Formulation and Characterization of Tegoprazan Loaded Gastroretentive Microballoons

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Abstract

Tegoprazan is a novel potassium-competitive acid blocker (P-CAB) used in the management of gastric acid-related disorders, including peptic ulcers and gastroesophageal reflux disease. However, maintaining prolonged gastric residence is essential to maximize its local therapeutic effect and improve treatment outcomes. The present study aims to formulate and characterize tegoprazan-loaded gastroretentive microballoons to enhance gastric retention, sustain drug release, and improve antiulcer activity. The microballoons were prepared using the solvent evaporation technique with suitable polymers, such as ethyl cellulose and hydroxypropyl methylcellulose (HPMC), to obtain hollow, low-density particles capable of floating in gastric fluid. The prepared formulations were evaluated for particle size, percentage yield, drug entrapment efficiency, buoyancy, surface morphology, in vitro drug release, and compatibility using analytical techniques including Fourier Transform Infrared Spectroscopy (FTIR). The optimized formulation exhibited high entrapment efficiency, excellent floating ability for more than 12 hours, and sustained drug release following controlled-release kinetics. The prolonged gastric residence and controlled drug release are expected to enhance the bioavailability and antiulcer efficacy of tegoprazan while reducing dosing frequency and improving patient compliance. These findings suggest that gastroretentive microballoons represent a promising oral drug delivery system for optimizing the therapeutic performance of tegoprazan in the treatment of gastric ulcers and other acid-related disorders.

Keywords: Tegoprazan, Pharmacokinetics, antiulcer activity, bioavailability, controlled-release kinetics, microballoons , gastric ulcers

Introduction

Oral administration remains the most common and convenient route for drug delivery. In recent years, controlled-release oral formulations have gained significant attention in pharmaceutical development as they offer improved therapeutic outcomes. These systems enhance patient adherence and provide greater flexibility in dosage form design. Compounds characterized by low bioavailability or short biological half-lives are cleared rapidly from the systemic circulation, often requiring frequent administration to maintain effective concentrations. To mitigate this, oral formulations designed for sustained release within the gastrointestinal tract are developed to ensure stable plasma levels and consistent therapeutic effects. Gastro-retentive drug delivery systems are specifically engineered to prolong the residence time of a dosage form within the stomach. By remaining in the gastric environment and releasing the drug slowly, these systems ensure a continuous supply of the medication to its primary absorption sites in the upper gastrointestinal tract. This approach is particularly advantageous for treating localized gastric pathologies. High concentrations of the drug at the gastric mucosa can facilitate the eradication of Helicobacter pylori residing deep within the tissue, which is essential for treating gastric and duodenal ulcers, gastritis, and esophagitis. Such targeted delivery may also lower the risk of developing gastric cancer.(1,2)

However, prolonged gastric retention is not suitable for all medications. Drugs that cause mucosal irritation, such as aspirin and other non-steroidal anti-inflammatory agents, should not be formulated into gastro-retentive systems. Similarly, these systems are inappropriate for drugs that degrade in acidic conditions. Furthermore, medications that exhibit uniform absorption across the entire gastrointestinal tract, such as isosorbide dinitrate, derive no additional therapeutic benefit from extended gastric residence.(3,4)

Microballoons:

Microballoons, also known as hollow microspheres, are a multiple-unit gastroretentive drug delivery system designed to prolong the residence time of drugs in the stomach. They are spherical, free-flowing particles with an internal hollow cavity that imparts low density, allowing them to float on gastric fluids without affecting the

normal gastric emptying process. Due to their buoyant nature, microballoons remain in the stomach for an extended period, enabling sustained drug release and improving the therapeutic efficacy of drugs that are absorbed primarily in the upper gastrointestinal tract or intended for local action in the stomach.

The principle of microballoons is based on buoyancy. These hollow particles have a density lower than that of gastric fluid (approximately 1.004 g/cm³), which enables them to float on the stomach contents for several hours. During this floating period, the drug is released gradually from the polymeric matrix by diffusion, erosion, or a combination of both mechanisms. Prolonged gastric retention enhances drug absorption, reduces fluctuations in plasma drug concentration, and improves overall bioavailability.(5)

Microballoons are generally prepared using techniques such as solvent evaporation, emulsion solvent diffusion, solvent extraction, spray drying, and ionotropic gelation. Among these, the emulsion solvent diffusion and solvent evaporation methods are the most commonly employed because they produce uniform hollow particles with good encapsulation efficiency and controlled release characteristics. The selection of preparation method depends on the physicochemical properties of the drug, the polymers used, and the desired release profile.[6]

A variety of natural and synthetic polymers are utilized in the formulation of microballoons. Hydrophobic polymers such as ethyl cellulose provide structural integrity and sustained drug release, while hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), Eudragit, sodium alginate, chitosan, and carbopol help regulate drug release and improve floating behavior. The type and concentration of polymers significantly influence particle size, drug loading, buoyancy, and release kinetics. (6,7)

Microballoons offer several advantages over conventional oral dosage forms. They provide prolonged gastric residence, sustained and controlled drug release, improved bioavailability, reduced dosing frequency, minimized plasma concentration fluctuations, and enhanced patient compliance. Because they are multiple-unit dosage forms, they are distributed more uniformly throughout the stomach, reducing the risk of dose dumping and local irritation while providing more predictable drug absorption. (8)

Despite these advantages, microballoons have certain limitations. Their preparation requires careful optimization of formulation variables and process parameters to achieve adequate buoyancy and drug entrapment efficiency. The manufacturing process may be relatively complex, and the floating ability can be influenced by factors such as gastric motility, food intake, and patient-specific physiological conditions. Additionally, microballoons are not suitable for drugs that are unstable in acidic conditions or those that are primarily absorbed in the lower gastrointestinal tract.(9)

Microballoons have been widely investigated for the delivery of drugs used in the treatment of gastric and duodenal ulcers, gastroesophageal reflux disease (GERD), *Helicobacter pylori* infection, and other gastrointestinal disorders. They are also useful for drugs with a narrow absorption window in the upper gastrointestinal tract, such as certain antibiotics, antihypertensive agents, and anti-inflammatory drugs. In the case of tegoprazan, gastroretentive microballoons can prolong the drug's residence in the stomach, sustain its release, improve local therapeutic action, and enhance antiulcer efficacy while reducing the frequency of administration. Overall, gastroretentive microballoons represent an effective and promising drug delivery approach for improving the therapeutic performance of drugs requiring prolonged gastric retention. Their ability to combine buoyancy with controlled drug release makes them an attractive formulation strategy for enhancing bioavailability, maintaining consistent drug levels, and improving treatment outcomes in gastric acid-related disorders. (10,11)

Methodology

Formulation of Tegoprazan loaded Microballoons

The methodology employed in this study involved the multiple emulsion technique, specifically the W/O/W (water-in-oil-in-water) process.It is essential to consider all relevant factors during the emulsification process, as they can significantly affect the outcome.Key factors include temperature, the intensity of agitation, and the concentration of emulsifiers.Microballoons were synthesized using the multiple emulsion technique to achieve the desired W/O/W emulsion structure. (12)In the initial batches, a specific amount of Tegoprazan and Ethyl Cellulose, mixed in various proportions, was dissolved in a measured volume of 10 mL of Dichloromethane.A fixed volume of water, 2 mL, was used as the internal phase and added to the drug-polymer solution to form a water-in-oil (W/O) type of primary emulsion.This primary emulsion was then subjected to re-emulsification in an aqueous phase containing different concentrations of Tween 80 to create a multiple water-in-oil-in-water (W/O/W) emulsion.The resulting mixture was stirred at a speed of 1000 rpm using a three-bladed propeller for 30 minutes at a temperature of 40°C to produce microballoons.The microballoons were subsequently separated by filtration through a sintered glass filter and dried in an oven at 40°C. (13-15)

Table 1: Formulation of microballoons preliminary trial batches

Batch Code	Drug:Polymer	Tween 80 %	Temperature O_C	Vol. of water in Emulsion (ml)
TF1	50:100	1	30	1
TF2	50:200	1	30	1
TF3	50:300	1	30	1

TF4	50:100	2	40	2
TF5	50:200	2	40	2
TF6	50:300	2	40	2
TF7	50:100	3	50	3
TF8	50:200	3	50	3
TF9	50:300	3	50	3

Yield of Microballoons

The microballoons from all batches were precisely measured. The amount of microballoons was then divided by the total quantity of all excipients and drug used in making the microballoons, resulting in the overall percentage yield of the floating microballoons.This experiment was carried out three times, and the average percentage yield was considered for analysis. (16)

Buoyancy

A sample of 100 mg of microballoons was placed on the surface of a 200 ml glass beaker containing 100 ml of 0.1 N hydrochloric acid with 0.02% v/v Tween 80.The mixture was left to stand for 12 hours overnight. The floating microballoons were separated by decantation, while the sinking particles were collected through filtration. Both types of particles were dried in a dessicator until they reached a constant weight. The mass of each fraction was then measured, and the percentage buoyancy was calculated using the provided formula.The results documented accordingly. (17)

Floating Time

Microspheres floating in a fluid to maintain their buoyancy is the definition. The microballoons float for as long as it took them to float after placing them in a beaker with 200 cc of 0.1N HCl. The time was noted. (18)

Factorial design and optimization of independent variables

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, TG1 to TG9, 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. (19,20)

Characterization of microballoons

Particle Size Analysis of Factorial Batches

Particle size analysis of the microballoons was carried out using optical microscopy with an electric microscope. This technique provides a direct measurement of the number distribution, which can be subsequently converted into weight distribution. The particle size of the microballoons was determined using a stage micrometer and an eyepiece micrometer. The eyepiece of the microscope was equipped with an eyepiece micrometer, which was calibrated against a stage micrometer. In this study, the projected diameter of the particles was expressed as the geometric mean. To prepare the sample slide, a small quantity of microballoons was placed on the slide. A drop of paraffin oil was added to create a uniform dispersion. A thin smear of this dispersion was spread over the glass slide. The slide was examined under the microscope using a 10X magnification lens. At least 200 particles were counted, and their sizes were recorded based on the number of eyepiece divisions they occupied. These measurements were then converted into micrometers using the eyepiece calibration factor. (21,22)

Drug loading of factorial batches

The amount of drug entrapped was determined by first crushing the microballoons using a mortar and pestle. The resulting powder was then immersed in 0.1 N hydrochloric acid. The mixture was sonicated for 15 minutes and allowed to stand at room temperature overnight. The suspension was filtered using Whatman filter paper, and the residue was washed to bring the volume up to the original. The filtrate was then analyzed using a UV spectrophotometer. The absorbance values were measured against a blank. The quantity of Tegoprazan encapsulated was calculated based on a standard calibration curve. The results were then recorded. (23,24)

Flow Properties of Microballoons

Irregular flow of microspheres can lead to the production of dosage forms with uneven weights.Consequently, achieving consistent content uniformity and accurate dosing becomes difficult. The flow characteristics of these

microspheres depend on factors such as their size, shape, porosity, and density. These flow properties can be assessed using parameters like the angle of repose, Carr's compressibility index, and Hausner's ratio.

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. (25)

Result

Formulation, characterization and optimization microballoons

The methodology used in this study involved the multiple emulsion technique (W/O/W).In the initial batches, a specific amount of Tegoprazan and Ethyl Cellulose, in various ratios, was dissolved in a measured volume of Dichloromethane, which was 10 ml.A predetermined volume of water, 2 ml, was added as the internal phase to the drug-polymer solution to form a W/O type primary emulsion.This primary emulsion was then re-emulsified in an aqueous phase containing different concentrations of Tween 80 to create a multiple W/O/W emulsion.The resulting mixture was stirred at 1000 rpm using a three-bladed propeller for 30 minutes at 40°C to produce microballoons.These microballoons were subsequently separated by filtration through a sintered glass filter and dried in an oven at 40°C.

Table 2: Result of the Preliminary Trial Batches.

Code	Yield %	Drug loading(%)	Buoyancy(%)
TF1	41.73±0.80	31.23±0.67	75.53±1.17
TF2	62.23±1.36	56.49±0.75	79.13±0.64
TF3	72.00±0.56	63.60±0.72	81.87±0.64
TF4	72.27±0.68	65.13±0.35	94.97±0.57
TF5	81.90±0.50	77.60±0.82	90.90±0.53
TF6	89.10±0.53	85.40±0.44	91.93±0.61
TF7	56.20±1.06	46.97±0.50	73.93±0.51
TF8	69.93±0.5	63.73±0.86	77.87±0.55
TF9	77.37±0.55	75.97±1.36	82±1.03

Factorial design and optimization of independent variables.

The three-level design is written as a 3k factorial design. It means k factors are considered, each at 3 levels. These are usually referred to as low, intermediate and high levels. These levels are numerically expressed as -1, 0 and +1. In this experiment, Drug Polymer ratio (X1), and Stirring Speed (X2) were considered as independent variable; whereas drug loading (Y1), particle size (Y2) and Drug release (Y3) were selected as a response.

In factorial design batches, EC1 to EC9, the quantity of drug was kept constant. The Polymer concentration and stirring speed both were used as per the formulation table 18. The effect of independent variables (X1&X2) on characteristics of the microballoons is summarized as response (Y1, Y2 and Y3).

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

Table 4: Consolidated result of microballoon formulations

Batch Code	**% 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±0.40	172.19	85.29±0.18	89.33±0.81	56.4± 1.68	10.4
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

Conclusion

The present study successfully formulated, characterized, and optimized tegoprazan-loaded gastroretentive microballoons as a floating drug delivery system for prolonged gastric residence and sustained drug release. The optimized formulation exhibited desirable physicochemical properties, including appropriate particle size, high production yield, satisfactory drug entrapment efficiency, and good flow characteristics. The hollow spherical morphology of the microballoons contributed to excellent buoyancy, enabling them to remain afloat in simulated gastric fluid for an extended period.

The in vitro release study demonstrated a controlled and sustained release of tegoprazan over an extended duration, indicating that the selected polymeric matrix effectively regulated drug diffusion. The optimized formulation provided a significantly slower and more uniform drug release profile than the pure drug, which is expected to maintain therapeutic drug concentrations for a longer period while reducing the frequency of dosing. Drug release kinetics suggested that the formulation followed a controlled-release mechanism suitable for gastroretentive delivery.

The gastric retention evaluation confirmed that the microballoons possessed excellent floating ability with a short floating lag time and prolonged total floating duration. Their low density and hollow structure enabled them to remain buoyant in gastric fluid, thereby increasing gastric residence time. This prolonged retention is expected to improve the local availability of tegoprazan in the stomach and enhance its therapeutic efficacy in the treatment of acid-related disorders and peptic ulcers.The TG5 is optimized formulation for prolonged retention in gastric fluid .The optimized formulation successfully combined prolonged gastric retention with sustained drug release, which has the potential to improve drug bioavailability, enhance antiulcer activity, reduce dosing frequency, and improve patient compliance

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