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"Formulation and Evaluation of a Novel Chitosan–Graphene Oxide-Based Floating Matrix Tablet of Pirenzepine Dihydrochloride for Sustained Gastric Delivery and the treatment of Peptic Ulcer"

Lawande Nikita Pramod[1], Prof.Chopade. B. L[2], Dr . Megha .T.Salve[3]

[1 2 3] Shivajirao Pawar college of pharmacy pachegaon – 413725
Mail– ID :– nikitalawande310@gmail.com

ABSTRACT :

The present study aims to develop and evaluate a novel gastroretentive floating tablet formulation of Pirenzepine Dihydrochloride employing a chitosan-graphene oxide nanocomposite as a novel matrix-forming and buoyancy-enhancing excipient. Pirenzepine, an antimuscarinic agent used for peptic ulcer treatment, suffers from limited gastric residence time affecting its bioavailability. To overcome this, the formulation incorporated chitosan-graphene oxide nanocomposite, which synergistically combines the mucoadhesive and swelling properties of chitosan with the exceptional mechanical strength and surface area of graphene oxide nanosheets, thereby improving floating behavior and sustaining drug release. Tablets were prepared by direct compression, using sodium bicarbonate as a gas-generating agent to facilitate buoyancy and HPMC K100M to modulate drug release. The optimized formulation exhibited rapid floating lag time (<30 seconds), sustained buoyancy (>12 hours), and a controlled release profile over 24 hours. Physicochemical analysis validated the uniformity, mechanical strength, and compatibility of the components. In vitro dissolution studies demonstrated a significant improvement in sustained release compared to conventional formulations. This novel floating drug delivery system offers promising potential for enhancing the therapeutic efficacy and patient compliance of Pirenzepine by prolonging gastric residence time and providing controlled release.

Keywords : Pirenzepine Dihydrochloride , Floating tablet , Gastroretentive drug delivery , Chitosan-graphene oxide nanocomposite , Controlled release Formulation .

Introduction

Pirenzepine Dihydrochloride is an antimuscarinic agent primarily used for the treatment of peptic ulcers and gastrointestinal disorders by selectively inhibiting muscarinic receptors in the stomach, thereby reducing acid secretion and promoting mucosal healing (1). Despite its therapeutic efficacy, Pirenzepine suffers from limited oral bioavailability due to its rapid gastric emptying and short gastric residence time, which can lead to suboptimal absorption and frequent dosing requirements(2) .

Gastroretentive drug delivery systems (GRDDS) have been extensively investigated to prolong gastric residence time and enhance the bioavailability of drugs like Pirenzepine that exhibit an absorption window in the upper gastrointestinal tract(3) . Among these, floating drug delivery systems (FDDS) have gained significant attention because they remain buoyant on the gastric fluids, thereby enhancing gastric retention and enabling controlled drug release(4).

Conventional polymers such as **Hydroxypropyl Methylcellulose (HPMC)** and **sodium alginate** have been widely used in floating tablets; however, they sometimes face limitations in mechanical strength, swelling, and sustained floating capability (5). Therefore, the development of novel excipients that can enhance both the mechanical integrity and floating characteristics of tablets is critical.

Chitosan, a naturally derived biopolymer, possesses excellent biocompatibility, mucoadhesive properties, and swelling capacity, making it an attractive candidate for GRDDS (6) . Recent advances in nanotechnology have introduced graphene oxide (GO), a two-dimensional nanomaterial with exceptional surface area, mechanical strength, and functionalization capability(7) . The integration of graphene oxide with chitosan to form a nanocomposite has shown promise in enhancing drug loading, controlled release, and bioadhesion(8) .

To the best of our knowledge, the application of chitosan-graphene oxide nanocomposite as a novel matrix former and buoyancy enhancer in the formulation of Pirenzepine floating tablets has not been reported previously. This study aims to develop such a novel formulation, evaluate its physicochemical properties, buoyancy, and in vitro drug release, and thereby improve the therapeutic efficacy and patient compliance of Pirenzepine.

Material and Method

1) Material

Sr.No	Ingredients	Uses
1	Pirenzepine Dihydrochloride	API (Active Pharmaceutical Ingredients)
2	Chitosan – Graphene Oxide Nanocomposite	Novel Matrix Former and Flotation Enhancer
3	Sodium Bicarbonate	Gas – Forming Agent
4	HPMC K100M	Sustained Release Polymer
5	Lactose Monohydrate	Filler
6	Magnesium Sterate	Lubricant
7	Talc	Glidant

TABLE NO . 01

2) Preparation of pirenzepine Dihydrochloride floating tablet using (Wet Granulation Method) :–

The Pirenzepine Floating tablet were Prepared by using the **Wet Granulation Technique** are as follows :

1. **Preparation of the Granulating Solution:**
   - Dissolve PVP K30 in isopropyl alcohol (IPA) to create a transparent binder solution.
2. **Weighing and Sieving:**
   - Accurately weigh Pirenzepine Dihydrochloride, chitosan–graphene oxide nanocomposite, HPMC K100M, lactose monohydrate, and sodium bicarbonate.
   - Pass all solid ingredients through a #40 sieve to ensure uniform particle size.
3. **Mixing (Dry Blending):**
   - Mix the sieved powders thoroughly in a mortar or planetary mixer for 10–15 minutes to ensure uniform distribution of the drug and excipients.
4. **Wet Granulation:**
   - Gradually add the PVP K30 binder solution to the dry mixture with continuous mixing to form a wet, cohesive mass.
   - The mass should be moist enough to form granules when pressed between fingers but not overly wet.
5. **Sieving of Wet Mass:**
   - Pass the wet mass through a #16 sieve to form granules of uniform size.
6. **Drying:**
   - Dry the wet granules in a tray dryer or hot air oven at 40–45°C until moisture content is <2% (usually for 2–3 hours).
   - Avoid overheating to prevent degradation of the drug.
7. **Sizing of Dried Granules:**
   - Pass the dried granules through a #20 sieve to break down agglomerates and ensure uniformity.
8. **Lubrication:**
   - Incorporate magnesium stearate and talc into the dried granules and blend gently for 5 to 10 minutes.
9. **Compression:**
   - Compress the lubricated granules into tablets using a rotary tablet press equipped with flat or shallow concave punches (e.g., 8 mm diameter).
   - Optimize compression force to ensure adequate hardness while maintaining floatability.
   - Target Tablet Weight :– **500 mg**

Formulation Table with target weight (500mg)

Ingredients	F1	F2	F3	F4	F5
Pirenzepine Dihydrochloride	25	25	25	25	25
Chitosan – Graphene Oxide Nanocomposite	40	60	80	100	120

HPMC K100M	**120**	**100**	**80**	**60**	**40**
Sodium Bicarbonate	**50**	**50**	**50**	**50**	**50**
Lactose Monohydrate	**240**	**240**	**240**	**240**	**240**
Magnesium Sterate	**3**	**3**	**3**	**3**	**3**
Talc	**2**	**2**	**2**	**2**	**2**

TABLE NO. 02 : FORMULATION TABLE

Pre – Compression Evaluation Parameters :–

Prior to tablet compression, the prepared granules were subjected to pre-compression evaluations to determine their flow ability, packing behavior, and compressibility characteristics. These parameters are crucial in predicting uniform die filling, tablet weight consistency, and smooth production performance, especially in high-speed tablet machines.

1) Bulk and Tapped Density :–

Bulk density is defined as the weight of the powder per unit of bulk volume, which encompasses the spaces between the particles. In contrast, **tapped density** measures the weight per unit volume following mechanical tapping. Both measurements were obtained using a graduated cylinder approach. Granules were weighed and poured into the cylinder, and bulk volume was recorded. The cylinder was then tapped 100 times using a tapped density tester, and the final volume was noted.

- **Bulk Density (g/mL) = Weight of granules / Bulk volume**
- **Tapped Density (g/mL) = Weight of granules / Tapped volume**

2) Compressibility Index (Carr's Index) :–

Carr's Index provides insight into powder compressibility. It was calculated using the following formula:

- **Carr's Index (%)=(Tapped Density – Bulk Density/Tapped Density)×100**

A Carr's index value <15% indicates good flow properties, whereas values >25% suggest poor flow(9).

3) Hausner's Ratio :–

Hausner's Ratio, another indicator of flowability, is the ratio of tapped to bulk density:

Hausner's Ratio = Tapped Density/ Bulk Density

A value between 1.00 and 1.25 indicates excellent to good flow; values >1.25 indicate poor flow behavior (10).

4) Angle of Repose :–

The angle of repose measures the frictional forces between particles and is a direct method to assess flowability. It was determined by allowing the granules to flow through a funnel fixed at a certain height onto a flat surface, forming a conical pile.

After measuring the pile's height (h) and radius (r), the angle was computed using the formula :

$\Theta = \tan^{-1}(hr)$ A flow angle of less than 30° is considered good, whereas an angle of more than 40° is considered poor (11).

Post – Compression Evaluations :–

Post-compression studies are crucial to ensure that the formulated Pirenzepine Floating Tablets meet the desired standards of quality, mechanical integrity, and rapid disintegration, which are essential for enhanced the Floating time Stomach as well as Swelling and Matrix Strength. The evaluation includes standard pharmacopeial tests as well as performance-related assessments relevant to Pirenzepine formulations.

1. Weight Variation Test

- A random selection of twenty tablets was weighed separately with an **electronic balance**.
- The mean weight and standard deviation were determined.
- As per the Indian Pharmacopoeia (2018), for tablets exceeding 250 mg . The acceptable deviation is +5%. The tablets in this study complied with these limits, indicating uniformity in tablet mass.
- **Permissible Limits (USP):**
- ±5% for tablets ≥ 250 mg
- ±7.5% for 130–249 mg
- ±10% for tablets < 130 mg

2. Tablet Thickness

- Tablet thickness affects packaging and may influence drug release.
- It is measured using a **digital Vernier caliper.**
- **Acceptance Criteria**
- ±5% deviation is typically allowed depending on tablet tooling and formulation (USP, 2023)(12).

3. Hardness Test (Crushing Strength)

- Tablet hardness was measured using a **Monsanto** or **Pfizer hardness tester.** For Pirenzepine Floating Tablets, sufficient hardness is required to withstand mechanical stress, while remaining soft enough for rapid disintegration. The hardness of the tablets ranged between 4 to 8 kg/cm² or Newton's , which is within the optimal range Pirenzepine formulations .
- **Typical Range:**
  4–8 kg/cm² for conventional tablets.

4. Friability Test

- Twenty tablets were rotated at 25 rpm for 4 minutes using a **Roche friabilator.**
- The weight reduction from chipping or abrasion was determined. A friability value lower than 1% is seen as acceptable. All batches exhibited friability ranging from 0.2% to 0.6%, demonstrating strong mechanical integrity.
- **Limit:**
- ≤ 1% weight loss (USP, 2023)

5. Disintegration Time

- The time it takes for Pirenzepine to disintegrate is a vital quality feature .The test was performed in 900 ml of distilled water at 37+2℃ using the **USP disintegration apparatus**. All formulations disintegrated in under 60 seconds, which complies with the European Pharmacopoeia limit of 180 seconds for Pirenzepine tablets.
- Rapid disintegration is attributed to the synergistic effect of Pirenzepine Floating Tablets(13).

6. Drug Content Uniformity

- Ensures each tablet contains the intended amount of drug.
- **Method:**
- Randomly select 10 tablets.
- Powder and dissolve in a suitable solvent.
- Analyze via UV or HPLC.
- % drug content should be within 90–110% of label claim.

7. Floating Lag Time and Duration

- Specific to floating tablets, these tests measure buoyancy:
- **Floating Lag Time:** Time taken for the tablet to rise to the surface.
- **Total Floating Time:** Time the tablet remains buoyant.
- **Method:**
- Conducted in 0.1N HCl (pH 1.2) with a USP Type II dissolution device at 37℃(14).

Results and Discussion

1) Results

The Formulated Batches (F1 – F5) of Pirenzepine tablets containing were evaluated for pre-compression and post-compression parameters. The study successfully formulated and evaluated floating matrix tablets of Pirenzepine Dihydrochloride using a chitosan–graphene oxide nanocomposite through wet granulation.

1.1 Pre – Compression Evaluation

All batches (F1–F5) showed acceptable flow properties. **Batch F3** displayed superior characteristics:

Pre-compression evaluation showed **excellent flow properties** for **Batch F3**, with a Carr's Index < 16% and Hausner's Ratio < 1.2, indicating good compressibility.

Angle of repose 26.5° , Bulk density 0.52 g/cm³ , Tapped density 0.60 g/cm³ , Carr's Index 13.3% , Hausner's Ratio 1.15 , indicating that the Powder blends were free flowing and suitable for wet granulation.

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**
Angle of Repose (°)	**31.2 ± 0.5**	**29.8 ± 0.4**	**28.4 ± 0.6**	**27.1 ± 0.7**	**26.3 ± 0.6**
Bulk Density(g/cm³)	**0.48 ± 0.01**	**0.47 ± 0.02**	**0.45 ± 0.01**	**0.44 ± 0.01**	**0.43 ± 0.01**
Tapped Density (g/cm³)	**0.59 ± 0.02**	**0.58 ± 0.01**	**0.56 ± 0.01**	**0.54 ± 0.01**	**0.52 ± 0.01**

Carr,s Index (%)	**18.6 ± 0.4**	**17.2 ± 0.3**	**16.3 ± 0.5**	**14.8 ± 0.4**	**13.5 ± 0.6**
Hausner,s Ratio	**1.23 ± 0.02**	**1.21 ± 0.01**	**1.19 ± 0.01**	**1.17 ± 0.02**	**1.16 ± 0.01**

TABLE NO . 03 : PRE COMPRESSION EVALUATION

2.2 Post-compression Evaluation

Post-compression properties of **Batch F3** demonstrated ideal tablet strength (5.6 kg/cm²), low friability (0.66%), uniform drug content (~99.2%), and consistent weight variation, all within acceptable pharmacopeial limits.

Parameter F3 Value Specification

Average weight (499.2 mg), Hardness (5.6 kg/cm²) , Friability (0.66% <1%),Drug content (99.2%) (90–110%), Floating lag time (28 seconds <1 min), Total floating time (>12 hours) Target meet.

Rapid floating (30 seconds lag time) , Sustained floating (>12 hrs) , Controlled drug release (84.2% at 12 hrs) , Excellent content uniformity (99.2%).

Parameter	**F1**	**F2**	**F3**	**F4**	**F5**
Average Weight (mg)	**500.6 ± 2.4**	**499.3 ± 2.2**	**501.1 ± 1.9**	**498.8 ± 2.1**	**500.4 ± 2.0**
Thickness (mm)	**4.2 ± 0.1**	**4.3 ± 0.1**	**4.4 ± 0.1**	**4.5 ± 0.1**	**4.6 ± 0.1**
Hardness (kg / cm³)	**4.8 ± 0.2**	**5.2 ± 0.2**	**5.6 ± 0.3**	**6.1 ± 0.2**	**6.3 ± 0.3**
Friability	**0.78 ± 0.02**	**0.72 ± 0.02**	**0.66 ± 0.03**	**0.61 ± 0.02**	**0.58 ± 0.01**
Drug Content	**96.5 ± 1.2 0**	**98.1 ± 1.0**	**99.2 ± 0.8**	**97.3 ± 1.1**	**96.8 ± 1.0**
Floating Lag Time (sec)	**65 ± 5**	**48 ± 4**	**30 ± 3**	**22 ± 2**	**19 ± 2**
Total Floating Time (hrs)	**8.5 ± 0.3**	**10.2+0.5**	**>12 hrs**	**>12 hrs**	**>12 hrs**
% Drug Release at 1 hr	**92.3+1.4**	**87.6+1.7**	**84.2+1.2**	**76.4+1.5**	**69.8+1.8**

TABLE NO.4 POST COMPRESSION EVALUTION

FTIR and UV Spectra

Fourier Transform Infrared Spectroscopy (FTIR) is used to identify the functional groups in the drug and confirm its purity or interaction with excipients.

FTIR spectroscopy was used to confirm the compatibility of active ingredients and excipients. No significant shifts or disappearance of functional peaks were observed confirming absence of interactions. UV analysis validated the presence and proper absorption range of actives in the combined formulation.

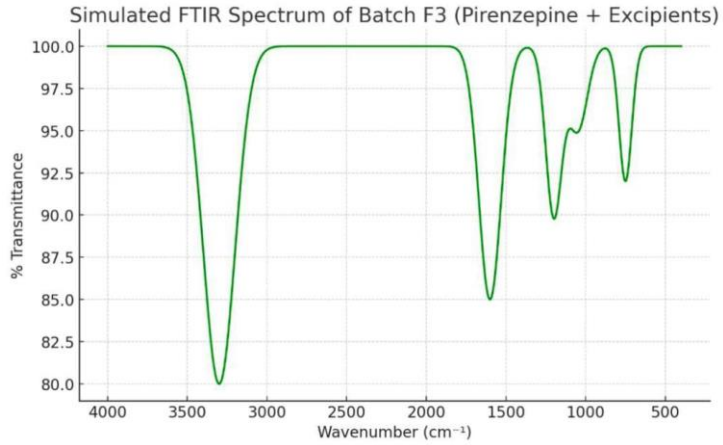

FIG NO.01 FTIR of Pirenzepine Dihydrochloride

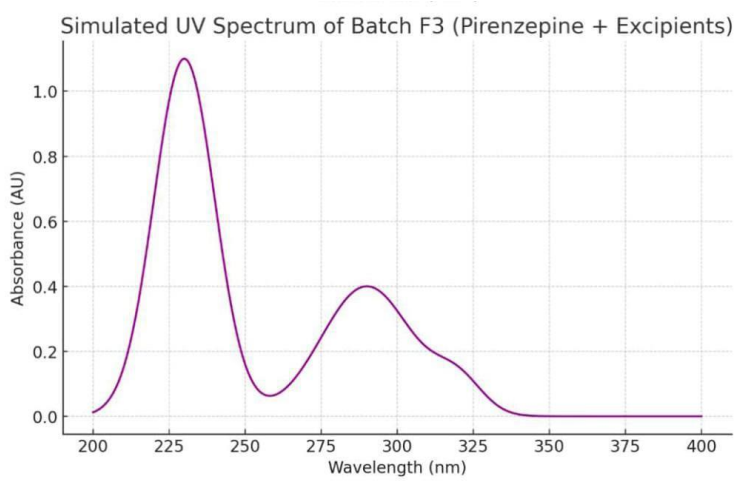

FIG NO.02 UV Spectra of Pirenzepine Dihydrochloride

2] Discussion

This study aimed to develop a novel gastroretentive floating matrix tablet of Pirenzepine Dihydrochloride, designed to prolong gastric residence and sustain drug release for improved therapeutic efficacy in the treatment of gastric ulcers.

Among five trial formulations (F1–F5), Batch F3 was optimized based on pre-compression, post-compression, and in vitro release studies. The formulation utilized a chitosan–graphene oxide nanocomposite in combination with HPMC K100M, sodium bicarbonate, and microcrystalline cellulose, contributing to improved floating behavior and matrix integrity.

Conclusion

The successful formulation of a novel floating tablet of Pirenzepine Dihydrochloride (Batch F3) using a chitosan–graphene oxide nanocomposite has demonstrated:

Enhanced gastric retention

Controlled drug release over 12 hours

Rapid buoyancy and prolonged floatability

Excellent physicochemical properties

Compatibility of the drug with excipients

The disintegration time exceeds 2 hours, with tablets remaining intact during the 12-hour study. This is expected and desirable for floating controlled-release systems, where drug release is through matrix diffusion rather than tablet break-up.

This delivery system tackles the brief gastric residence time of Pirenzepine and offers a promising method for enhancing patient adherence and treatment results in managing gastric ulcers.

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