Development and Characterization of Gastroretentive Microballoons of Tegoprazan for Antiulcer Activity

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Abstract

Peptic ulcer disease remains one of the most prevalent gastrointestinal disorders, primarily caused by excessive gastric acid secretion, *Helicobacter pylori* infection, and prolonged use of nonsteroidal anti-inflammatory drugs. Although Tegoprazan, a novel potassium-competitive acid blocker (P-CAB), provides rapid and effective suppression of gastric acid secretion, its therapeutic performance may be improved through a gastroretentive drug delivery system that prolongs its residence in the stomach. The present study focuses on the development and characterization of gastroretentive floating microballoons of Tegoprazan to enhance gastric retention, provide sustained drug release, and improve antiulcer efficacy. The optimized formulation demonstrated excellent floating behavior, remaining buoyant for more than 12 hours, with high entrapment efficiency and satisfactory production yield. In vitro drug release studies indicated sustained release of Tegoprazan over an extended period, following controlled-release kinetics and providing a gradual release profile suitable for gastroretentive delivery. The antiulcer potential of the optimized gastroretentive microballoons was evaluated using suitable experimental ulcer models. The formulation exhibited superior gastroprotective activity compared with the conventional Tegoprazan formulation, as evidenced by a significant reduction in ulcer index, enhanced gastric mucosal protection, and prolonged acid suppression. The improved therapeutic performance was attributed to extended gastric residence time, sustained drug release, and enhanced local availability of Tegoprazan at the site of action. Overall, the developed gastroretentive floating microballoons of Tegoprazan demonstrated desirable physicochemical characteristics, prolonged buoyancy, controlled drug release, and enhanced antiulcer activity. The study suggests that floating microballoons represent a promising oral gastroretentive drug delivery system capable of improving the therapeutic efficacy of Tegoprazan while reducing dosing frequency and enhancing patient compliance. Further pharmacokinetic and clinical investigations are recommended to establish their potential for the effective management of peptic ulcer disease.

Keywords: Tegoprazan; Gastroretentive drug delivery system; Floating microballoons; Potassium-competitive acid blocker (P-CAB); Antiulcer activity; Emulsion solvent diffusion.

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Introduction

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by the formation of ulcers in the lining of the stomach or the proximal part of the small intestine. It results from an imbalance between aggressive factors such as gastric acid, pepsin, *Helicobacter pylori* infection, and nonsteroidal anti-inflammatory drugs (NSAIDs), and defensive mechanisms including mucus secretion, bicarbonate production, prostaglandins, and mucosal blood flow. Despite advances in medical therapy, peptic ulcer disease continues to be a significant global health concern due to its high prevalence, recurrence, and associated complications such as bleeding, perforation, and gastric obstruction. Therefore, the development of effective drug delivery systems capable of providing prolonged therapeutic action remains an important area of pharmaceutical research.[1,2]

The management of acid-related disorders has evolved considerably with the introduction of proton pump inhibitors (PPIs), which have been the cornerstone of antiulcer therapy for several decades. However, PPIs exhibit certain limitations, including delayed onset of action, variable bioavailability, dependence on acid activation, and interpatient variability caused by genetic polymorphism of

CYP2C19 enzymes. These drawbacks have encouraged the development of newer classes of acid-suppressive agents that offer rapid and sustained inhibition of gastric acid secretion.[3,4]

Tegoprazan is a novel potassium-competitive acid blocker (P-CAB) that reversibly inhibits the H^+/K^+-ATPase enzyme by competing with potassium ions at the gastric proton pump. Unlike conventional PPIs, Tegoprazan provides rapid onset of action, prolonged acid suppression, higher stability in acidic environments, and does not require acid activation before exerting its pharmacological effect. These characteristics make Tegoprazan an effective therapeutic option for the treatment of peptic ulcers, gastroesophageal reflux disease (GERD), and other acid-related gastrointestinal disorders. Nevertheless, maintaining adequate drug concentration in the stomach for an extended period may further improve its therapeutic efficacy.[5,6]

Gastroretentive drug delivery systems (GRDDS) have emerged as an innovative approach to prolong the residence time of dosage forms within the stomach. These systems are particularly beneficial for drugs that are primarily absorbed in the upper gastrointestinal tract, exhibit local action in the stomach, or possess pH-dependent solubility. By increasing gastric retention time, gastroretentive formulations enhance drug bioavailability, reduce dosing frequency, minimize fluctuations in plasma drug concentration, and improve patient compliance. Various GRDDS approaches have been investigated, including floating systems, bioadhesive systems, expandable systems, high-density systems, and raft-forming formulations.[7]

Among the various gastroretentive approaches, floating microballoons have gained considerable attention because of their excellent buoyancy, low density, large surface area, and ability to remain suspended in gastric fluids for prolonged periods. Floating microballoons are hollow microspheres prepared using polymers such as ethyl cellulose and hydroxypropyl methylcellulose (HPMC). Their hollow internal cavity enables them to float on gastric contents, thereby extending gastric residence time and facilitating controlled drug release. In addition, microballoons provide uniform drug distribution, high encapsulation efficiency, improved stability, and reduced risk of dose dumping compared with conventional dosage forms.[8,9]

The formulation of Tegoprazan into gastroretentive floating microballoons offers a promising strategy to enhance its therapeutic performance. Prolonged gastric residence allows sustained release of the drug at the site of action, resulting in continuous inhibition of gastric acid secretion and improved healing of gastric ulcers. Such a delivery system may also reduce the frequency of administration, improve patient adherence, and minimize adverse effects associated with repeated dosing. The selection of suitable polymers and optimization of formulation variables are essential to achieve desired floating characteristics, drug entrapment efficiency, and controlled release behavior.[10]

Characterization of gastroretentive microballoons is an important step in ensuring formulation quality and performance. Various physicochemical parameters including particle size, percentage yield, drug entrapment efficiency, buoyancy, swelling index, surface morphology, flow properties, in vitro drug release, and stability are evaluated to determine the suitability of the developed formulation. Advanced analytical techniques such as Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), Powder X-ray Diffraction (PXRD), and Scanning Electron Microscopy (SEM) are commonly employed to investigate drug–polymer compatibility, crystallinity, thermal behavior, and surface characteristics.[11]

The present study aims to develop and characterize gastroretentive floating microballoons of Tegoprazan using suitable polymeric carriers to achieve prolonged gastric retention and sustained drug release. The optimized formulation is expected to enhance antiulcer activity by maintaining effective drug concentration in the stomach for an extended period, thereby improving gastric mucosal protection and ulcer healing. The successful development of this gastroretentive delivery system may provide a promising alternative to conventional oral formulations for the effective management of peptic ulcer disease and other acid-related gastrointestinal disorders.[12,13]

Methodology:

Characterization of drug

i) Bulk Density: To determine the bulk density of a powder, the volume of a known mass of the powder is measured.Before this measurement, the powder sample is first passed through a sieve with a mesh size of number 40 and then placed into a graduated measuring cylinder.[13]

ii) Particle Size Analysis of Drug: In this study, the average particle size, specifically the projected diameter, of the drug was determined using optical microscopy with an electron microscope.The eyepiece micrometer was calibrated using a stage micrometer.A small amount of the drug powder was placed onto a glass slide to prepare a sample.A drop of paraffin oil was added to the powder to create a dispersion.A thin smear of the drug dispersion was then spread over the glass slide.The slide was examined under the microscope at various magnification levels, and the particle size was recorded in terms of eyepiece divisions.[14]

iii) Flow Properties of Drug: The flowability of the drug powder was assessed by determining the angle

of repose.A measured amount of the drug sample was let flow through a funnel that was securely attached to a stand, allowing the powder to form a conical pile.The average height and average diameter of the resulting pile were then measured.[15,16]

iv) Partition coefficient: Equal volumes, specifically 10 ml each of buffer with a pH of 1.2 and n-octanol, were added to a 50 ml stoppered separating funnel containing 10 mg of the drug. The mixture was allowed to stand for 24 hours at room temperature with periodic shaking.After this time, the two phases were separated, and the concentration of the drug in the aqueous phase was determined using spectrophotometric analysis.The partition coefficient was then calculated and recorded.[17-19]

Factorial design and optimization of independent variables

This field involves modifying a process to achieve the best possible results for certain parameters while following specific limitations. Common objectives in this area include reducing costs, increasing production capacity, and improving efficiency. It is a key quantitative method used in making decisions within industries. Typically, older optimization techniques focus on changing one variable at a time, as this approach is simpler from a statistical standpoint. Yet, in many situations, two variables may be connected, making it difficult or inaccurate to study them separately using traditional methods. To address this, a 3^2 full factorial design was used to optimize the variables.[20,21]

The Three-Level design

The three-level design is represented as a 3k factorial design, which involves considering k factors, each at three distinct levels. These levels are commonly referred to as low, intermediate, and high. Numerically, these levels are represented as -1, 0, and 1.In this experiment, Drug Polymer ratio (X1) and Stirring Speed (X2) were identified as independent variables, while drug loading (Y1), particle size (Y2), and Drug release (Y3) were selected as response variables. In the factorial design batches, EC1 to EC9, the amount of drug was kept constant. The Polymer concentration and stirring speed were adjusted according to the formulation. The impact of the independent variables (X1 and X2) on the characteristics of the microballoons is summarized through the response variables (Y1, Y2, and Y3).A polynomial equation was developed, and non-significant interactive terms were removed based on the ANOVA results to explain the influence of the independent variables on drug loading, particle size, and drug release. The responses (Y) were measured for each trial and then either.[22]

Characterization of microballoons

Buoyancy Study and Floating Behavior of microballoons

Microballoons of 100 mg were placed on the surface of a 200 ml glass beaker containing 100 ml of 0.1 N HCl with 0.02% v/v Tween 80. The mixture was left undisturbed for 12 hours. Floating microballoons were collected by decantation, while the sinking particles were separated through filtration. Both types of particles were dried in a dessicator until they reached a constant weight. The weights of both fractions were recorded, and the percentage buoyancy was calculated. The floating behavior of all the formulation batches was evaluated by measuring their floating time in pH 1.2 medium.[23]

In-vitro drug release study

In-vitro dissolution studies were conducted using the US Pharmacopoeia XXIII Dissolution apparatus of type I, which is a basket-type setup.A precisely weighed amount of the sample, equivalent to 7.5 mg of Tegoprazan-loaded microballoons, was placed in 900 ml of hydrochloric acid buffer at pH 1.2.The buffer was maintained at a temperature of 37.0°C ± 0.5°C and stirred at a speed of 50 revolutions per minute.At various time intervals, 5 ml of the sample solution was removed, and the same volume was replaced with fresh dissolution medium kept at 37°C.The collected samples were filtered and analyzed using a UV-Visible spectrophotometer, with the hydrochloric acid buffer at pH 1.2 used as the reference blank.[24]

In-vivo Evaluation of Optimized microballoons

Ethanol induced ulcer model:

The stable rats were divided into four groups, each containing five animals.All animals in the research groups were orally administered 1 ml per 100 grams of body weight of an 80% ethanol solution, which is known to induce stomach lesions.The dosing schedule for the study is outlined as follows: Group 1: Animals received 10 ml/kg of standard saline solution and served as the negative control group. Group 2: Animals were orally given 80% ethanol and acted as the favorable control group. Group 3: Animals were administered 1 ml/100gm of ethanol and simultaneously treated with 5 mg/kg of pure tegoprazan. Group 4: Animals were given ethanol and also received a formulation equivalent to 5 mg

of tegoprazan. The formulations were administered 30 minutes prior to ethanol, based on the gastric emptying rate in fasted rats. One hour after the formulation treatment, the animals were humanely euthanized. The stomachs were then removed and opened along the greater curvature. Using a magnifying glass, the gastric lesions were examined, and the ulcer index (UI) was measured after thoroughly washing the stomach with normal saline.[25,26]

In-Vivo bioavailability studies (Pharmacokinetic Analysis)

The study on bioavailability was conducted using albino rats of both sexes. Prior to the experiment, the animals had free access to water and were divided into three groups, each containing five rats. The dose of the pure drug and the formulated microballoons was administered orally at a dosage of 20 mg per kilogram of body weight. This was done after the animals were briefly anesthetized with diethyl ether. Blood samples of 0.3 ml were collected from the retro-orbital plexus at predetermined time intervals of 0.1, 1.5, 2, 4, 8, 12, and 24 hours. The samples were placed in heparinized tubes. For 10 minutes, the blood samples were centrifuged at 4000 rpm, and the separated samples were stored at -20°C prior to further processing.[27]

Results:

Micromeritic properties of the Tegoprazan

Table 1: Micromeritic properties of the Tegoprazan

Sr. No	Drug	Bulk Density (g/cc)	Avg Particle size (µm)	Angle of repose (θ^0)
01	**Tegoprazan**	0.7±0.02	26.2±0.03	32.10±0.012

Table 2: Partition Coefficient of the Tegoprazan

S. No.	Aqueous phase	Oily Phase	Tegoprazan
01	Distilled Water	n-Octanol	**3.18**
02	Buffer pH 1.2	n-Octanol	3.44
03	Buffer pH 6.8	n-Octanol	3.43

Table 3: Formulation of 3^2factorial batches for Microballoons

Batch Code	Drug mg	Independent variables		Dependant variables		
		Polymer Ratio (X1)	RPM (X2)	Loading% (Y1)	Particle size (um) (Y2)	%Drug Release (Y3)
TG1	50	-1	0	76.5±0.45	142.89	91.11±0.09
TG2	50	+1	0	90.5±0.40	178.64	79.01±0.18
TG3	50	+1	-1	91.1±0.15	183.23	78.66±0.00
TG4	50	0	-1	82.1±0.40	172.19	85.55±0.09
TG5	50	+1	+1	91.5±0.10	162.55	78.20±0.27
TG6	50	0	+1	86.97±0.36	161.81	84.46±0.09
TG7	50	-1	-1	75.16±0.2	157.76	91.08±0.12
TG8	50	0	0	83.1±0.38	165.96	82.72±0.23
TG9	50	-1	+1	77.16±0.53	137.40	89.11±0.13

Code Value	Actual Values X1	Actual Values X2	Variable Levels
-1	200	500	**Low**
0	300	1000	**Medium**
+1	400	1500	**High**

** n = 3, all values ± standard deviation, statistically significant at 0.05 level. X1 is polymer concentration (mg), and X2 is stirring speed (rpm). All batches contained 50 mg Tegoprazan.*

Characterization of Microballoons

Table 4: Micromeritic Properties of microballoons

Batch Code	Tapped Density g/cc	Fluff Density g/cc	True Density	Angle of Repose (θ)	Carr's Index	Hausner's ratio
TG1	0.831±0.002	0.725±0.005	1.33±0.006	26.0±0.058	12.72±0.686	2.56±0.021
TG2	0.803±0.002	0.682±0.002	1.38±0.012	24.9±0.058	15.14±0.480	1.17±0.005
TG3	0.805±0.003	0.692±0.003	1.39±0.006	26.4±0.021	14.05±0.508	1.17±0.011
TG4	0.821±0.004	0.720±0.003	1.37±0.010	26.1±0.069	12.33±0.136	1.17±0.007
TG5	0.803±0.004	0.683±0.002	1.25±0.006	21.0±0.035	15.02±0.417	1.13±0.005
TG6	0.781±0.004	0.661±0.004	1.29±0.006	18.4±0.061	15.32±0.040	1.14±0.012
TG7	0.805±0.004	0.689±0.002	1.28±0.006	18.4±0.006	14.49±0.522	1.15±0.010
TG8	0.777±0.005	0.654±0.002	1.26±0.006	29.3±0.057	15.78±0.757	1.20±0.008
TG9	0.804±0.004	0.687±0.002	1.26±0.006	19.4±0.006	15.49±0.522	1.45±0.010

Cumulative Drug Release of drug loaded Microballoons formulations

Table 5: Cumulative drug release of drug loaded Microballoons formulations

Time	G1	G2	G3	G4	G5	G6	G7		G9
0.5	12.65±1.10	10.09±0.555	14.95±0.333	14.45±0.111	14.30±0.008	16.30±0.466	21.34±0.16	15.34±0.663	15.14±1.04
1	25.12±0.600	16.14±1.133	21.80±1.266	25.22±0.333	24.57±0.666	22.74±1.333	29.88±0.29	30.35±0.002	31.79±0.733
2	30.33±0.85	23.35±0.667	33.04±1.399	34.36±1.411	33.43±0.334	36.90±0.933	38.49±0.38	37.87±0.93	39.10±0.500
3	41.10±0.622	33.13±0.755	42.48±0.866	40.21±1.109	42.20±0.733	48.50±0.222	56.62±0.71	51.92±0.722	55.16±0.388
4	51.61±0.611	41.64±1.266	50.62±0.733	49.55±0.588	50.51±1.066	53.39±0.700	68.37±0.37	59.45±0.533	62.06±0.900
5	56.37±0.300	57.66±1.244	58.92±0.655	58.03±0.111	57.92±1.733	60.91±0.277	74.91±0.64	65.10±0.322	69.28±0.822
6	72.82±0.	65.87±0.	65.71±1.	68.16±0.	62.48±0.	69.92±1.	79.27±0.42	71.37±1.	74.69±1.

	38	08	13	43	63	21		41	03
7	83.55±0.24	73.76±0.12	74.03±0.37	79.49±0.51	69.94±0.31	79.08±0.35	86.53±0.46	76.28±0.37	82.52±0.02
8	91.18±1.2	79.91±0.62	80.27±0.94	85.29±0.18	78.20±0.22	86.75±0.65	91.85±1.04	83.47±0.54	89.11±0.57

Table 6: Consolidated result of microballoon formulations

BatchCode	% Drug Loading	Particle Size	% Drug Release	% Buoyancy	FLT (sec)	Floating duration (h)
TG1	76.5±0.45	142.89	91.18±1.2	84.37±1.86	56.7±2.57	11.38
TG2	90.5±0.40	178.64	79.91±0.62	91.37±1.31	48.4±2.51	13.6
TG3	91.1±0.15	183.23	80.27±0.94	92.03±0.93	46.6±1.73	11.6
TG4	82.1±	172.	85.29±0.1	89.33±	56.4±	10.4
	0.40	19	8	0.81	1.68	
TG5	91.5±0.10	162.55	78.20±0.22	92.10±0.26	35.6±2.48	9.6
TG6	86.97±0.36	161.81	86.75±0.65	87.13±0.75	39.8±2.08	14.2
TG7	75.16±0.2	157.76	91.85±1.04	87.83±0.60	55.4±1.76	14.9
TG8	83.1±0.38	165.96	83.47±0.54	88.10±0.61	49.6±2.35	15.3
TG9	77.16±0.53	137.40	89.11±0.57	87.90±0.70	44.1±1.45	17.8

Antiulcer activity of the microballoon formulation in ethanol induced ulcer

Table7 : Antiulcer activity of the microballoon formulation in ethanol induced ulcer

Groups	Induction	Dose	Ulcer Index
Group –I	Normal saline	10 ml/kg	1.090 ±0.04
Group –II	Ethanol(Diseased)	1ml/gm	23.92 ± 0.58
Group –III	Pure Tegoprazan(standard)	5mg/kg	8.12 ± 0.28
Group –IV	Formulation (Tegoprazan loaded)	5mg/kg	4.83± 0.86

The ulcer score in the ethanol-treated group was 23.92 ± 0.58, while the normal saline-treated group did not show any ulcers. The ulcer index of the formulation was significantly lower than that of the ethanol-treated group. However, the pure drug-treated group showed a much greater reduction in ulcer index compared to the positive control group. The pure Tegoprazan demonstrated less effectiveness in preventing mucosal damage compared to the microballoons. The improved

effectiveness of the microballoons was attributed to their sustained release and gastroretentive properties, indicating that the microballoons help in strengthening and protecting the gastric mucosal barrier.

***In vivo* bioavailability study:**

The goal of designing a dosage form is to ensure the drug is available to the body and effectively produces its therapeutic effect. A bioavailability study of the floating microballoons formulation was conducted using a rat model. The rat model is commonly used for studying the bioavailability of various drugs. Following oral administration of pure Tegoprazan and Tegoprazan-loaded floating microballoons at a dose of 5mg/kg to rats, the plasma drug concentration over time was recorded. The plasma concentration–time profile was established.

Table 8: Phamacokinetic Profile

Parameters	Tegoprazan Standard	Formulation
C_{max}	575.14 ± 55.43	206.58 ± 7.71
T_{max}	2	8
$AUC_{(0-24)}$	2064.07	2272.22
Fr	_	110.07

Conclusion

The present study successfully developed and characterized gastroretentive floating microballoons of Tegoprazan with the objective of enhancing gastric residence time, achieving sustained drug release, and improving antiulcer efficacy. The microballoons were formulated using the emulsion solvent diffusion technique with suitable polymer combinations, resulting in hollow, spherical particles possessing excellent floating characteristics. The developed formulations demonstrated desirable physicochemical properties, indicating the suitability of this approach for gastroretentive drug delivery. In vitro buoyancy studies demonstrated that the optimized formulation remained floating in simulated gastric fluid for an extended duration, thereby increasing the gastric residence time of the dosage form. Drug release studies showed a controlled and sustained release profile over several hours, suggesting that the selected polymers effectively regulated the release of Tegoprazan. Release kinetic analysis indicated that the optimized formulation followed controlled-release behavior, making it suitable for prolonged therapeutic action in the stomach. The gastroretentive microballoons are expected to enhance the antiulcer activity of Tegoprazan by maintaining prolonged contact with the gastric mucosa and providing continuous suppression of gastric acid secretion. Sustained drug release within the stomach may improve ulcer healing, reduce fluctuations in drug concentration, decrease dosing frequency, and improve patient compliance. These advantages highlight the potential of floating microballoons as an effective oral drug delivery system for the management of peptic ulcer disease and other acid-related gastrointestinal disorders. Overall, the findings of this study demonstrate that gastroretentive floating microballoons are a promising carrier system for Tegoprazan. The optimized formulation exhibited excellent floating ability, favorable physicochemical characteristics, high encapsulation efficiency, and sustained drug release, indicating its potential to improve therapeutic outcomes compared with conventional oral formulations. Further in vivo pharmacokinetic, pharmacodynamic, and clinical studies are recommended to establish the long-term safety, efficacy, and commercial feasibility of the developed gastroretentive microballoon formulation.

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