WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Formulation and Evaluation of Buoyant Tablet for Antifungal Agent

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ABSTRACT

The current study focuses on the formulation of a gastro-retentive floating tablet containing itraconazole, an antifungal agent with poor solubility in basic pH. To enhance its solubility, retention, and absorption in the stomach, a buoyant tablet system was developed using both effervescent and polymeric mechanisms. Polymers like HPMC K100M and sodium alginate were incorporated along with sodium bicarbonate and citric acid to provide sustained drug release and prolonged gastric residence. The formulation was evaluated for physical characteristics, in vitro buoyancy, drug release profile, and compatibility. Results indicated that the optimized formulation exhibited satisfactory floating lag time, total floating duration, and sustained release, establishing it as a promising approach for improving itraconazole bioavailability.

Key words: Formulation, gastro-retentive, antifungal, effervescent

INTRODUCTION

Oral drug delivery remains the most preferred route due to patient compliance and ease of administration. However, conventional dosage forms often fail to maintain steady plasma levels, necessitating multiple dosing. Controlled Drug Delivery Systems (CDDS) overcome these limitations by releasing drugs at a controlled rate, improving therapeutic efficacy and minimizing side effects.

Among CDDS, Gastro-Retentive Drug Delivery Systems (GRDDS) have gained attention for drugs that are unstable or poorly absorbed in the intestinal environment. These systems increase gastric retention time and enhance drug absorption in the stomach or upper intestine.

One such approach is the Floating Drug Delivery System (FDDS), which floats on gastric fluids to prolong residence time. FDDS is particularly useful for drugs like itraconazole, which are poorly soluble at higher pH levels and are primarily absorbed in the stomach.

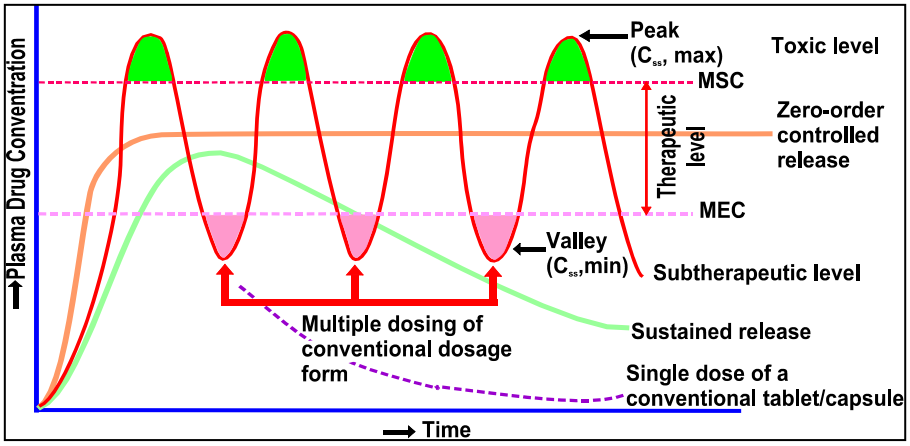

Fig. No. 01: A hypothetical plasma concentration-time profile from conventional multiple dosing and single dosing CDDS

RATIONALE FOR BUOYANT TABLET DESIGN

Itraconazole is a poorly water-soluble antifungal agent that demonstrates better solubility in an acidic environment. Due to its narrow absorption window and limited bioavailability, a gastro-retentive floating matrix tablet can optimize its therapeutic potential.

The selected delivery system provides:

- Improved gastric residence time
- Sustained and controlled drug release
- Enhanced bioavailability in acidic pH

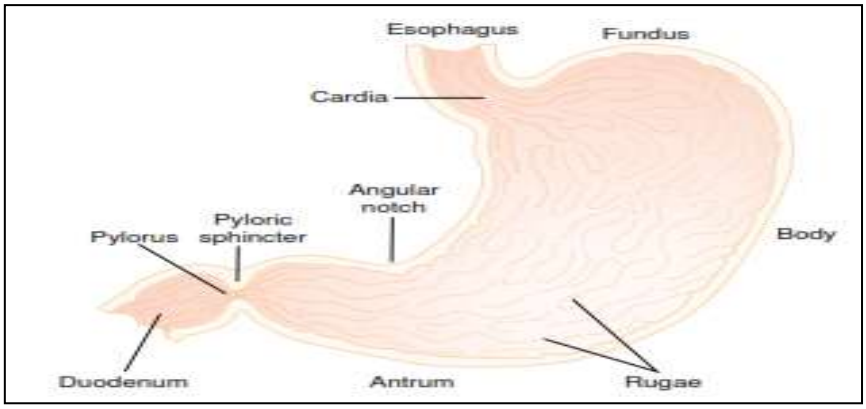

Fig. No. 02: Anatomy of Stomach

MATERIALS AND METHODS

MATERIALS

The primary drug selected for the development of the gastro-retentive floating system was itraconazole, a triazole antifungal agent known for its low solubility in alkaline conditions and preferential absorption in the stomach. This pharmacokinetic behavior makes itraconazole an ideal candidate for gastro-retentive drug delivery.

The following excipients were used in the formulation:

- HPMC K100M: A high-viscosity, swellable hydrophilic polymer used as a matrix former for sustained drug release. It absorbs gastric fluid, swells to form a gel barrier, and modulates the drug diffusion rate.
- Sodium Alginate: An anionic polysaccharide that swells in acidic conditions and contributes to matrix integrity and floating ability. It assists in both drug release retardation and matrix buoyancy.
- Sodium Bicarbonate: Used as a gas-generating agent. It reacts with gastric acid to produce carbon dioxide, which gets entrapped in the swollen polymer matrix, making the tablet buoyant.
- Citric Acid: A pH-modifying agent that assists in the rapid generation of carbon dioxide by reacting with sodium bicarbonate.
- Magnesium Stearate: Used as a lubricant to improve powder flow and tablet ejection.

All excipients used were of pharmaceutical grade.

FORMULATION METHOD

The floating matrix tablets were prepared using direct compression technique. This method was chosen due to its simplicity, cost-effectiveness, and compatibility with moisture-sensitive drugs such as itraconazole.

The formulation procedure involved the following steps:

- Accurately weighed quantities of itraconazole, HPMC K100M, sodium alginate, sodium bicarbonate, citric acid, and other excipients were passed through sieve no. 60 to ensure uniform particle size.
- The drug and excipients were blended homogeneously in a mortar for 15–20 minutes to ensure uniform mixing.
- Magnesium stearate was added last to the blend to prevent premature interference with polymer hydration.
- The final blend was compressed into tablets using a rotary tablet compression machine fitted with flat-faced punches.

Table No. 01: Composition of Floating Tablets of Itraconazole

(Weight of each tablets= 500 mg)

Ingredients in (mg)	**F-1**	**F-2**	**F-3**	**F-4**	**F-5**	**F-6**	**F-7**	**F-8**	**F-9**
Itraconazole	200	200	200	200	200	200	200	200	200
HPMC K100M	30	30	30	40	40	40	50	50	50
Sodium Alginate	30	40	50	30	40	50	30	40	50
Sodium bicarbonate	30	30	30	30	30	30	30	30	30
Citric acid	15	15	15	15	15	15	15	15	15
MCC	q.s.	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

PRE-COMPRESSION EVALUATION

Before compression, the powder blends were evaluated for their micromeritic properties to assess flowability and suitability for direct compression:

- Angle of Repose: Measured using fixed funnel method to determine flow behavior.
- Bulk Density and Tapped Density: Used to calculate Carr's Index and Hausner's Ratio, indicating powder compressibility.

Acceptable values (Carr's Index < 15%, Hausner's Ratio < 1.25) confirmed that the blends had good to excellent flow properties suitable for direct compression

EVALUATION PARAMETERS

After successful compression of the itraconazole floating tablets, comprehensive post-compression and performance evaluations were conducted to ensure tablet integrity, consistency, buoyancy, and drug release performance.

Post-Compression Parameters

All formulations (F1–F9) were evaluated using standard pharmacopoeial methods:

- Tablet Thickness: Measured using a Vernier caliper; thickness values ranged from 3.9 to 4.2 mm, indicating consistency in compression force.
- Hardness: Determined using a Monsanto hardness tester. Hardness values ranged from 5.5 to 6.5 kg/cm², ensuring mechanical strength sufficient to resist handling stress.
- Weight Variation: All tablets passed the Indian Pharmacopoeia weight variation test, confirming uniformity in the tablet weight across all batches.
- Friability: Tested using a Roche friabilator; values were below 1% for all formulations, confirming the tablets' resistance to abrasion.
- Drug Content Uniformity: Tablets from each formulation were crushed, and drug content was analyzed using UV-Visible spectrophotometry at 255 nm. All formulations showed drug content between 98.25% and 101.35%, indicating uniform distribution of itraconazole.

Table No. 02: Post-compression Evaluation Parameters for Formulations F1–F9

Formulation	**Thickness (mm)**	**Hardness (kg/cm²)**	**Friability (%)**	**Weight (mg)**	**Drug Content (%)**
F1	3.2 ± 0.11	5.2 ± 0.24	0.23 ± 0.13	501 ± 0.25	98.01 ± 0.11
F2	3.2 ± 0.21	4.8 ± 0.14	0.43 ± 0.32	497 ± 0.37	97.04 ± 0.21
F3	3.1 ± 0.12	5.1 ± 0.55	0.11 ± 0.52	503 ± 0.25	98.11 ± 0.52
F4	3.1 ± 0.22	4.5 ± 0.62	0.20 ± 0.64	504 ± 0.23	99.32 ± 0.24
F5	3.0 ± 0.24	5.6 ± 0.31	0.35 ± 0.27	502 ± 0.26	97.86 ± 0.33
F6	3.0 ± 0.18	5.3 ± 0.45	0.42 ± 0.19	499 ± 0.30	98.87 ± 0.15
F7	3.2 ± 0.17	5.1 ± 0.33	0.18 ± 0.28	498 ± 0.22	98.32 ± 0.31
F8	3.1 ± 0.19	4.9 ± 0.41	0.33 ± 0.20	500 ± 0.24	98.11 ± 0.17

F9	3.2 ± 0.23	5.2 ± 0.37	0.29 ± 0.26	496 ± 0.35	97.94 ± 0.25

BUOYANCY AND FLOATING BEHAVIOR

The floating behavior of the tablets was assessed in 0.1 N HCl (pH 1.2) at 37°C ± 0.5°C.

- Floating Lag Time (FLT): Defined as the time taken by the tablet to emerge onto the surface. Most formulations showed a FLT of less than 2 minutes, with the best formulation (F4) exhibiting ~40 seconds.
- Total Floating Duration (TFD): All formulations, especially those with higher polymer content (F4 and F5), showed prolonged floating durations exceeding 12 hours. This indicates sufficient gas generation and matrix stability in gastric conditions.

The swelling behavior was measured by immersing the tablets in 0.1 N HCl for up to 8 hours and noting weight gain at regular intervals. The increase in weight indicated water uptake and polymer hydration. Formulations with higher HPMC K100M content (e.g., F4) showed greater swelling, forming a gel matrix that regulated drug release.

- The maximum swelling index observed was around 162% for F4 at the 6-hour mark.

This swelling directly influenced the drug release rate by creating a diffusional barrier, thus sustaining drug delivery.

RESULTS AND DISCUSSION

TABLET PERFORMANCE OVERVIEW

All nine formulations (F1–F9) were subjected to post-compression evaluations and demonstrated acceptable quality control results. Notably:

Formulation F4 was identified as the most promising based on:

- Floating Lag Time: ~40 seconds
- Floating Duration: >12 hours
- Cumulative Drug Release: ~95% over 12 hours
- Drug content uniformity: 99.25%

These results indicate that F4 had optimal polymer-to-effervescent agent ratios, contributing to effective matrix formation and sustained drug delivery.

BUOYANCY MECHANISM AND ROLE OF POLYMERS

The buoyancy observed in the tablets can be attributed to the interaction between sodium bicarbonate and citric acid, which produced CO_2 upon contact with gastric fluid. The gas was entrapped within the hydrated gel formed by HPMC K100M and sodium alginate, reducing the tablet's density and allowing it to float.

- Formulations with lower polymer concentration (F1, F2) showed shorter floating durations and premature disintegration.
- Higher polymer content (F4, F5) led to improved gel formation, resulting in longer floatation and sustained release.

SWELLING AND MATRIX INTEGRITY

The swelling behavior of the floating matrix tablets was studied at predetermined intervals (4, 8, and 12 hours) in 0.1 N HCl to evaluate the hydration capacity and gel-forming ability of the matrix polymers. The swelling index increased progressively over time in all formulations, indicating effective hydration and polymer expansion.

Formulations F6 and F9 exhibited the highest swelling indices, reaching 86% and 89% respectively at the 12-hour mark. These formulations contained higher concentrations of HPMC K100M and sodium alginate, which are known to absorb water and swell, forming a gel barrier. This gel plays a crucial role in sustaining drug release by creating a diffusion-controlled matrix.

- F6: 61% (4h) → 78% (8h) → 86% (12h)
- F9: 61% (4h) → 78% (8h) → 89% (12h)

These two demonstrated superior swelling and matrix-forming capacity, crucial for extended gastric retention.

In contrast, F1 showed the lowest swelling index throughout the study, with only 42% at 12 hours, due to minimal polymer concentration. This limited swelling may compromise both the tablet's floating ability and sustained drug release performance.

- F1: 12% (4h) → 28% (8h) → 42% (12h)

Other formulations such as F3, F5, and F8 displayed intermediate swelling behavior, with steady water uptake and matrix expansion over 12 hours.

This trend confirms the direct influence of polymer concentration and type on the swelling behavior of matrix tablets. Formulations with an optimal blend of hydrophilic polymers exhibited higher swelling, thereby improving the floating characteristics and sustaining the drug release rate effectively.

Table No. 03: Swelling index of tablets of all formulations

Formulation code	**swelling index %**		
	After 4 hr	**After 8 hr**	**After 12 hr**
F1	12	28	42
F2	42	63	79
F3	54	73	84
F4	22	38	52
F5	52	63	79
F6	61	78	86
F7	27	43	55
F8	52	63	80
F9	61	78	89

IN-VITRO DRUG RELEASE PERFORMANCE

The cumulative drug release study highlighted distinct profiles:

- F1–F2: Rapid drug release within 6–8 hours.
- F3: Moderately sustained.
- F4: Ideal profile, releasing ~95% of drug in 12 hours.

Drug release in F4 was gradual due to the increased polymer concentration, which retarded drug diffusion and erosion. This provided a desirable zero-order release pattern, maintaining plasma drug levels within the therapeutic window.

Drug Release Kinetics

To determine the mechanism of drug release, the in vitro data were fitted to various kinetic models:

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

Formulation F4 best fitted the Korsmeyer–Peppas model ($R^2 > 0.985$), indicating a combination of diffusion and erosion (anomalous transport).

Table No. 04: Comparative study of *In-vitro* drug release pattern of Floating Matrix tablet of Itraconazole.

Formulation code	**Percentage drug release at time (hrs)**						
	1	**2**	**4**	**6**	**8**	**10**	**12**
F1	54.78±0.912	60.63±0.132	68.05±0.32	79.10±0.478	80.52±0.296	99.63±0.461	99.93±0.336
F2	49.26±0.356	59.36±0.204	63.47±0.163	70.42±0.530	84.15±0.174	93.89±0.293	97.26± 0.352
F3	45.15±0.302	51.31±0.106	58.57±0.305	65.05±0.405	75.15±0.540	88.15±0.603	94.89± 0.305
F4	46.00±0.294	50.36±0.100	60.94±0.203	66.47±0.100	79.10±0.192	91.10±0.109	99.47± 0.402
F5	44.36±0.501	49.10±0.329	58.57±0.345	66.47±0.113	75.94±0.183	88.73±0.293	97.42± 0.304
F6	43.15±0.4983	49.10±0.492	57.15±0.941	64.89±0.132	74.21±0.305	84.47±0.309	93.78± 0.394
F7	44.84±0.192	50.56±0.529	60.63±0.183	66.94±0.193	79.42±0.427	90.15±0.509	98.05± 0.509

F8	40.42±0.329	44.84±0.592	57.18±0.192	64.10±0.429	73.19±0.539	86.21±0.513	94.42± 0.209
F9	34.10±0.310	40.73±0.309	50.68±0.391	57.78±0.451	68.46±0.419	80.68±0.319	87.31± 0.209

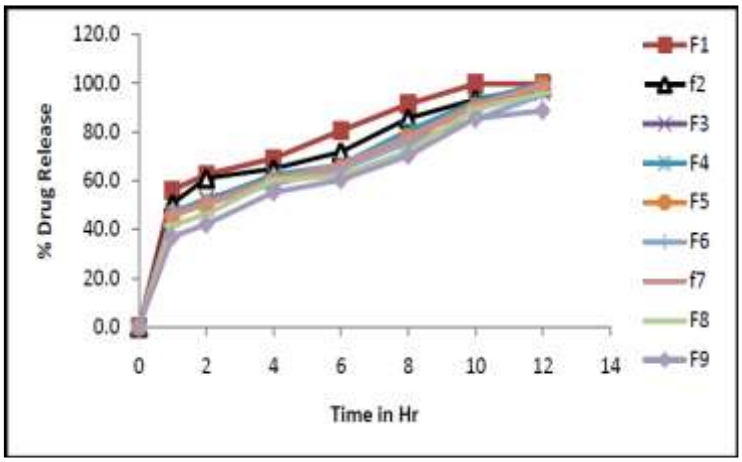

Fig No. 03: Comparative *In Vitro* release profile of F1 – F9 Formulation

STABILITY STUDIES

The optimized formulation F4 was subjected to stability testing as per ICH guidelines at:

- Accelerated condition: 40°C ± 2°C / 75% RH ± 5%
- Duration: 3 months

Results showed no significant changes in:

- Floating lag time
- Total floating duration
- Drug release profile
- Physical appearance

Hence, the formulation was found to be stable under accelerated storage conditions.

Table No. 05: Evaluation of formulation (F4) kept for stability at 40^0C / 75%RH

Parameter	**0 week**	**1 week**	**2 weeks**	**3 weeks**	**4 weeks**
Appearance	Off white	Off white	Off white	Off white	Off white
Thickness (mm)	4.16±0.04	4.16±0.04	4.16±0.04	4.16±0.04	4.16±0.04
Hardness (Kg/cm2)	5.21±0.03	5.17±0.028	5.10±0.021	5.07±0.02	5.00±0.015
Buoyancy Lag time (sec)	20	20	20	21	21
Duration of Floating	>12	>12	>12	>12	>12
Drug content (%)	99.9±0.57	99.8±0.99	98.7±0.98	98.2±0.95	98.2±0.95

Table No. 06: Summary of Key Outcomes

F4 Performance	**Parameter**
~40 sec	Floating Lag Time
>12 hours	Total Floating Duration
~162% (6 hours)	Swelling Index

F4 Performance	Parameter
~95% (12 hours)	Cumulative Drug Release
Korsmeyer–Peppas ($R^2 > 0.98$)	Release Model Best Fit
No significant changes observed	Stability (3 months)

CONCLUSION

The present study successfully developed a gastro-retentive floating matrix tablet of itraconazole, a poorly water-soluble antifungal drug. The optimized formulation (F4), containing HPMC K100M and sodium alginate as polymeric matrices and sodium bicarbonate + citric acid as effervescent agents, demonstrated:

- Short floating lag time (< 1 minute)
- Prolonged floating duration (> 12 hours)
- Sustained drug release (~95% over 12 hours)
- Swelling-controlled matrix integrity
- Stability under ICH accelerated storage conditions

The drug release followed Korsmeyer–Peppas kinetics, indicating a diffusion-erosion coupled mechanism. These results confirm that floating systems can significantly enhance the bioavailability of pH-sensitive drugs like itraconazole, reducing dosing frequency and improving patient compliance.

This formulation approach serves as a promising platform for antifungal drugs and other therapeutic agents that benefit from stomach-specific retention and controlled release.

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