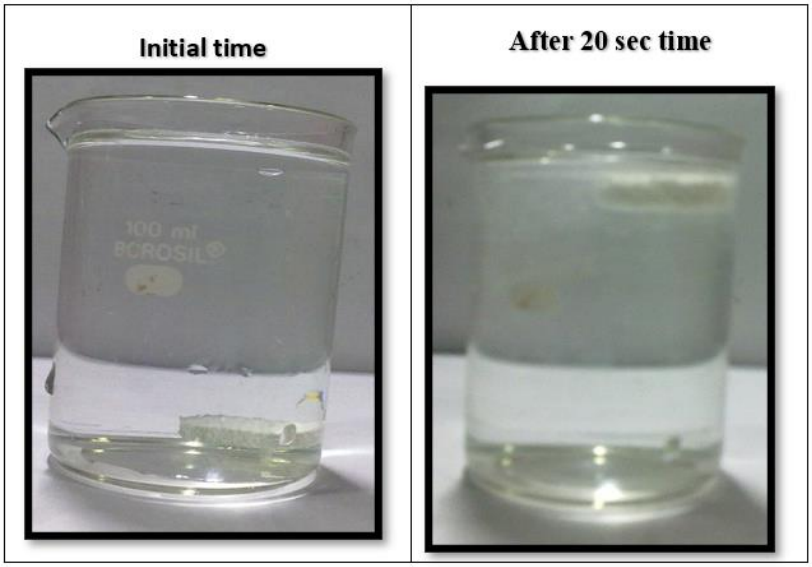


Fig. 4. Buoyancy character of formulated tablets

4.7 Floating Test

Carbon dioxide is generated within the tablet containing the effervescent agent when it comes into contact with an acidic medium (0.1 N HCl). Upon immersion in 0.1 N HCl at 37°C, the tablets floated and remained buoyant without disintegration. The results of the floating lag time for all seven formulations were within 1 minute. The total floating time for F1 and F4 formulations exceeded 6 hours, while the total floating time for F2, F3, F5, F6, and F7 formulations exceeded 10 hours.

4.8 Swelling Study

The swelling ratio characterizes the amount of water held within the hydrogel at equilibrium and is influenced by factors such as network structure, hydrophilicity, and ionization of functional groups. Swelling studies were conducted on all batches for 8 hours. The results indicate that swelling increased up to 4-5 hours for all formulations but decreased afterward.

The swelling index results are presented in Table 15, while the plot of swelling index against time is

shown in [Fig 5]. The swelling increases with time as the polymer gradually absorbs water due to its hydrophilicity. The outermost layer of the polymer hydrates, swells, and forms a gel barrier at the outer surface. As the gelatinous layer progressively dissolves and/or disperses, the hydration swelling release process is repeated toward new exposed surfaces, maintaining the integrity of the dosage form.

4.9 *In-vitro* Dissolution Study

4.9.1 Cumulative % drug release

The in-vitro drug release profiles of tablets from each batch using USP dissolution apparatus Type II are summarized in Table 10. The plot of % cumulative drug released vs. time (hr) was generated for all formulations.

In this study, the hydrophilic nature of HPMC played a key role in drug release, involving:

1. Hydration and swelling of the polymer
2. Dissolution of active ingredients
3. Transfer of the dissolved drug and soluble components into the bulk

The results for formulation F3, which used HPMC (K100M, K4M, and E50) in a ratio of 1:1:1, exhibited slow drug release of 79.98% within 10 hours. Formulation F1 (ratio 1:2:3) and F4 (ratio 2:1:3) demonstrated faster drug release of 99.82% and 99.34%, respectively, within 6 hours.

Formulations F2, F5, F6, and F7, using HPMC (K100M, K4M, and E50) in ratios 1:3:2, 2:3:1, 3:1:2, and 3:2:1, respectively, showed drug releases of 91.38%, 90.66%, 94.65%, and 95.10%, respectively. The formulations F2, F5, F6, and F7 exhibited satisfactory dissolution profiles. Consequently, these formulations are deemed suitable for future studies.

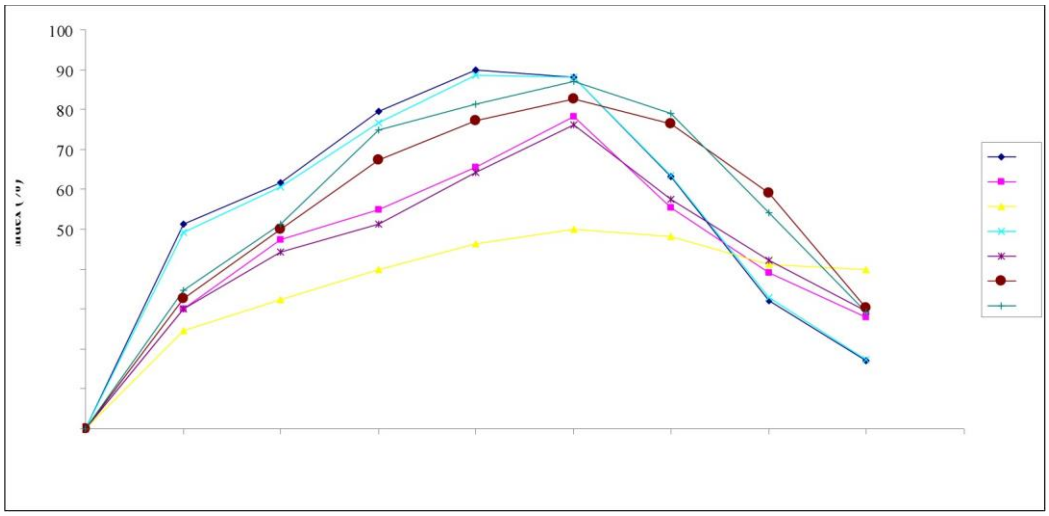


Fig. 5. Swelling index of ciprofloxacin floating tablets

Table 11. *In-vitro* Dissolution study of Ciprofloxacin Floating Tablets

Time (hrs)	Cumulative % Drug released						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
1	32.69	22.93	17.72	30.39	22.12	27.25	29.40
2	45.08	32.20	21.45	42.16	30.55	38.71	40.85
3	59.26	46.25	29.83	51.73	43.14	50.22	54.62
4	72.37	51.07	35.76	69.98	49.72	55.34	61.73
5	81.61	59.14	40.41	80.93	56.43	63.66	74.43
6	99.82	67.31	49.92	99.34	65.18	75.76	80.17
7		72.43	57.33		70.92	79.38	82.59
8		80.27	65.04		78.71	80.70	85.10
9		88.79	74.37		86.12	89.26	91.48
10		91.38	79.98		90.66	94.65	95.10

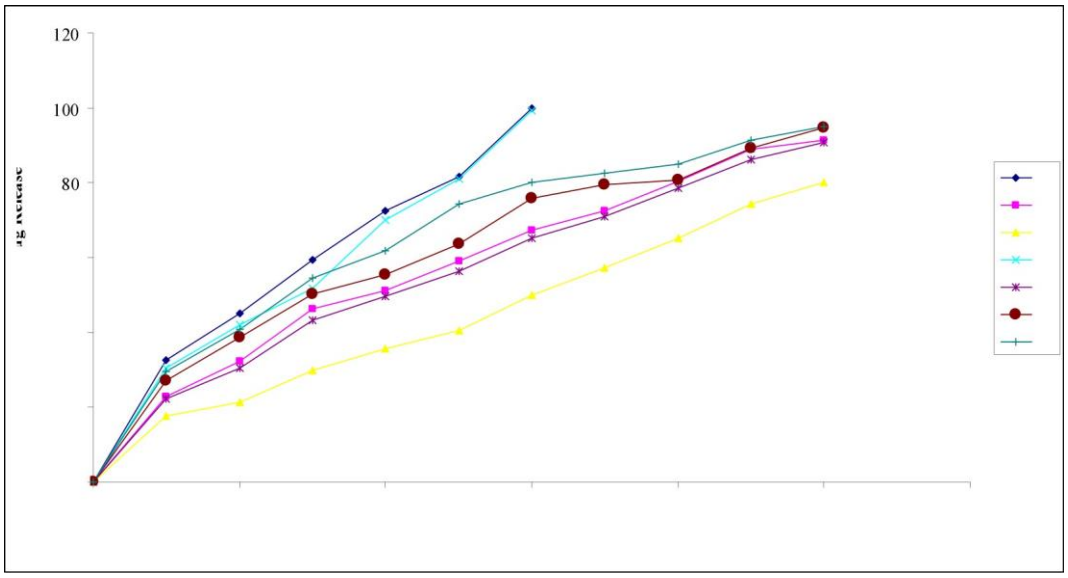
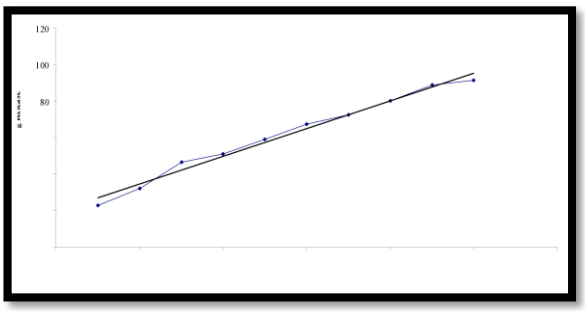
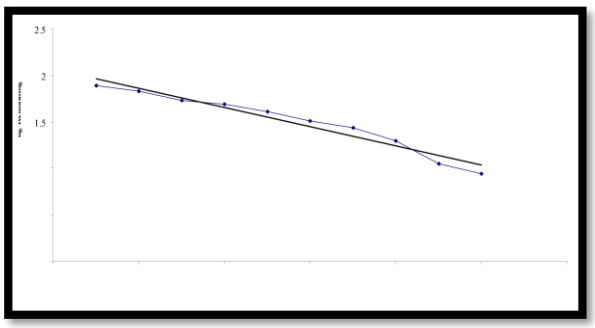


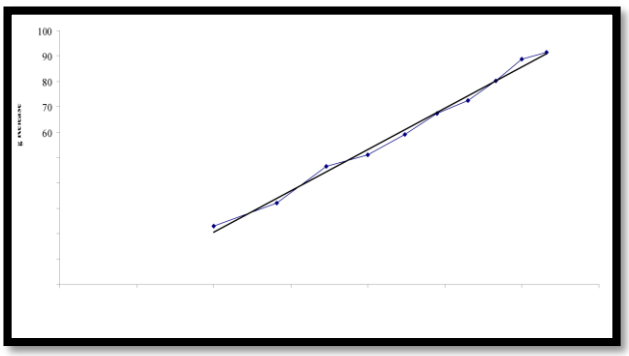
Fig. 6. *In – vitro* Dissolution study of formulated tablets

Zero order drug release kinetics

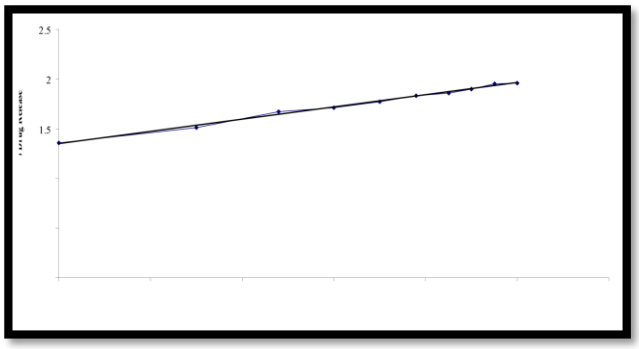


First order drug release kinetics





Higuchi drug release kinetics



Korsmeyer - Pepps drug release kinetics

Fig. 7. Kinetic studies of formulation F2

4.10 Kinetics of Drug Release

The dissolution data were subjected to fitting with various drug release kinetic equations. The korsmeyer–Peppas release equation yielded the highest regression coefficient (R^2) values for formulation F2. The obtained R^2 values for the drug release kinetics of formulations F2 is presented. The drug release kinetics for formulations F2 are depicted in the Figures

Formulation F2:

- Zero Order
- First Order
- Higuchi Matrix
- Korsmeyer–Peppas

The highest R^2 values for korsmeyer–peppas model were obtained for formulations F2, F5, F6, and F7. The 'n' values obtained ranging from 0.521 to 0.633 indicate non-Fickian diffusion [12].

4.11 Stability Studies

Stability studies of the formulated tablets were conducted under various conditions, including ambient humidity, room temperature, 40°C, and refrigeration, over a period of 60 days. Samples were withdrawn at intervals of 15 days, 30 days, 45 days, and 60 days for analysis of appearance, hardness, friability, floating test, drug content, and in-vitro release. The results are summarized.

Table 12. Kinetics of drug release of R^2 value for F_2

	Regression Coefficient (R^2)				
				Korsmeyer - Peppas	
Batch No.	Zero Order	First Order	Higuchi	R^2	n
F2	0.9860	0.9511	0.9930	0.9944	0.612

Table 13. Drug release kinetics of formulation F2

Time	Log Time	Square root of Time	Cumulative % Drug Released	Log Cumulative Drug Released	Cumulative % Drug Remained	Log Cumulative % Drug Remained
1	0	1	22.93	1.36	77.07	1.89
2	0.30	1.41	32.20	1.51	67.80	1.83
3	0.48	1.73	46.45	1.67	53.55	1.73
4	0.60	2	51.07	1.71	48.93	1.69
5	0.70	2.24	59.14	1.77	40.86	1.61
6	0.78	2.45	67.31	1.83	32.69	1.51
7	0.85	2.65	72.43	1.86	27.57	1.44
8	0.90	2.83	80.27	1.90	19.73	1.30
9	0.95	3	88.79	1.95	11.21	1.05
10	1	3.16	91.38	1.96	8.62	0.94

Table 14. Formulations F2, F5, F6 and F7 stored in Refrigerator (2-8ºC)

Formulation	Tested after time (days)	Hardness (kg/cm^2)	Friability (%)	Floating Test BLT (sec)	Floating Test TFT (hrs.)	Drug Content(%)	Cum. % Drug Released (in 10th hours)
F2	15	4.5	0.52	30	>10	98.62	91.28
	30	4.5	0.52	30	>10	98.47	90.81
	45	4.5	0.53	31	>10	98.16	90.69
	60	4.4	0.53	31	>10	97.94	90.41
F5	15	4.5	0.52	35	>10	98.07	90.52
	30	4.5	0.52	35	>10	97.91	90.37
	45	4.5	0.53	36	>10	97.73	89.99
	60	4.4	0.53	37	>10	97.62	89.63
F6	15	5.0	0.56	15	>10	98.76	94.47
	30	4.9	0.56	15	>10	98.49	94.18
	45	4.9	0.56	16	>10	98.25	94.02
	60	4.9	0.57	16	>10	98.18	93.86
F7	15	4.5	0.54	20	>10	99.02	95.06
	30	4.5	0.54	20	>10	98.93	94.97
	45	4.4	0.54	20	>10	98.74	94.75
	60	4.4	0.55	21	>10	98.51	94.53

Table 15. % swelling index of formulated floating tablets

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
1hr	19.54	25.15	18.22	20.1	19.99	19.26	13.05	16.12	11.15
2hr	32.22	42.1	33.15	28.98	32.14	30.9	18.55	28.76	17.01
3hr	44.1	56.16	46.1	42.1	45.88	41.1	27.85	43.1	21.85
4hr	61.12	70.11	63.01	52.9	58.22	53.1	39.75	51.1	31.96
6hr	69.02	76.12	71.11	63.89	71.03	60.8	46.1	59.65	43.11

The findings indicate that there were no significant changes in appearance, floating test, and drug content for formulations F2 during the storage period. While hardness, friability, and drug release showed little variation in formulations F2 stored at the three different conditions up to 30 days, a decrease in hardness, an increase in friability, and enhanced in-vitro drug release were observed after 30 days for samples stored at room temperature (34±2°C) and 40°C [13]. Conversely, no significant changes were noted in formulations stored in the refrigerator. This suggests that Ciprofloxacin floating tablets remain stable when stored at 2 to 8°C. In summary, the stability studies indicate that formulations F2 exhibit stability over a 30-day period under various conditions, with optimal stability observed when stored in a refrigerated environment [14,15].

5. SUMMARY

In this study, an effort was made to develop a gastro retentive drug delivery system for Ciprofloxacin, aiming to enhance its bioavailability by prolonging the drug absorption phase. The formulated floating tablets of Ciprofloxacin HCl employed sodium bicarbonate as a gas-generating agent and HPMC as a water-swellable polymer using the direct compression technique.

Key findings and observations include:

1. **Compatibility Studies:**
   - FT-IR spectral studies indicated compatibility between the drug and polymer used.
2. **Pre-Compression Parameters:**
   - Formulations showed good flow properties based on compressibility index, Hausner ratio, and angle of repose values.
3. **Post-Compression Parameters:**
   - Tablets exhibited desirable characteristics, including caplet shape, biconvex form, and uniformity in weight and thickness.
   - Hardness, friability, and drug content were within acceptable limits.
4. **Floating Test**
   - Tablets demonstrated excellent buoyancy characteristics, with all formulations floating within 1 minute.
   - Total floating time exceeded 6 hours for formulations F1 and F4 and surpassed 10 hours for formulations F2, F3, F5, F6, and F7.
5. **Swelling Study**
   - Swelling ratios increased up to 4-5 hours for all formulations and gradually decreased afterward.
6. **In-vitro Dissolution Study:**
   - Formulations F2, F5, F6, and F7 exhibited satisfactory drug release profiles, with cumulative release percentages ranging from 90.66% to 99.82% within 6 to 10 hours.
7. **Kinetics of Drug Release**
   - Korsmeyer–Peppas model showed the highest regression coefficient (R2) values, indicating non-Fickian diffusion.
8. **Stability Studies:**
   - Formulations F2, F5, F6, and F7 remained stable at room temperature, 40°C, and 2-8°C for up to 30 days.
   - Refrigerated storage (2-8°C) maintained stability over the entire 60-day period,

indicating this as the most suitable storage condition.

In conclusion, the developed Ciprofloxacin floating tablets demonstrated promising characteristics for extended drug release and stability, suggesting potential benefits for enhancing bioavailability and localized drug delivery in the upper gastrointestinal tract.

6. CONCLUSION

The formulation and development of hydrodynamically balanced tablets of Ciprofloxacin HCl, with a focus on increasing gastric residence time for improved drug bioavailability, were successfully achieved. Key conclusions from the study are as follows:

1. **Formulation Approach:**
   - Floating tablets of Ciprofloxacin HCl were formulated using sodium bicarbonate as a gas-generating agent and HPMC as a hydrophilic polymer through the direct compression technique.
2. **Physicochemical Compliance**
   - The formulated tablets demonstrated compliance with various physicochemical parameters, including tablet dimensions, total floating time, tablet density, and drug content.
3. **Dissolution Studies**
   - Formulations F2, F5, F6 exhibited good drug release profiles, while F7 formulation demonstrated excellent release characteristics.
4. **Kinetics of Drug Release**
   - Kinetic treatment of data revealed that formulations F2, F5, F6, and F7 followed the Korsmeyer–Peppas model, indicating non-Fickian diffusion with 'n' values ranging from 0.521 to 0.633.
5. **Stability Studies**
   - Stability studies indicated that the most suitable storage temperature for Ciprofloxacin floating tablets was 2-8°C for a period of 60 days.
   - Formulations F2, F5, F6, and F7 remained stable at room temperature, 40°C, and 2-8°C for up to 30 days, with refrigerated storage maintaining stability over the entire 60-day period.

In conclusion, the developed hydrodynamically balanced tablets of Ciprofloxacin HCl, with their favorable physicochemical characteristics, dissolution profiles, and stability, hold promise for enhancing drug bioavailability and could be a viable option for localized drug delivery in the upper gastrointestinal tract.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Garg S, Sharma S. Gastro Retentive Drug Delivery Systems; 2021. Available:http://www.bbriefings.com/pdf Accessed May 20, 2022
2. Chawla G, Gupta P, Koradia V, Bansal AK. Gastro retention: A means to address regional variability in intestinal drug absorption. Pharm Tach 2021;27(7):50- Available:http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id= 62499 Accessed February 12, 2004.
3. Tayade P. Gastro retentive drugs: A review 2020. Available:http://www.expresspharmapulse.com/20030417/ndds1.shtml. Accessed March 18, 2004.
4. Shivakumar HG, Gowda DV, Pramod Kumar TM. Floating controlled drug delivery systems for prolonged gastric residence. Indian J Pharm Educ. 2018;38(4):172-80.
5. Robinson JR, Li HK, Lee VHL. Influence of drug properties and routes of administration on design of sustained and controlled release systems. In: Robinson JR, Lee VHL, editors. Controlled drug delivery: Fundamentals and applications. 2nd ed. New York: Marcel Dekker Inc. (Drugs and the pharmaceutical sciences. 2016;29:5-12.

6. Welling PG, Dobrinska MR. Dosing considerations and bioavailability assessment of controlled drug delivery systems. In: Robinson JR, Lee VHL, editors. Controlled drug delivery: Fundamentals and applications. 2nd ed. New York: Marcel Dekker Inc; (Drugs and the pharmaceutical sciences. 1987;29:253-64
7. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastro retentive dosage forms. J Control Release. 2013;90:143-62.
8. Rocca JG, Omidian H, Shah K. Progress in gastro retentive drug delivery systems; 2003.
Available:http://www.bbriefings.com/pdf/17/ACF8D8E.pdf
Accessed May 20, 2004.
9. Garg R, Gupta GD. Progress in controlled gastro retentive delivery systems. Trop J Pharm Res, September. 2012;7(3):1059-60.
10. Gronia R, Heun G, Oral dosage forms with controlled gastrointestinal transit. Drug Dev Ind Pharm. 1984;10:527-39.
11. Atyabi F, Sharma HL, Mohammad HAH, Fell JT. In-vivo evaluation of a novel gastro retentive formulation based on ion exchange resins. J Control Release.1996;42:105-13.
12. Chien YW. Oral drug delivery and delivery systems. In: Swarbrick J, editor 1992.
13. Novel drug delivery systems. 2nd rev ed. New York: Marcel Dekker Inc; (Drugs and the pharmaceutical sciences. 1992;50:139-72
14. Singh BN, Kim HK. Floating drug delivery systems. An approach to oral controlled drug delivery via gastric retention. J Control Release. 2000;63:235-59.
15. Ashford M. The gastrointestinal tract physiology and drug absorption. In: Aulton ME, editor. Pharmaceutics: The science of dosage form design. 2nd ed. New York: Churchill Livingstone. 2012;217-27.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/114661