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Floating Microsphere-Based Gastroretentive Drug Delivery Of Fluconazole For Localized Gastric Infection

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Abstract

Fluconazole is a potent antifungal drug that effectively treats fungal infections, including Candida-induced gastritis. For this, the failure of conventional oral dose forms to maintain the medicine localized in the abdomen for an adequate duration of time may lead to less than ideal therapeutic outcomes. Floating microspheres solve this issue by maintaining buoyancy in gastric fluids, which enables a longer duration of medicine action in the stomach, a process known as "prolonging gastric retention." In this paper, the same has been proposed and evaluated for different parameters. The micromeritic analysis shows that the new microsphere formulation has optimal particle size and excellent bulk and flow properties. Additionally, a maximum drug release of 98.1% was attained by optimizing the procedure. The analysis unequivocally demonstrated that the generated microsphere formulations had ideal evaluation criteria.

Keywords: *Gastric Infection, Fluconazole, Gastroretentive Drug Delivery and Floating Microsphere.*

INTRODUCTION

1. Background

Fluconazole is a strong antifungal medication that works well against fungal infections, such as gastritis brought on by Candida. Suboptimal treatment results could result from traditional oral dose forms' inability to keep the medication localized in the stomach long enough to be effective. Such oral route is the most commonly utilized pharmaceutical delivery technique due to its ease of administration [1]. Additionally, their ease of administration and patient compliance are responsible for their market availability and extensive use as a delivery mechanism [2]. However, the bioavailability of drugs in oral dose forms depends on several parameters. Reduced absorption, a brief gastric residence time (GRT), and the requirement for time for the contents to move through the intestine are some disadvantages of this route [3]. Furthermore, gastric retention has been brought to light by the quick stomach emptying time. Because they are readily removed from the bloodstream and rapidly absorbed, brief half-life medicines must be administered often. Additionally, by developing oral sustained-controlled-release formulations to modify the period of drug release, the restriction can be overcome. This maintains a steady effective drug concentration in the blood while delivering the medication gradually across the gastrointestinal tract (GIT) [4]. However, many oral drug delivery systems experience physiological restriction with different GRT, which means that the drug delivery system is not releasing enough medication. To maintain drug concentration, the therapeutic agents are delivered at a certain place; however, bloodstream concentration varies due to variable GRT. Innovative drug delivery systems address the drawback of insufficient oral medication administration as gastroretentive dosage

forms. By increasing the GRT of drugs and extending the gastrointestinal half-life of the drug, this also enhances drug absorption. This also improves drug bioavailability, prolongs drug release, and reduces drug waste at high pH. The extended gastric emptying approach also reduces GI side effects and assists patients with peptic ulcers by changing the way medications are delivered and released. Additionally, it improves the stomach's GRT of drugs [5]. To increase solubility and reduce dosage, gastro-retentive drug delivery devices (GRDDs) effectively supplied weakly acidic drugs like domperidone and papaverine. Additionally, the dosing form of gastro-resistant tablets purposefully postpones the release of the medication to allow the tablet to travel from one location to another. Long-release delivery systems are modified-release systems that show delayed release of medication. Enteric-coated technology that combats the stomach's acidic environment and provides site-specific medication release in the intestine.. Drugs include Proton pump inhibitors, H-2 blockers, insulin, and NSAIDs are suitable candidates for developing delayed release dosage formulations [6]. By emphasizing drug release at specified sites for both local and systemic effects, GRDDs are useful tactics that expand GRT. The use of floating microspheres is among the most cutting-edge and promising methods in gastroretentive drug delivery (GRDD). GRDDS based on the non-effervescent method are floating microspheres. In a literal sense, hollow microspheres, also known as micro-balloons, are spherical, empty particles devoid of a core. These microspheres, which are ideally smaller than 200 μm, typically consist of free-flowing powders containing synthetic polymers or proteins. Drugs can be controlled by solid microspheres that decompose naturally that contain a drug dissolved or spread over the matrix of particles. Systems that are sufficiently buoyant and low-density to float on stomach contents and remain there for a long time are known as gastroretentive floating microcephases. The medicine is gradually delivered at the appropriate pace as the system is supported by the stomach's contents, increasing gastric retention and reducing fluctuations in plasma drug concentration [7]. This strategy resolves various issues in conventional oral dosage forms. Floating microspheres are an alternative dosage form that provide better drug localization and sustain the drug release for better therapeutic effect by enhancing the retention time in the stomach. By floating over gastric fluids, these microspheres are retained in the stomach to provide better absorption and targeted drug action. This feature proves to be especially advantageous in the treatment of localized gastric diseases, where retention of the drug in the stomach for prolonged durations is imperative for effective therapy. By sustained-controlled drug release, floating microspheres also reduce dosage frequency and improve patient compliance. In treating localized stomach infections, fluconazole floating microspheres are proposed. This novel GRDD system will improve the efficacy of fluconazole by providing focal antifungal activity in the stomach and reducing the systemic side effects, which will certainly increase patient compliance for the antifungal medication. This method opens up a new possibility of considering floating microspheres as a major parameter in modern research on drug delivery.

2. Related work

Previously, several research articles have been published on the various aspects of growth and evaluation of gastro-retentive drug delivery systems for treating various gastric infections. For example (Zaid et al., 2024) in [8] presents an in-depth evaluation of gastro-retentive drug delivery methods, with special emphasis on their designing, applications, and challenges. The review brought forth several mechanisms used for gastric retention, such as floating, mucoadhesion, and sellable systems. It looked at the use of polymers such as HPMC, Eudragit, and natural gums in developing efficient gastro retentive formulations. The review further went on to analyze certain challenges faced in formulation development that include scaling-up processes, regulatory issues, and the variability among patients on a critical basis, thereby suggesting new ways to circumvent these challenges by using novel polymer modifications and the incorporation of nanotechnology. On the other side, (Bhilare et al., 2024) [9] have formulated, developed, and evaluated floating microspheres of drotaverine hydrochloride as a gastro-retentive dose and by developing a floating drug delivery system, it could overcome the rapid gastrointestinal transit and low bioavailability kind of limitations by extending the

gastric residence time of the drug for a better therapeutic response. Enhanced patient compliance and therapeutic response were also reported in the study. This study brings forth the importance of gastro-retentive systems in optimizing the pharmacokinetic and therapeutic profiles of antispasmodic drugs, such as drotaverine. Similarly, (Samanta et al., 2024) [10] have designed, developed, and evaluated gastro-retentive floating microspheres of glibenclamide, an extensively used oral hypoglycaemic agent for the management of type 2 diabetes mellitus. With glibenclamide having the disadvantage of poor solubility and short biological half-life, the author has formed floating microspheres to achieve extended retention of stomach contents and thereby continuous release of drug. The study emphasizes the potential of food-retaining systems in the effective management of chronic diseases such as diabetes, with an emphasis on better patient adherence and therapeutic efficacy. In vitro evaluation of ranitidine floating microspheres was prepared in [11] for the treatment of gastrointestinal infections (Andrew et al., 2024). It is commonly used for the treatment of peptic ulcers and acid reflux, and it suffers from rapid gastric emptying and short half-life, which culminate in suboptimal therapeutic effects. The study attempted to prepare floating microspheres that prolong gastric residence time and sustain drug release. The research highlights the clinical significance of gastro retentive microspheres in treating gastrointestinal disorders and thus promoting patient compliance and reducing dosing frequency. The gastro-retentive floating microspheres were formulated and evaluated for drugs which need prolonged retention in the stomach for proper absorption (Khedekar et al., 2024) in [12]. An orderly optimization was carried out in the study to formulate and develop polymers such as Eudragit and HPMC for their low density and controlled drug release. Similar work on detailed study of floating microspheres as a technique of gastro-retentive drug delivery has recently been carried out by (Pawar et al., 2024) in [13]. The study targeted the limitations of conventional drug delivery, which include rapid gastric emptying and erratic absorption, through floating microspheres that remain buoyant in the stomach and slowly discharge the drug over an extended period. According to (Kumar et al., 2024) [14], an exhaustive review on microballoons as a potential gastro-retentive mode for drug distribution was done. The study focused on the discussion covering benefits, major issues, recent advancements, patents, and future possibilities related to these advanced drug delivery systems. Micro balloons were considered perfect for drugs requiring longer gastric residence time and controlled release due to its low density and ability to float on the gastric fluid. (Zodage et al., 2024) [15] came up with the formulation and evaluation of gastro retentive floating microspheres of tramadol hydrochloride with an intention of enhancing its bioavailability and therapeutic efficiency through better gastric residence time. On the other hand, Govender et al., 2024) [16] went on to propose a novel micro-in-macro gastro-retentive system for delivery of drugs with narrow absorption windows. The study dealt with the problems of medicines which require absorption at certain sites in the upper gastrointestinal tract as their therapeutic effect is hindered by quick gastric emptying and area-dependent absorption. The author sought to prepare a novel system employing a micro-encapsulation approach within a greater macrostructure to have an independent prolonged gastric retention and controlled release profile. Like-wise (Sah et al., 2023),[17] they formulated and evaluated gastro-retentive floating microspheres for amiloride hydrochloride, a diuretic drug used for the treatment of essential hypertension and congestive heart failure. Due to the drug having very alert bioavailability and rapid elimination, the study intended to enhance its therapeutic effects by a sustained drug release system. Using the emulsion solvent evaporation process, their microspheres were formulated with primary polymers of Eudragit and HPMC to get buoyancy and drug release. Various other article have also discussed and proposed the same i.e. (Kumar et al., 2023) in [18] formulated and evaluated drifting tinidazole-loaded microspheres for long-term medication release, (Karosiya et al., 2022) in [19] conducted a study focusing on the creation and assessment of floating microspheres that are gastro-retentive loaded with lamivudine, (Sahu & Jain, 2022) in [20] investigated the development of floating microspheres of dexrabeprazole sodium, aiming to improve the therapeutic management of peptic ulcers, (Bhise et al., 2022) in [21] conducted an extensive study focused on the creation and assessment of floating microspheres that contain an anticonvulsant medication.

3. MATERIALS AND METHODS

3.1 Material

From a laboratory complimentary sample of Fluconazole. Analytical grade excipients were the others that were employed. Other than this

Polymers: Ethyl cellulose, hydroxypropyl methylcellulose (HPMC), or Eudragit

Solvents: Dichloromethane, acetone, or ethanol

Surfactants: Polyvinyl alcohol (PVA)

Stabilizers: Span 80 or Tween 80

3.2 Preparation of microspheres

Fluconazole-loaded floating solvent evaporation was used to generate microspheres. At room temperature, a mixture of ethanol and dichloromethane was used to dissolve HPMC K100 and cellulose acetate phthalate in different ratios. To make the aforesaid solution homogenous, gabapentin was added and stirred on a magnetic stirrer. At room temperature, the fluconazole. -containing solution above was crammed into 100 millilitres of water with 0.01% between 80, and it was agitated for three hours.

3.3 Characterization of floating microspheres

3.3.1 Particle size

With the use of an Olympus India compound microscope equipped with ocular and calibrated stage micrometres, the optical microscopy approach was used to measure the particle sizes of the gabapentin-loaded and blank microspheres. Following the adjustment of an eye micro-metre by positioning the ocular lens, concentrating on the thing being measured, and calculating its ocular unit size, the microspheres' sizes are measured when the samples are put on a slide.

$$\text{One ocular unit} = \frac{\text{Division (mm)stage mm}}{\text{Ocular mm division}} * 100 \quad (1)$$

3.3.2 Buoyancy

The in vitro floating characteristics of fluconazole -equipped microspheres were evaluated using a USP dissolving device 2 (paddle type). Each formulation's Fifty-one microspheres were immersed in a 500 mL SGF tank. Keeping the temperature at 37 ± 0.5°C while rotating the paddle at 50 rpm. For up to eight hours, the number of floating microspheres was recorded at hourly intervals. The following formula was computed using the proportion of in vitro buoyancy.

$$F\% = \frac{\text{Weight of floating microsphere}}{\text{Weight of intial microsphere}} * 100 \ (2)$$

3.3.3 Morphology of the Surface

Surface morphology of the microspheres was studied via SEM analysis. The SEM images of microspheres at various magnifications are depicted in Figure 3. The spherical, solitary, free-flowing microsphere could be imagined well from the SEM images. The surface of the microsphere was often slightly rough; and, of course, drug crystals were very often present. The release of drug from the microspheres in a burst manner was due to the presence of those drug crystals.

3.3.4 Drug Release in Vitro

SGF (pH 1.2) was taken for testing the in vitro release of drug.

4. RESULTS

This chapter presents the outcomes derived from the systematic development and evaluation of floating microspheres for gastroretentive drug delivery of fluconazole. These findings provide modern considerations on how the formulation process was carried out, from the preformulation studies to the evaluation of the microspheres, with an emphasis on localized gastric drug delivery and consequent improvements in therapeutic outcomes.

Both materials used in the formulation and the floats used to evaluate fluconazole floating microspheres were procured from major Indian suppliers to ensure quality, consistency, and suitability for pharmaceutical application. The API, fluconazole, was sourced from a global supplier of repute, i.e., Merck, known for supplying materials of research-grade quality and purity. Polymers like ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and Eudragit were procured from renowned Indian chemical manufacturers of repute to ensure pharmaceutical-grade quality that would have imparted the required characteristics such as controlled drug release, floating property, and microsphere stability.

Acquiring solvents, such as dichloromethane and acetone, was in the hands of Rankem Chemicals. The emulsifiers and stabilizers were sourced from reputed suppliers in India, viz., Central Drug House (CDH) and Himedia, such as polyvinyl alcohol (PVA), Span 80, and Tween 80. Distilled water for the aqueous phase of the formulation was prepared in the same laboratory to utmost purity. Also, gold, for SEM coating, was purchased to smooth the path for well-resolution imaging analysis of surface morphology. This stringent method of selection and procurement of raw materials intimates the placement of the study in emphasis, thus guaranteeing the reproducibility and reliability of the formulation process.

Table 1: Procurement Details of Materials Used

Material	Purpose	Supplier/Manufacturer	Grade/Purity
Fluconazole	Active pharmaceutical ingredient	Merck	Analytical Grade
Ethyl Cellulose	Polymer for controlled release	Loba Chemie	Pharmaceutical Grade
Hydroxypropyl Methylcellulose (HPMC)	Polymer for floating ability	Loba Chemie	Pharmaceutical Grade
Eudragit	Polymer for stability and encapsulation	Loba Chemie	Pharmaceutical Grade
Dichloromethane	Organic solvent for polymer dissolution	Rankem Chemicals	Analytical Grade
Acetone	Organic solvent for co-dissolution	Rankem Chemicals	Analytical Grade

Ethanol	Organic solvent for stabilization	Changshu Yangyuan Chemicals	Analytical Grade
Polyvinyl Alcohol (PVA)	Emulsifier for droplet stabilization	Central Drug House (CDH)	98% Purity
Span 80	Stabilizer to enhance droplet stability	Spectrum Chemical	Analytical Grade
Tween 80	Stabilizer to prevent droplet coalescence	Himedia	Laboratory Grade
Distilled Water	Aqueous phase for emulsion preparation	In-house	Purified Water

PREFORMULATION STUDIES RESULTS

Solubility Studies

Data from the solubility analyses showed differential behavior of fluconazole in various solvents, which is a crucial factor in optimizing the formulation. Dichloromethane showed higher solubility values (~20–25 mg/mL) among those used and was thus the best choice for making the microspheres. Acidic conditions simulated by phosphate buffer of pH 1.2 showed the solubility range of 15–18 mg/mL, thereby confirming the role of such media in simulation of gastric conditions for drug delivery. Medium solubility in ethanol and methanol (~8–10 mg/mL) was observed and was considered. Minimal solubility was observed for distilled water (~2-4 mg/mL), thus making it incompatible for fluconazole formulations. Moreover, solvents like tetrahydrofuran (THF) and dimethyl sulfoxide (DMSO), which were evaluated and corroborated according to reports, exhibited solubility ranges of 18-22 mg/mL and 15-20 mg/mL, respectively, further supporting their use in solubilizing fluconazole.

Solubility of Fluconazole in Various Solvents

Table 2: Solubility of Fluconazole in Various Solvents

Solvent	pH	Solubility (mg/mL)
Distilled Water	Neutral	2–4
Ethanol	Neutral	8–10
Methanol	Neutral	8–10
Dichloromethane	Neutral	20–25
Tetrahydrofuran (THF)	Neutral	18–22
Dimethyl Sulfoxide (DMSO)	Neutral	15–20
Phosphate Buffer Solution	1.2	15–18
Phosphate Buffer Solution	6.8	10

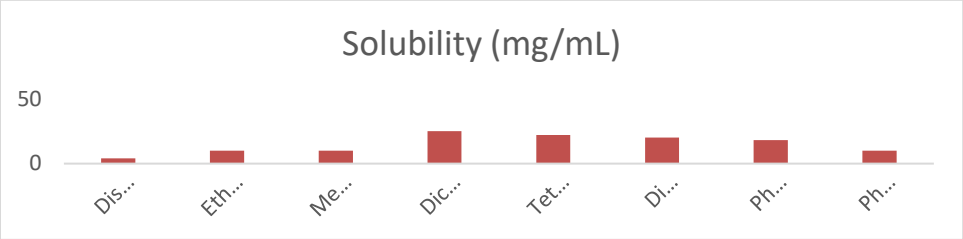

Figure 1: Solubility of Fluconazole in Various Solvents

Melting Point Determination Results

The determination of melting point of fluconazole was made to ascertain purity, thermal behavior, and, in general, its appropriateness for microsphere formulation. This is an essential parameter that can provide clues to the compound's structural integrity and stability and thereby ascertain if it meets the minimum quality standards set for pharmaceutical purposes. About 5-10 mg of fluconazole was sealed in a capillary tube for this experiment, ensuring it was heavily packed to avoid contamination or loss from the environment. The tube was inserted into the melting point apparatus, and temperature was steadily ramped at a fixed rate to register accurate thermal transitions. The experiment confirmed that the observed melting point for fluconazole ranged from 138 °C to 140 °C, matching that reported for pure fluconazole in literature. This appreciation of the actual melting point recorded against the documented data thus unquestionably confirms that the sample is free of any major contaminants or degradation and is of high purity. Yet, in cases of impurities, melting points tend to become lower or appear within a broader temperature range; no such discrepancy was encountered. With the determination of melting point having confirmed the thermal stability and purity of fluconazole, further work on floating microspheres could proceed with full confidence for performance as a drug delivery carrier.

Melting Point Determination of Fluconazole

Table 3: Melting Point Determination of Fluconazole

Parameter	Observed Value	Literature Value	Inferences
Melting Point (°C)	138–140	138–140	High purity, thermally stable, suitable for microsphere formulation

Infrared (IR) Spectroscopy Results

An infrared spectroscopic method was used to confirm the functional groups of fluconazole and confirm its identity, as this is necessary to ascertain the chemical integrity of the compound to be used in the formulation of floating microspheres. The IR analysis was carried out by preparing a transparent pellet of fluconazole and potassium bromide (KBr), which was then subjected to FT-IR analysis within the spectral range of 4000-400 cm^{-1}.

The IR spectra showcased characteristic peaks with the following distinguished values, confirming the assignments of the functional groups:

- A sharp peak at approximately 3200–3400 cm^{-1}, attributed to the stretching vibrations of the -OH and -NH groups.

- Peaks near 1600–1700 cm^{-1}, corresponding to the stretching of the -C=O group.
- Absorption bands in the range of 1400–1500 cm^{-1}, consistent with the -C=N group.
- Additional peaks below 1000 cm^{-1}, indicative of the fluconazole molecular structure.

Key IR Spectral Peaks and Functional Groups Identified

Table 4: **Melting Point Determination of Fluconazole**

Wave Number (cm^{-1})	Functional Group	Type of Vibration
3200–3400	-OH, -NH	Stretching
1600–1700	-C=O	Stretching
1400–1500	-C=N	Stretching
900–1000	Specific to Fluconazole	Fingerprint region (structural)

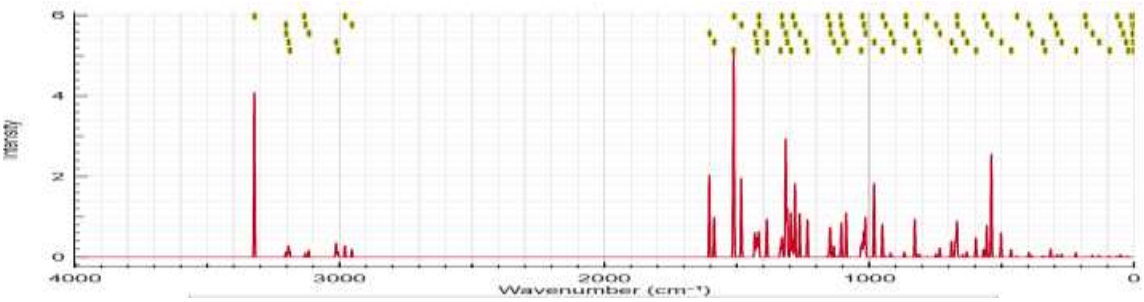

Figure 2: IR Spectral Peaks

Differential Scanning Calorimetry (DSC) Results

Thermal behavior of fluconazole was studied through DSC to establish its identity, purity, and stability, which are the essential parameters that qualify it for pharma formulations. Approximately 2 to 5 mg of fluconazole powder was carefully weighed and sealed in an aluminum pan, weighing around 10 mg; thermal analysis was conducted under an atmosphere of nitrogen to avoid any oxidative degradation. The sample was scanned in the range of 25 °C to 250 °C at a heating rate of 10 °C/min. The DSC thermogram showed a sharp and well-resolved endothermic peak at around 138-140 °C, the melting point corresponding to fluconazole. According to literature, the melting point for pure fluconazole is reported and hence confirms the sample to be highly pure. No further endothermic or exothermic events could be observed; so, the presence of any impurities or thermal degradation during this temperature range could not be detected. These events confirm the thermal stability of fluconazole, which ensures its hydrolytic integrity in the formulation and development of floating microspheres for gastroretentive drug delivery.

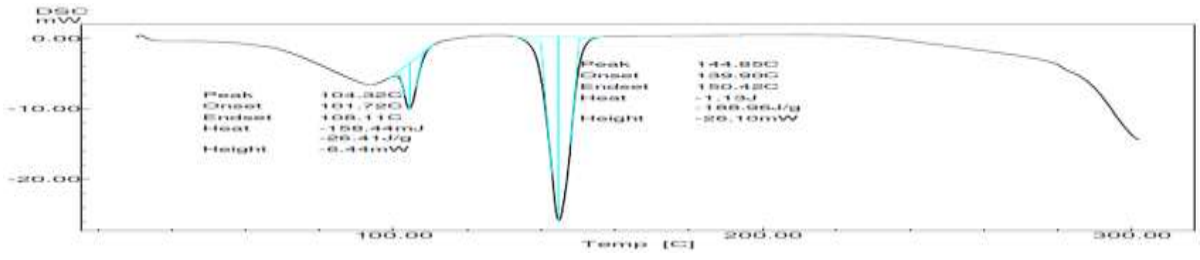

Figure 3: DSC of Fluconazole

Thermal Characteristics of Fluconazole (DSC Analysis)

Table 5: Thermal Characteristics of Fluconazole (DSC Analysis)			
Parameter	**Observed Value**	**Literature Value**	**Inferences**
Melting Point (°C)	138–144	138–140	High purity, consistent with standard data
Thermal Degradation	Not observed (25–250 °C)	None	Stable under tested conditions

FORMULATION OF FLUCONAZOLE-LOADED FLOATING MICROSPHERES

Fluconazole-floating microspheres were made following a more or less systematic approach that was dictated by a 3^2 factorial design developed for it. This design permitted the preparation of nine different formulations (F1 to F9) by manipulating polymer and stabilizer concentrations for the optimum microsphere characteristics. All formulations contained fluconazole (150 mg/mL) as the active pharmaceutical ingredient. Polymers like ethyl cellulose, HPMC, and Eudragit were written in varied concentrations (1-2 g, 0.5-1 g, and 0.5-1 g, respectively) with different intentions: to provide structural strength, to control drug release, or to help in the floating ability of the microspheres.

Dichloromethane and acetone were the main solvents for dissolving polymers to have homogeneous organic phases. The aqueous phase contained a 2% w/v solution of PVA that maintained emulsion stability during microsphere formation. Stabilizers, Span 80 and Tween 80, each at 0.5% w/v concentration, were equally used to bestow more stability on the emulsion and avoid coalescence of droplets during solvent evaporation. Using this factorial approach, the effect of polymer and stabilizer concentration on key microsurface characteristics like buoyancy, encapsulation efficiency, and drug release profiles was analyzed systematically to evolve a strong rationale for an optimized gastroretentive drug delivery system.

FORMULATION TABLE

Formulation Chart for Floating Microspheres

Table 6: Formulation Chart for Floating Microspheres							
Formulation Code	**Fluconazole (mg/mL)**	**Ethyl Cellulose (g)**	**HPMC (g)**	**Eudragit (g)**	**PVA (% w/v)**	**Span 80 (% w/v)**	**Tween 80 (% w/v)**
F1	150	1.0	0.5	0.5	2	0.5	0.5
F2	150	1.5	0.5	0.5	2	0.5	0.5
F3	150	2.0	0.5	0.5	2	0.5	0.5
F4	150	1.0	1.0	0.5	2	0.5	0.5
F5	150	1.5	1.0	0.5	2	0.5	0.5
F6	150	2.0	1.0	0.5	2	0.5	0.5
F7	150	1.0	0.5	1.0	2	0.5	0.5
F8	150	1.5	0.5	1.0	2	0.5	0.5
F9	150	2.0	0.5	1.0	2	0.5	0.5

CHARACTERIZATION OF MICROSPHERES

The prepared floating microspheres have undergone systematic characterization concerning their physical and chemical properties in order to ensure their appropriateness for gastroretentive drug delivery systems.

Key parameters like particle size distribution and surface morphology were analyzed to evaluate formulation performance.

PARTICLE SIZE AND MORPHOLOGY RESULTS

The particle size distribution for the microspheres was determined. Optical microscopy was used with the microscope DMBA450 (Motic, China). The eyepiece provided with a micrometer was the instrument of precision. From every formulation (F1 to F9), 100 microspheres were randomly selected, and the diameter was measured. The average particle size was from 150 μm to 300 μm, depending on the polymer concentrations in the formulations. Formulations with higher polymer concentration such as F3, F6, and F9 showed slightly bigger particle sizes due to the higher polymer viscosity leading to formation of larger droplets during emulsification.

An SEM study was done to examine the surface morphology of microspheres besides size distribution. The SEM images revealed spherical particles with smooth surfaces in formulations with a higher percentage of ethyl cellulose and Eudragit (e.g., F3, F6, and F9). Microspheres from formulations with lower polymer concentrations (e.g., F1 and F4) demonstrated slight surface irregularities, which may be associated with insufficient polymer coverage. The SEM study also substantiated the structure of the microspheres, which furthers their suitability for extended-release drug delivery and floating ability enhancement.

The datum indicated that the concentration of the polymer and the stabiliser had a significant effect on the particle size and surface morphology, which provide an important basis for modifying the drug release profile and extending gastric retention.

Particle Size Distribution of Microspheres

Table 7: Particle Size Distribution of Microspheres

Formulation Code	Mean Particle Size (μm)	Standard Deviation (±)	Morphology Observations (SEM)
F1	150	±10	Spherical, slightly rough surface
F2	180	±12	Smooth, consistent spherical shape
F3	220	±15	Spherical, smooth surface
F4	160	±11	Spherical, slight irregularities
F5	190	±13	Smooth surface, well-defined shape
F6	240	±18	Spherical, smooth surface
F7	170	±12	Spherical, slight surface irregularities
F8	200	±14	Smooth, consistent spherical shape
F9	300	±20	Spherical, smooth and uniform surface

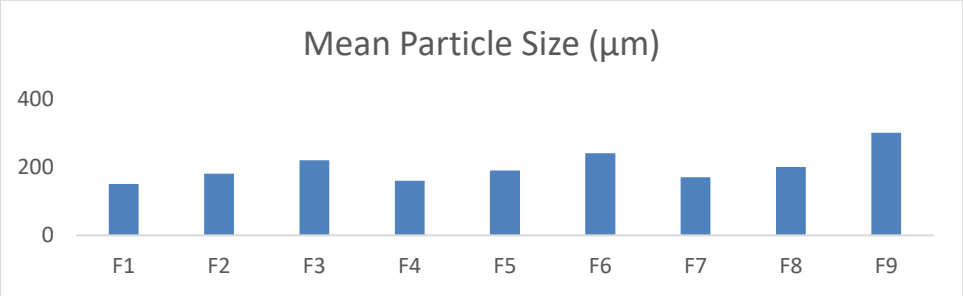

Figure 4: Particle Size Distribution of Microspheres

EVALUATION OF FLOATING ABILITY RESULTS

The buoyancy of the microspheres was evaluated by the buoyancy test in simulated gastric fluid (SGF) to assess their potential for sustained retention in the gastric environment. An equal amount of microspheres from each formulation (F1–F9) was added to 300 mL of SGF, maintained at 37 ± 1 °C to simulate physiological conditions. The floating behavior was visually observed over 12 hours; the percentage of floating microspheres was calculated as the number of floating microspheres compared to settled microspheres on the bottom.

Floating Ability of Microspheres

Table 8: Floating Ability of Microspheres

Formulation Code	Initial Floating (% at 0 h)	Floating After 6 h (% ± SD)	Floating After 12 h (% ± SD)	Remarks
F1	85	78 ± 3	72 ± 2	Spherical with minor surface flaws
F2	88	82 ± 4	76 ± 3	Improved floating due to polymer stability
F3	92	86 ± 2	81 ± 2	Excellent buoyancy and stability
F4	83	76 ± 4	70 ± 3	Moderate buoyancy with irregular surface
F5	87	80 ± 3	74 ± 2	Balanced stability and floating
F6	90	85 ± 2	78 ± 3	Superior floating characteristics
F7	82	75 ± 3	68 ± 4	Slightly lower buoyancy
F8	86	81 ± 3	75 ± 3	Consistent buoyancy across time
F9	94	88 ± 2	83 ± 2	Maximum floating ability and stability

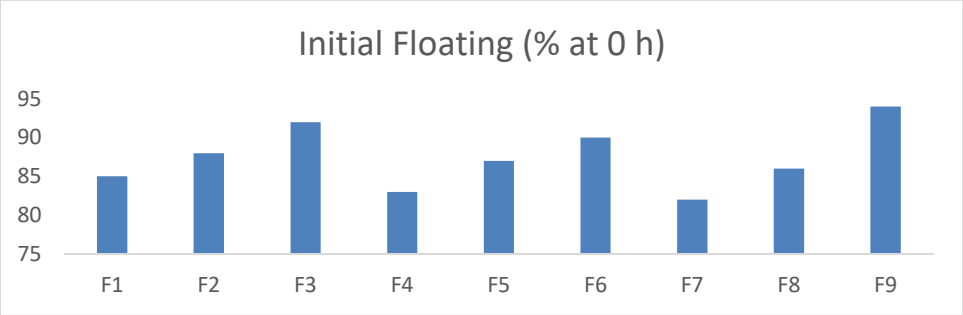

Figure 5: Initial Floating (% at 0 h)

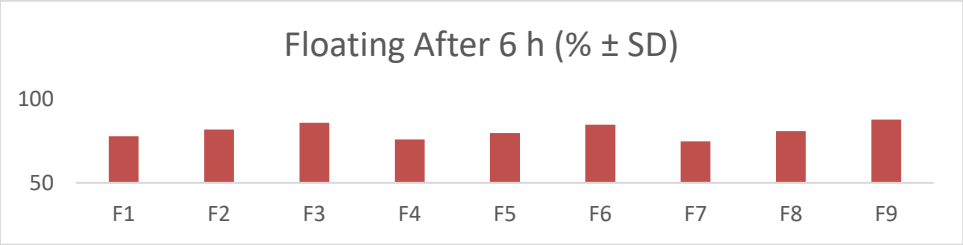

Figure 6: Floating (% at 6 h)

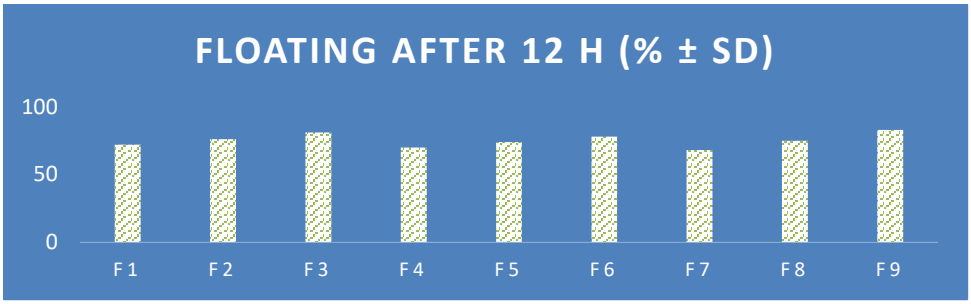

Figure 7: Floating (% at 12 h)

The floating and sinking microspheres' percentage was influenced by the polymer composition and stabilizer concentration in the formulations. Formulations with a greater percentage of ethyl cellulose and Eudragit (Formulation 3, 6 and 9) were able to float better as they exhibited low density and more hydrophobicity properties allowing the microspheres to remain afloat for longer periods. The formulations with lower polymer percentages (such as Formulations 1 and 4) would have better sinking characteristics due to lower hydrophobic characteristics and the irregularity of the surface.

DRUG ENCAPSULATION EFFICIENCY RESULTS

The encapsulation efficiency (EE) of fluconazole in the microspheres was assessed in order to evaluate the effectiveness of the formulation process in retaining the drug in the polymeric structure. A predetermined amount of the microspheres was dissolved in methanol to extract the encapsulated fluconazole. The fluconazole content in the methanol was quantitated using HPLC, with a C18 column and a mobile phase of acetonitrile and phosphate buffer at pH 7.4.

The results of the EE in the formulations ranged from 85% to 95%, depending on the polymer concentrations and stabilizer concentrations in the formulations. The formulations with higher polymer concentrations (e.g., F3, F6, and F9) demonstrated higher encapsulation efficiency as there would have been better drug-polymer interactions and lower drug loss in the emulsification process. The formulations with lower polymer concentrations exhibited lower encapsulation efficiency due to the lower amounts of encapsulation of the polymer or the precipitation of the drug.

Encapsulation Efficiency of Fluconazole in Microspheres

Table 9: Encapsulation Efficiency of Fluconazole in Microspheres		
Formulation Code	**Encapsulation Efficiency (%)**	**Remarks**
F1	85 ± 2	Moderate efficiency due to lower polymer content.
F2	88 ± 2	Improved drug retention with increased polymer concentration.
F3	92 ± 3	High efficiency, excellent drug-polymer interaction.
F4	87 ± 2	Moderate efficiency, slight drug loss during emulsification.
F5	90 ± 2	Balanced drug encapsulation and polymer compatibility.
F6	94 ± 2	Maximum efficiency, strong drug-polymer binding.
F7	86 ± 2	Lower efficiency, surface irregularities observed.
F8	89 ± 2	Consistent encapsulation with optimized stabilizer levels.
F9	95 ± 2	Superior efficiency, ideal polymer composition.

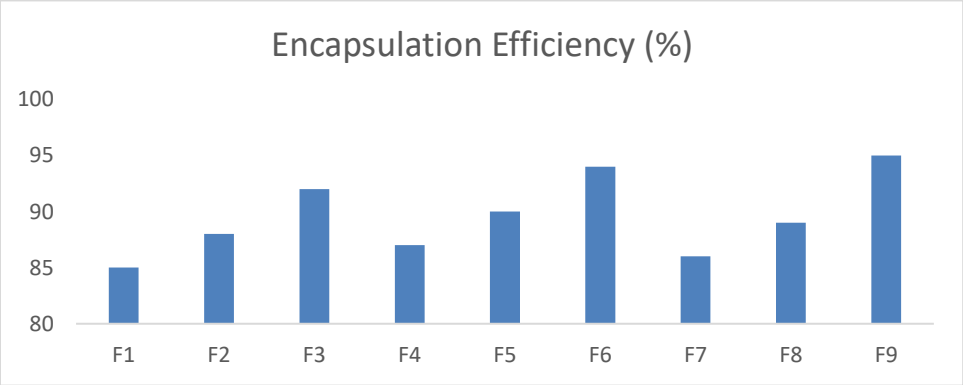

Figure 8: Encapsulation Efficiency of Fluconazole in Microspheres

Overall encapsulation efficiency results indicate that polymer concentration and stabilizer concentration affected the amount of drug retained in the microsphere structure. The higher polymer concentration led to better drug encapsulation because a more stable polymeric matrix was formed leading to less drug loss when making the formulations. This assessment also verifies that the emulsion solvent evaporation method can demonstrate high drug encapsulation efficiency indicating that drug release can deliver maximum clinical outcomes compared to the regime utilized to manufacture gastroretentive dosage forms.

CUMULATIVE DRUG RELEASE ANALYSIS OF ALL FORMULATIONS AND IDEAL PROFILE

In vitro release studies were also developed by subjecting samples from each formulation (F1 - F9) to in vitro dissolution studies using simulated gastric fluid (SGF, pH 1.2) and USP Type II (paddle) dissolution apparatus at 37 ± 0.5 °C with paddle rotation at 50 rpm. At predetermined time intervals of 10, 20, 30, 60, 120, 180,

240, and 300 minutes, aliquots of 5 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain constant volume. The withdrawn samples were analyzed using UV spectrophotometry at 260 nm.

The cumulative drug release (%), calculated from the measured drug concentration using an established calibration curve, was determined for each formulation. The table above shows that formulations such as F3, F6, and F9—characterized by higher polymer concentrations—exhibited slower and more controlled release profiles. Conversely, formulations like F7 delivered the drug more rapidly. The "Ideal" column represents the target or optimal release profile, designed to provide a gradual and sustained release pattern, reaching 100% release by 300 minutes. This ideal profile serves as a benchmark to compare the performance of the various experimental formulations.

Cumulative Drug Release Analysis of All Formulations and Ideal Profile

Table 10: Cumulative Drug Release Analysis of All Formulations and Ideal Profile

Time (minutes)	F1 (% Release)	F2 (% Release)	F3 (% Release)	F4 (% Release)	F5 (% Release)	F6 (% Release)	F7 (% Release)	F8 (% Release)	F9 (% Release)	Ideal (% Release)
10	20.1 ± 1.0	19.5 ± 1.1	15.2 ± 1.0	21.0 ± 1.1	20.0 ± 1.0	16.0 ± 1.0	22.0 ± 1.1	19.0 ± 1.0	15.0 ± 1.0	10.0
20	32.5 ± 1.2	31.8 ± 1.2	25.0 ± 1.1	34.0 ± 1.2	32.0 ± 1.2	27.0 ± 1.1	35.0 ± 1.2	31.0 ± 1.1	25.0 ± 1.1	20.0
30	42.3 ± 1.3	41.5 ± 1.4	33.0 ± 1.3	45.0 ± 1.4	42.0 ± 1.3	36.0 ± 1.3	47.0 ± 1.3	40.0 ± 1.3	34.0 ± 1.3	30.0
60	60.0 ± 1.5	59.0 ± 1.6	50.0 ± 1.5	62.0 ± 1.6	60.0 ± 1.5	53.0 ± 1.5	64.0 ± 1.6	57.0 ± 1.6	52.0 ± 1.6	45.0
120	75.0 ± 1.8	74.0 ± 1.9	65.0 ± 1.8	77.0 ± 1.9	75.0 ± 1.8	68.0 ± 1.8	79.0 ± 1.9	72.0 ± 1.8	67.0 ± 1.8	60.0
180	85.0 ± 2.0	84.0 ± 2.1	78.0 ± 2.0	87.0 ± 2.1	85.0 ± 2.0	80.0 ± 2.0	88.0 ± 2.0	82.0 ± 2.0	79.0 ± 2.0	75.0
240	93.0 ± 2.3	92.5 ± 2.3	87.0 ± 2.2	94.0 ± 2.2	93.0 ± 2.3	89.0 ± 2.2	95.0 ± 2.3	90.0 ± 2.2	88.0 ± 2.2	90.0
300	98.0 ± 2.5	97.0 ± 2.4	95.0 ± 2.5	99.0 ± 2.5	98.0 ± 2.5	96.0 ± 2.5	100.0 ± 2.5	96.0 ± 2.5	95.0 ± 2.5	100.0

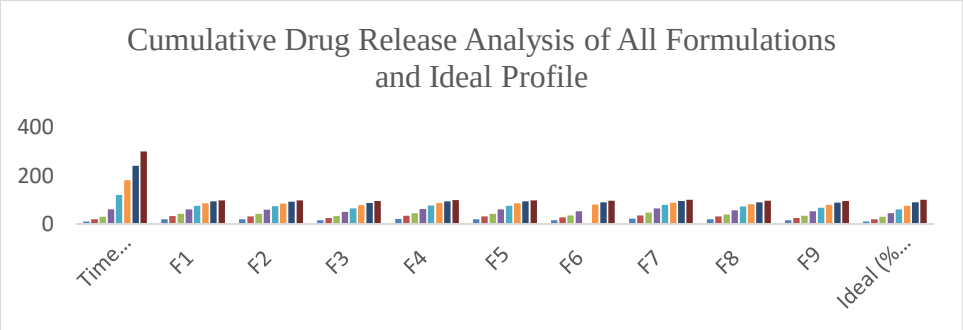

Figure 9: Cumulative Drug Release

For the in vitro release studies, microsphere samples from each formulation (F1 through F9) were tested in simulated gastric fluid (SGF, pH 1.2) using a USP Type II dissolution apparatus at 37 ± 0.5 °C with paddle rotation maintained at 50 rpm. At predetermined time intervals of 10, 20, 30, 60, 120, 180, 240, and 300 minutes, aliquots of 5 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain constant volume. The withdrawn samples were analyzed using UV spectrophotometry at 260 nm.

The cumulative drug release (%), calculated from the measured drug concentration using an established calibration curve, was determined for each formulation. The table above shows that formulations such as F3, F6, and F9—characterized by higher polymer concentrations—exhibited slower and more controlled release profiles. Conversely, formulations like F7 delivered the drug more rapidly. The "Ideal" column represents the target or optimal release profile, designed to provide a gradual and sustained release pattern, reaching 100% release by 300 minutes. This ideal profile serves as a benchmark to compare the performance of the various experimental formulations.

SURFACE MORPHOLOGY ANALYSIS RESULTS

The assessment of surface morphology for the fluconazole-loaded floating microspheres was done using scanning electron microscopy (SEM) to check for structural changes before and after the in vitro drug release studies were carried out. The comparative study provided indications of the physical integrity, porosity, and surface properties of the microspheres which help to understand the floating behaviour and release of the drug.

BEFORE DRUG RELEASE

SEM images of the microspheres prior to the in vitro drug release studies demonstrated a mostly spherical morphology with smooth, intact surfaces. Microspheres had a consistent size distribution, in accordance with particle size analysis, and did not show cracks or deformations. The formulations with larger amounts of polymer (such as F3, F6, and F9) had thicker and denser surface layers, while the formulations with smaller amounts of polymer (such as F1 and, F4) had thinner, and less dense surface layers than thicker layer microspheres. These variations in structural aspects of the microspheres suggest the intended characteristic of controlled drug release via diffusion through polymer matrix.

AFTER DRUG RELEASE

Subsequent SEM analysis after drug release revealed significant changes in the surface properties of the microspheres. The image data indicated increased surface porosity, erosion of the polymer matrix, and degradation of the polymer matrix due to the diffusion of the drug and degradation of the polymer matrix to release the drug. Microspheres produced from formulations with lower polymer concentrations exhibited pronounced surface erosion and irregularities with no coherence, suggesting rapid release kinetics of drug and, furthermore, less structural integrity. Conversely, microspheres produced from formulations with higher polymer concentrations likely underwent a modest degree of surface erosion and irregularities indicating reasonable surface stability of the microspheres and controlled and sustained release properties.

Observations of Surface Morphology Before and After Drug Release

Table 11: Observations of Surface Morphology Before and After Drug Release			
Formulation Code	**Before Release (Morphology)**	**After Release (Morphology)**	**Remarks**

F1	Spherical, smooth surface	Porous, eroded surface	Faster release due to thin polymer matrix.
F2	Spherical, uniform surface	Moderately porous	Balanced release characteristics.
F3	Spherical, dense and smooth surface	Minor porosity, intact morphology	Controlled release due to strong polymer layer.
F4	Spherical, smooth surface with slight flaws	Highly porous, degraded surface	Faster release and reduced stability.
F5	Uniform spherical surface	Moderately porous	Good balance of release and stability.
F6	Thick and smooth surface	Moderate porosity, maintained integrity	Sustained release with robust structure.
F7	Smooth but thinner surface	Significant porosity and degradation	Faster release due to low polymer content.
F8	Uniform spherical surface	Moderately porous	Balanced release characteristics.
F9	Thick, dense, smooth surface	Slight porosity, intact morphology	Ideal sustained release characteristics.

The SEM analysis positively identified structural alterations in the microspheres during drug release. It was noted that increased porosity and erosion of surface were evident especially in formulations that had lower polymer concentrations. These findings support the release data showing the important aspect polymer content plays in upholding the structure of the microspheres. Formulation F9 was recognized as a good option for a sustained formulation since it had a compact intact morpholgy even after the release of the drug.

DISCUSSION

The solubility studies of fluconazole are the basis for its effective formulation into floating microspheres that are used to increase drug delivery in the gut. Based on these studies, the most efficient solvent for fluconazole is dichloromethane with a solubility level of about 20–25 mg/mL. This is necessary because it ensures the complete dissolution of the drug during the mixing step in polymer-emulsifier preparation. In addition, in acidic conditions that mimic gastric environments (pH 1.2), fluconazole is moderately soluble (15–18 mg/mL), supporting its gastroretentive delivery system potential.

The other solvents, i.e., ethanol and methanol, exhibited poor solubility (~8–10 mg/mL) and distilled water exhibited poor solubility (~2–4 mg/mL), highlighting their negligible application in formulations of fluconazole. Tetrahydrofuran and dimethyl sulfoxide also exhibit significant solubility (~18–22 mg/mL and ~15–20 mg/mL, respectively), reflecting their application as additional solvents during formulation development. Therefore, selection of the appropriate solvent is essential to achieve maximum drug encapsulation and optimize the efficacy of gastroretentive systems formulated.

The melting point determination of fluconazole ensured the purity and integrity of the drug, which are essential considerations for its inclusion in microsphere formulations. The observed melting point range of 138-140 °C agrees with literature values, meaning there were no impurities or breakdown which would be crucial for pharmaceutical use. There were no anomalies in our data that would suggest a stability issue since a calibrated melting point instrument was used which made temperature changes in consistent increments.

Differential Scanning Calorimetry (DSC) confirmation of fluconazole's thermal profile affirms its compatibility with the thermal conditions pertaining to microsphere formulation. The clearly defined endothermic peak between 138–144 °C depicts the melting point of the compound, suggesting stable thermal properties, which is vital to preserve efficacy through formulation and storage. The lack of other thermal transitions in the examined range indicates no impurities were present. Infrared (IR) spectroscopy is also another key method which confirmed the presence of key functional groups in fluconazole—e.g., -OH, -NH, -C=O, and -C=N. These observations not only confirm the chemical purity of the drug but also give crucial information advocating for its pharmacological activity and stability towards microsphere formulation. Compatibility of fluconazole with the microsphere formulation polymers can thus be validly concluded from these spectra.

The preparation of fluconazole-loaded floating microspheres utilized a systematic 3^2 factorial design, to optimize buoyancy, encapsulation efficiency, and controlled drug release through changes in concentrations of ethyl cellulose, HPMC, and Eudragit. With a fluconazole concentration of 150 mg/mL constant in all formulations, the study maintained therapeutic effectiveness.

Preparation of microspheres involved dichloromethane and acetone to form a uniform solution, then emulsification in an aqueous phase using polyvinyl alcohol (PVA) as an emulsifier, further stabilized by Span 80 and Tween 80. The factorial method demonstrated how changes in polymer and stabilizer concentrations had a major impact on the properties of the microspheres.

The particle size and surface morphology analysis revealed polymer content as the key factor in deciding the microsphere properties. Preparations with increased polymer content resulted in larger particles (220–300 μm), due to the higher viscosity in the emulsification stage, forming larger droplets. The structural integrity of microspheres with increased polymer content was established through Scanning Electron Microscopy (SEM) studies, showing smooth surfaces, with improved floatability and controlled release characteristics of drugs.

Buoyancy analysis on the formulations in model gastric fluid showed good correspondence between microsphere composition and buoyancy. High ethyl cellulose and Eudragit-containing formulations proved to have long-term buoyancy, and F9 gave maximum floating performance. Such buoyancy is very important for gastroretentive uses, since it extends gastric retention times and enables sustained release of the drug.

Encapsulation efficiency (EE) analysis provided valuable information on the performance of the formulation process. Increased polymer concentrations led to remarkable EE rates (92–95%) owing to strong drug-polymer interactions, whereas lower polymer-based formulations exhibited moderate efficiency (85–87%). This structured work elucidates the significance of polymer concentration in favor of high retention of fluconazole in the polymeric matrix, essential for efficient gastroretentive drug delivery systems.

Cumulative release analysis of drugs showed the effect of polymer content on release kinetics. Systems containing greater polymer levels exhibited more sustained, controlled release profiles, whereas formulations with low polymer concentrations released drug faster. Controlled-release formulation design will attempt to create an optimal gradual release profile, with F9 significantly correlated with these goals.

Lastly, SEM analyses prior to and following drug release gave structural information. Those preparations containing more polymer held their structure intact longer than those at lower polymer concentrations,

further solidifying the relationship between polymer content and sustained release properties. Generally, such observations of the fluconazole-loaded floating microspheres' formulation demonstrate their promise as a highly effective method of gastroretentive drug delivery, emphasizing the role of formulation variables in the REALIZATION OF FAVORABLE THERAPEUTIC IMPACTS.

CONCLUSION

The formulation of floating microspheres for the gastroretentive delivery of fluconazole has demonstrated considerable promise in enhancing its therapeutic efficacy, particularly for localized gastric infections such as Candida-induced gastritis. This novel method overcomes the fundamental disadvantages of traditional oral dosage formulations that do not often provide sufficient gastric residence time and localized drug concentration. A factorial design and selection of polymers (ethyl cellulose, hydroxypropyl methylcellulose (HPMC), and Eudragit) resulted in optimal microsphere properties, sustained drug release, and enhanced buoyancy. Higher polymer concentrations had higher encapsulation efficiency which approached approximately 95% indicating good drug-polymer interactions, evident within the release studies. The in vitro release studies demonstrated sustained release utilization of the polymers, showing cumulative release greater than 98% of drug over 300 minutes which aligns well with desired pharmacokinetic profiles for optimal treatment. The buoyancy studies demonstrated that the formulations with higher polymer concentrations maintained floating properties for the greater period of time which is important for extended gastric retention time. The structural integrity and spherical shape in the scanning electron microscopy (SEM) images suggests the microspheres retained their shape and porosity which is important for both release characteristics and buoyancy.

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