RESEARCH PAPER

Design and In Vitro Characterization of Ilaprazole Microspheres Prepared by Ionotropic Gelation to Increase Bioavailability

Patil Dipak Ashok[1*], Phool Singh Yaduwanshi[1], Kavita R Loksh[1]

[1]IES Institute of Pharmacy, IES University, Bhopal, Madhya Pradesh- 462044

ABSTRACT

Floating microspheres are a promising gastroretentive drug delivery system designed to prolong gastric residence time and improve the bioavailability of drugs with narrow absorption windows, poor intestinal stability, or local action in the stomach. These low-density multiparticulate systems remain buoyant on gastric fluids for extended periods, enabling sustained and controlled drug release. Floating microspheres are commonly prepared using techniques ionotropic gelation method. Ilaprazole-loaded microspheres were prepared by the ionotropic gelation technique using sodium alginate and Eudragit polymers to achieve controlled gastric retention and sustained drug release. The formulated microspheres exhibited satisfactory entrapment efficiency, particle size distribution, buoyancy, and prolonged release characteristics, demonstrating their potential as an effective gastroretentive drug delivery system. Their performance is evaluated based on particle size, buoyancy, drug entrapment efficiency, surface morphology, and in vitro drug release characteristics. Advantages include reduced dosing frequency, enhanced therapeutic efficacy, improved patient compliance, and minimized fluctuations in plasma drug concentrations. The findings suggest that ionotropically gelled Ilaprazole microspheres represent a promising oral drug delivery system capable of enhancing bioavailability, prolonging therapeutic action, and improving patient compliance. Therefore, the developed microsphere formulation may serve as an effective alternative to conventional dosage forms for the treatment of acid-related gastrointestinal disorders.

Keywords: Ilaprazole, Microspheres, Ionotropic Gelation, Bioavailability Enhancement, Controlled Drug Release, Proton Pump Inhibitor, Oral Drug Delivery.

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INTRODUCTION:

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials [1]. Glass microspheres, polymer microspheres and ceramic microspheres are commercially available. Solid and hollow microspheres vary widely in density and, therefore, are used for different applications. Hollow microspheres are typically used as additives to lower the density of a material. Solid microspheres have numerous applications depending on material and size [2]. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. Thus, gastro retentive dosage forms, which prolong the residence time of the drugs in the stomach and improve their bioavailability, have been developed. A well-designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimal side effects [3]. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having a particle size less than 200 μm. Ionotropic gelation is based on the ability of polyelectrolytes to cross link in the presence of counter ions to form hydrogel beads also called as microsphere [4]. Microsphere are spherical crosslinked hydrophilic polymeric entity capable of extensive gelation and swelling in simulated biological fluids and the release of drug through it controlled by polymer relaxation. The hydrogel beads are produced by dropping a drug-loaded polymeric solution into the aqueous solution of polyvalent cations. The cations diffuse

into the drug-loaded polymeric drops, forming a three-dimensional lattice of ionically crosslinked moiety. Biomolecules can also be loaded into this microsphere under mild conditions to retain their three-dimensional structure. In Ionotropic gelation technique, there has been a growing interest in the use of natural polymers as drug carriers due to their biocompatibility and biodegradability [5]. The natural or semisynthetic polymers i.e. Alginates, Gellan gum, Chitosan, Pectin and Carboxymethyl cellulose are widely use for the encapsulation of drug by this technique. These natural polyelectrolytes contain certain anions/cations on their chemical structure, these anions/cations forms meshwork structure by combining with the counter ions and induce gelation by cross linking. In spite of having a property of coating on the drug core these natural polymers also act as release rate retardant [6]. Ionotropic gelation under a high voltage electrostatic field is a modified ionotropic gelation method by combining it with a high voltage electrostatic field to prepare protein-loaded chitosan microspheres. This is new method for sustain delivery of Bovine Serum Albumin (BSA) by encapsulating in chitosan microsphere also reported that the microspheres exhibited good sphericity and dispersibility when the mixture of sodium tripolyphosphate (TPP) and ethanol was applied as coagulation solution [7]. The results from the literature survey suggest that ionotropic gelation method combined with a high voltage electrostatic field is an effective method for sustained delivery of protein by microsphere**.** Ilaprazole is a substituted benzimidazole prodrug with selective and irreversible proton pump inhibitor activity. A weak base, ilaprazole accumulates in the acidic environment of the secretory canaliculus of the gastric parietal cell where it is converted to an active sulfenamide form that binds to cysteine sulfhydryl groups on the luminal aspect of the proton pump hydrogen-potassium adenosine triphosphatase (H+/K+ ATPase), thereby inhibiting the pump's activity and the parietal cell secretion of H+ ions into the gastric lumen, the final step in gastric acid production [8]. The present study aimed to formulate and evaluate Ilaprazole-loaded microspheres using the ionotropic gelation technique to enhance drug bioavailability and achieve controlled drug release. Microspheres were prepared using sodium alginate as the primary polymer in combination with suitable mucoadhesive polymers and calcium chloride as the cross-linking agent. The objective of the present study was to develop microspheres of ilaprazole sodium by Ionotropic Gelation Technique using hydrophilic carrier to sustain the release so as to reduce the frequency of dosing and to improve patient compliance in SGF in stomach for increase bioavailability of drug candidate.

Material And Methods

Preparation of calibration curve: An accurately weighed quantity of Ilaprazole (50 mg) was transferred into a 50 mL volumetric flask containing 0.1 N HCl. The solution was sonicated for 20 min in a bath sonicator to ensure complete dissolution of the drug, and the volume was adjusted to obtain a stock solution of concentration 1000 µg/mL From the stock solution, 1 mL was withdrawn and transferred into a 100 mL volumetric flask. The volume was made up to the mark with 0.1 N HCl and sonicated for 20 min, yielding a working standard solution of 10 µg/mL. Aliquots of 2, 4, 6, 8, and 10 mL were then transferred separately into 10 mL volumetric flasks and diluted to volume with 0.1 N HCl to obtain solutions of appropriate concentrations. The absorbance of each solution was measured at 305 nm using a UV–Visible spectrophotometer, with 0.1 N HCl used as the blank. A standard calibration curve was constructed by plotting concentration (µg/mL) on the X-axis against the corresponding absorbance values on the Y-axis [9].

Preparation of Ilaprazole-loaded floating microspheres: Ilaprazole-loaded floating microspheres were prepared using the ionotropic gelation technique. Initially, the required quantities of polymers, namely sodium alginate, Eudragit S100, Eudragit L100 were dissolved in distilled water under continuous stirring to obtain a homogeneous polymeric solution. Ilaprazole was then gradually dispersed into the polymer solution with constant stirring to ensure uniform distribution of the drug. The release-retarding polymers were incorporated at different concentrations according to the formulation design and mixed thoroughly to obtain a uniform suspension. Sodium bicarbonate was added as a gas-generating agent to impart buoyancy to the microspheres. The resulting dispersion was subsequently extruded dropwise through a 23-gauge syringe needle into a calcium chloride solution serving as the cross-linking medium. Upon contact with the calcium chloride solution, spherical microspheres were formed through ionic gelation. The formed microspheres were allowed to remain in the cross-linking solution for 30 minutes to achieve complete hardening. Thereafter, the microspheres were collected by filtration, washed repeatedly with distilled water to remove excess calcium ions, and dried at room temperature [10].

Table 1: Various formulation of floating microspheres

Formulation Code	Ilaprazole (mg)	Sodium Alginate (% w/v)	Eudragit S100 (mg)	Eudragit L100 (mg)	Sodium Bicarbonate (mg)	Calcium Chloride (% w/v)
IIM1	10	10	50	30	50	2.5
IIM2	10	20	40	30	50	2.5
IIM3	10	30	30	30	50	2.5
IIM4	10	40	20	30	50	2.5
IIM5	10	50	10	30	50	2.5
IIM6	10	30	50	10	50	2.5
IIM7	10	30	40	20	50	2.5
IIM8	10	30	30	30	50	2.5
IIM9	10	30	20	40	50	2.5
IIM10	10	30	10	50	50	2.5

Evaluation of Ilaprazole Floating Microspheres

Particle Size Analysis: The particle size of the prepared microspheres was determined using an optical microscope (Besto Microscope, India) equipped with an ocular micrometer and a stage micrometer. Approximately 200–300 microspheres were randomly selected, and their diameters were measured. The mean particle size was calculated and expressed as the average diameter of the microspheres [11].

Micromeritic Properties: The prepared microspheres were evaluated for various micromeritic properties, including tapped density, true density, compressibility index, angle of repose, and Hausner's ratio.

Shape and Surface Morphology: The surface morphology and structural characteristics of the microspheres were examined using Scanning Electron Microscopy (SEM) (Philips XL-30, equipped with an image analysis system). Both freshly prepared and stored samples from different batches were analyzed [12].

Percentage Yield of Microspheres: The prepared microspheres were collected, dried, and accurately weighed. The percentage yield was calculated by comparing the actual weight of microspheres obtained with the total weight of drug and non-volatile excipients used in the formulation.

% Yield = (Actual Weight of Microspheres Obtained / Total Weight of Drug and Excipients) × 100

Drug Encapsulation Efficiency: Drug encapsulation efficiency was determined after removing the drug adsorbed on the surface of the microspheres. An accurately weighed quantity of microspheres was dispersed in 10 mL of phosphate buffer (pH 6.8) and shaken intermittently for 10 minutes. The suspension was centrifuged at 3000 rpm for 5 minutes, and the supernatant was collected. The sedimented microspheres were subjected to the same procedure once again. Both supernatants were combined and analyzed spectrophotometrically at 305 nm using a UV-visible spectrophotometer to determine the amount of surface drug. The encapsulation efficiency was calculated from the difference between the total drug content and surface drug content [13-14].

In Vitro Buoyancy Studies: The buoyancy behavior of the microspheres was evaluated using USP Dissolution Apparatus Type II (Paddle Method). Microspheres (100 mg) were dispersed in 900 mL of 0.1 N hydrochloric acid maintained at 37 ± 0.5°C and stirred at 100 rpm. After 12 hours, the floating and settled microspheres were collected separately, dried, and weighed [15]. The percentage buoyancy was calculated using the following equation:

% Buoyancy = (Weight of Floating Microspheres / Total Weight of Microspheres) × 100

In Vitro Drug Release Study: In vitro drug release studies were carried out using USP XXIII Dissolution Apparatus Type II (Paddle Method). Microspheres

equivalent to 10 mg of ilaprazole were accurately weighed and enclosed in a non-reactive muslin cloth with a mesh size smaller than the microspheres. The cloth was securely tied with a nylon thread, and a glass bead was placed inside to ensure immersion in the dissolution medium. The dissolution study was performed in 900 mL of 0.1 N HCl (pH 1.2) maintained at 37 ± 0.5°C and stirred at 100 rpm. At predetermined time intervals, 5 mL samples were withdrawn, filtered, appropriately diluted, and analyzed spectrophotometrically at 305 nm using a UV-visible spectrophotometer (Shimadzu UV-1800). An equal volume of fresh dissolution medium was added after each sampling to maintain sink conditions. All experiments were performed in triplicate, and the cumulative percentage drug release was calculated and reported as mean ± standard deviation [16].

RESULTS:

All formulations exhibited satisfactory flow properties. The angle of repose ranged from 24.5° to 31.8°, Carr's index from 11.2% to 18.4%, and Hausner ratio from 1.12 to 1.23, indicating good to excellent flow behavior suitable for further processing and capsule filling. Scanning electron microscopy revealed that the prepared microspheres were predominantly spherical with smooth external surfaces. Minor surface wrinkles and pores were observed due to the liberation of carbon dioxide generated by sodium bicarbonate during microsphere formation. Formulation IIM8 showed uniform spherical particles with minimal aggregation. The particle size of microspheres increased with increasing sodium alginate concentration due to enhanced viscosity of the polymeric solution. Percentage yield ranged from 78.3% to 88.7%, indicating efficient preparation of microspheres. Drug encapsulation efficiency increased with polymer concentration and was found highest in IIM5 (86.4%) and IIM8 (85.6%). The buoyancy study demonstrated prolonged floating behavior for all formulations, with buoyancy values ranging from 74.2% to 90.8% after 12 h. Increased alginate concentration improved floating ability by reducing microsphere density. In vitro drug release studies showed sustained release characteristics. Formulations containing lower polymer concentrations released drug more rapidly, whereas higher concentrations produced slower and more controlled release. Formulation IIM8 exhibited an optimal balance of buoyancy (89.4%), encapsulation efficiency (85.6%), and sustained drug release (89.6% at 12 h), suggesting its suitability as the optimized floating microsphere formulation for gastroretentive delivery of Ilaprazole.

Summary: The prepared ilaprazole floating microspheres demonstrated satisfactory micromeritic properties, with angle of repose, Carr's index, and Hausner ratio values indicating good to excellent flow behavior suitable for large-scale processing and capsule filling. Scanning electron microscopy confirmed the formation of predominantly spherical microspheres with smooth surfaces, while minor wrinkles and pores were attributed to carbon dioxide generation during preparation. Particle size increased with higher sodium alginate concentration due to increased solution viscosity. The percentage yield ranged from 78.3% to 88.7%, reflecting efficient microsphere production. Drug encapsulation efficiency improved with increasing polymer concentration, reaching maximum values in formulations IIM5 (86.4%) and IIM8 (85.6%). Buoyancy studies showed excellent floating characteristics, with buoyancy values ranging from 74.2% to 90.8% over 12 h. Increased alginate concentration enhanced floating ability by reducing microsphere density. In vitro drug release studies revealed sustained-release behavior, with higher polymer concentrations providing more controlled drug release. Among all formulations, IIM8 exhibited the most favorable performance, combining high buoyancy (89.4%), excellent encapsulation efficiency (85.6%), and sustained drug release (89.6% after 12 h). Therefore, IIM8 was identified as the optimized formulation for gastroretentive delivery of ilaprazole.

Table 2: Characterization formulation of floating microspheres

Formulation Code	Particle Size (µm)	Percentage Yield (%)	Encapsulation Efficiency (%)	Buoyancy after 12 h (%)	Drug Release at 12 h (%)
IIM1	312.4 ± 8.5	78.3 ± 1.4	72.5 ± 2.1	74.2 ± 1.8	96.8 ± 1.2
IIM2	328.7 ± 7.2	80.5 ± 1.2	75.8 ± 1.8	78.6 ± 1.5	94.5 ± 1.4
IIM3	346.2 ± 6.8	83.6 ± 1.6	79.4 ± 1.5	82.7 ± 1.7	91.3 ± 1.8
IIM4	361.8 ± 8.1	86.2 ± 1.3	83.6 ± 1.2	86.9 ± 1.4	88.5 ± 1.6

IIM5	379.5 ± 7.4	88.7 ± 1.5	86.4 ± 1.4	90.8 ± 1.3	85.2 ± 1.9
IIM6	334.6 ± 6.9	81.4 ± 1.7	77.8 ± 1.6	79.5 ± 1.6	95.4 ± 1.5
IIM7	342.5 ± 7.3	84.8 ± 1.3	81.2 ± 1.7	84.1 ± 1.5	92.7 ± 1.4
IIM8	349.8 ± 6.5	86.9 ± 1.2	85.6 ± 1.3	89.4 ± 1.2	89.6 ± 1.3
IIM9	357.3 ± 7.1	85.7 ± 1.4	82.8 ± 1.5	87.5 ± 1.4	87.8 ± 1.7
IIM10	365.9 ± 6.7	84.5 ± 1.6	80.3 ± 1.8	85.2 ± 1.6	84.3 ± 1.5

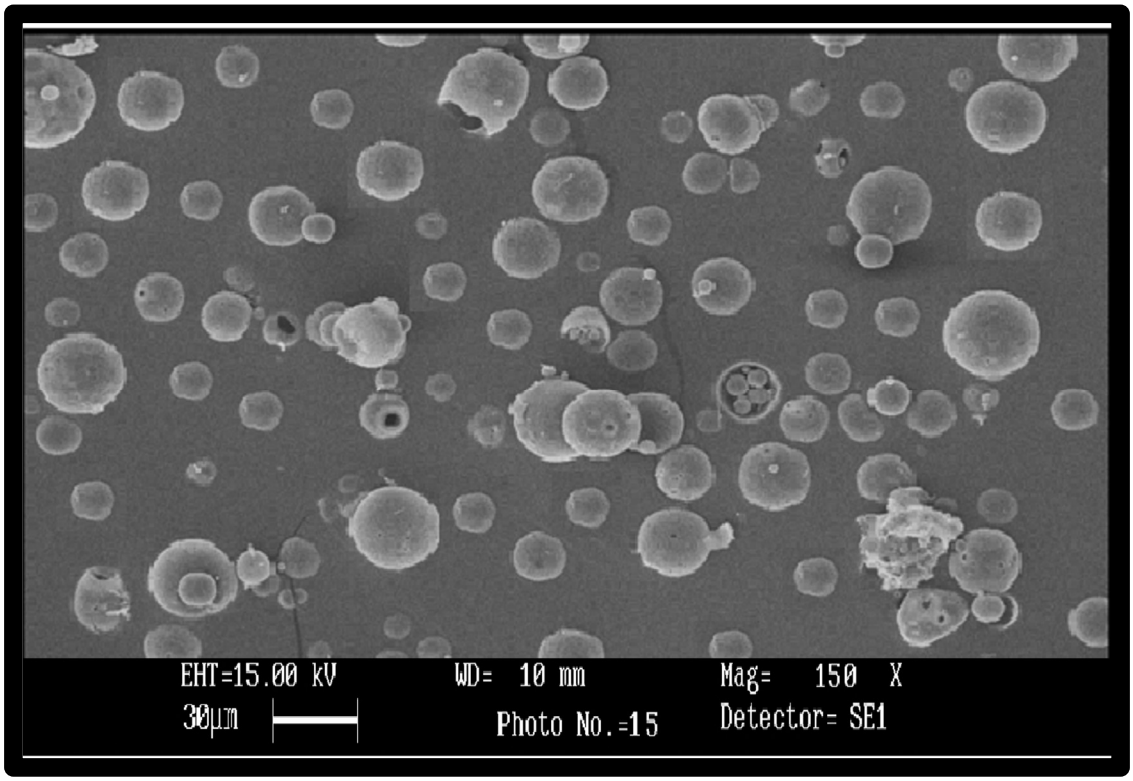

Figure 1: Scanning electron microphotograph of microsphere of IIM5.

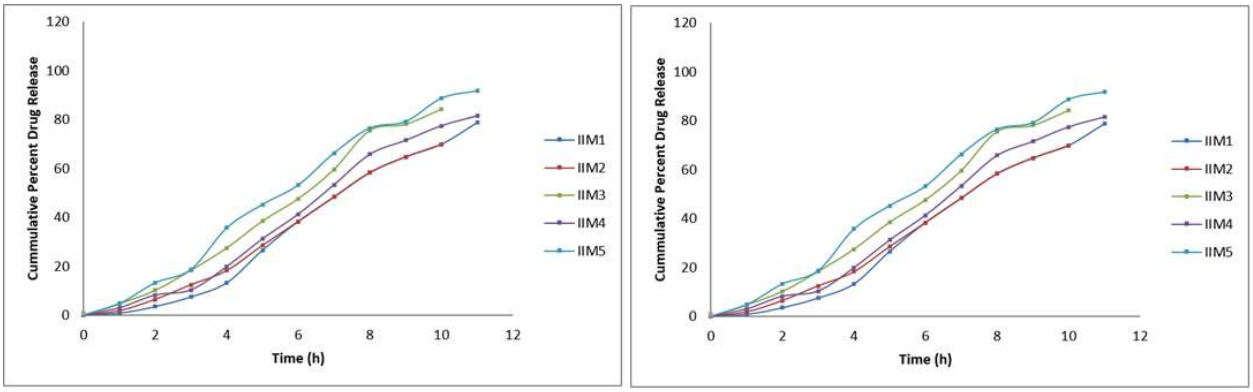

Figure 2: zero-order kinetic plot for various formulation of floating microspheres

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