Research Article

Design and Development of Esomeprazole Loaded Polymeric Microballons as A Gastroretentive Delivery System

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Abstract

Background: Gastric retention provides advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of small intestine, for example in the treatment of peptic ulcer. Microballons have received considerable attention in pharmaceutical and biomedical application, specifically achieving sustained release and controlled release. **Objectives:** Thus, it is a useful method for prolonging drug release from dosage forms, reducing adverse effects and to deliver drugs in a controlled manner. **Material and methods**: The Esomeprazole loaded floating microballons were prepared by solvent evaporation method and effect of different variables like, drug concentration, polymer concentration, stirring time, stirring speed, and temperature was observed on their average particle size, % drug entrapment and % cumulative drug release. The optimized formulation was evaluated for parameters including average particle size, surface morphology, % cumulative drug release. **Results and conclusion**: The *in vitro* drug release study performed in all pH, confirmed that floating microballoons resulted in sustained and prolonged release of drug in the GIT fluids. It was found that more than 90 % of entrapped drug was released in 24 hours.

***Keywords*:** Peptic Ulcer; Gastric retention; Microballons; Controlled drug delivery; Esomeprazole

Introduction

Peptic ulcer disease embraces both gastric and duodenal ulcers and has been a major threat to the world's population over the past two centuries, with a high morbidity and substantial mortality. Epidemiological data for this disease and its complications have shown striking geographical variations in incidence and prevalence. Development of ulcer disease and death from it has been associated with the birth of urbanization and was interpreted as a birth-cohort event with the peak of disease in those born during the late 19th century (Alsoud et al. 2021). Our understanding of the disease changed greatly with the discovery of Campylobacter pyloridis (renamed Helicobacter pylori in 1989 because of a revised taxonomic classification) in 1984 by Warren and Marshall. This discovery switched the notion from an acid-driven disease to an infectious disease, opening a huge area for intensive research that resulted in the reconciliation of previously suggested mechanisms of pathogenesis.

The fall of the acid dogma in peptic ulcer disease, which had found its undisputed acceptance during and after the introduction of histamine H2-receptor antagonists, led to the present therapeutic principle. Maintenance acid suppressive therapy for duodenal ulcer, which followed decades of dominance of surgical interventions (subtotal gastric resections, several forms of vagotomy), was replaced with a short-term antibiotic regimen targeting eradication of H pylori infection (Kim et al., 2015).

Peptic ulcers are a broad term that includes ulcers of digestive tract in the stomach or the duodenum. Peptic ulcer disease (PUD) refers to painful sores or ulcers in the lining of the stomach or first part of the small intestine, called the duodenum. It is now found that an ulcer is the end result of an imbalance between digestive fluids in the stomach and duodenum. Peptic ulcer disease is a serious gastrointestinal disorder that requires a well targeted therapeutic strategy (Bereda, 2022). Peptic ulcer occurs in that part of the gastrointestinal tract (G.I.T.) which is exposed to gastric acid

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and pepsin, i.e., the stomach and duodenum. A variety of psychosomatic, humoral and vascular derangements have been implicated and the importance of Helicobacter pylori infection as a contributor to ulcer formation and recurrence has been recognized. The major factors that disrupt the equilibrium between aggressive factors and defensive factors are Helicobacter pylori, acid–pepsin hyper secretion, non-steroidal anti- inflammatory drugs, sometimes idiopathic due to usage of tobacco, psychological stress, rapid gastric emptying and Zollinger-Ellison syndrome where there is a high and uncontrollable production of acid also leads to ulcer formation (Metz and Jensen, 2022).

An estimated 15,000 deaths occur each year as a consequence of Peptic ulcer disease (PUD). In India, PUD is common. In the Indian Pharmaceutical industry, antacids and antiulcer drugs share 6.2 billion rupees and occupy 4.3% of the market share (Tyagi et al., 2023).

Currently, the worldwide population infected is around 50%, being even higher in developing countries. Prevalence rates of H. pylori infection varies according to race/ethnicity, socioeconomic conditions and age, being highest with ageing. Commonly, their colonization is asymptomatic, resulting only in histological signs of chronic gastritis. However, approximately 20% of the infected population evolves into a clinical condition, commonly chronic gastritis and peptic ulcer (Lopes et al., 2014).

Drug treatment of peptic ulcers is targeted at either counteracting aggressive factors (acid–pepsin, active oxidants, PAF, leukotrienes, endothelins, bile or exogenous factors including NSAIDs) or stimulating the mucosal defenses (mucus, bicarbonate, normal blood flow, prostaglandins, nitric oxide). Synthetic drugs such as proton pump inhibitors, H2 receptors, cytoprotectants, demulcents, anticholinergics, antacids and prostaglandin analogues are used for the treatment of ulceration. A number of drugs including proton pump inhibitors and H2 receptor antagonists are available for the treatment of peptic ulcer, but clinical evaluation of these drugs has shown incidence of relapses, side effects, and drug interactions. This has been the rationale for the development of new antiulcer drugs and the search for novel molecule has been extended to drugs that offer better protection and decreased relapse (Périco et al., 2020).

Historically, oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached. Although some important applications, including oral administration of peptide and protein drugs, can be used to prepare colonic drug delivery systems, targeting drugs to the colon by the oral route (Kamada et al., 2021). More often, drug absorption has been unsatisfactory and highly variable among and between individuals, despite excellent in vitro release patterns. The reasons for this are essentially physiological and usually affected by the gastrointestinal (GI) transit of the form, especially its gastric residence time (GRT), which appears to be one of the major causes of the overall transit time variability. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the GI tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. Stomach specific (gastric retention) will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease (Wannasarit et al., 2020). It has been reported that floating delivery systems can prolong the gastric retention time and thus increase the overall drug bioavailability of certain drugs.

Hyaluronic acid, which is mixed with a polymer in specified quantity for preparation of floating microspheres has the added advantage of providing targeted affinity for lesions having ulcers (Gao et al., 2023). In addition to this Hyaluronic acid also provides viscoprotective property i.e., it provides protective coating over the inflammatory lesions and hence prevent direct contact of those inflammated lesions from stomach acid secretion. Microspheres of Esomeprazole could localize the bioactive within the peptic region to enhance the drug absorption process in a site specific manner.

Materials and Methods

Materials

Esomeprazole was obtained as a gift sample from Ipca Laboratory, Indore (India). Eudragit S100 and Hyaluronic acid were obtained as gift samples from Rohm Pharma, Germany. All other chemicals, excipients and solvents used were of either analytical or pharmaceutical grade.

Preparation of microballoons by solvent diffusion evaporation method (Wavhule and Devarajan; 2021)

Microballoons with an internal hollow structure were prepared by solvent diffusion evaporation method. Accurate quantity of polymer mixture i.e., Eudragit S 100

(50 mg) and Hyaluronic acid (50 mg) was dissolved in 8ml ethanol followed by the addition of 8 ml dichloromethane. The 100 mg of drug was homogeneously dispersed in this polymer solution. This solution was slowly introduced into 200 ml of polyvinyl alcohol (0.75%w/v PVA solution) aqueous solution with stirring at 350-400 rpm using a mechanical stirrer (Remi India) equipped with a blade propeller. The solution was stirred for 3-4 hrs. and microballoons were collected by filtration, washed three times with distilled water and dried at room temperature for 24 hrs.

Characterization of prepared microballoons

The prepared microballoons were characterized for shape and surface morphology, size and size distribution, percent drug loading and *in vitro* drug release.

Shape and surface morphology

The microballoons were examined by optical and scanning electron microscopy. Microballoons were suspended in water; a drop was placed on a glass slide, covered with a cover slip and viewed under the optical microscope (Leitz-Biomed, Germany) to examine their shape.

In order to examine the surface morphology, the formulations were viewed under scanning electron microscope (Figure 1). The samples for SEM were prepared by lightly sprinkling the microballoons powder on a double adhesive tape, which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300°A using a sputter water. The samples were then randomly scanned for studying surface morphology but show the images of coating to prove internal surface.

Particle size and size distribution

Microballoons were studied microscopically for their size and size distribution using calibrated ocular micrometer. Least count of the ocular micrometer was calculated as 16.2 m. Around 100 particles from each formulation were seen and the observed data for each formulation are recorded in Table 1 to 5.

Drug content

100 mg of microballoons was dispersed in 100 mL of PBS (pH 7.4) and shaken vigorously for 10 min. and supernatant was kept aside. Similarly, the sediment was again treated in the same manner and second supernatant was mixed with first supernatant. The microballoons obtained after two washings were dissolved in 20 mL of PBS (pH 7.4) for 2 hrs. and was centrifuged at 3000 rpm for 5 min. The solution was then filtered through 0.45µm syringe filter (Millipore Millex HN, USA) and the filtrate was assayed for Esomeprazole spectrophotometrically. The percent drug entrapped was calculated and reported in Table 1-5.

***In vitro* drug release study in simulated gastrointestinal fluids of different pH**

All formulations of microballoons were evaluated for the *in vitro* drug release study. The dissolution test of Esomeprazole microballoons was carried out by the paddle type dissolution apparatus specified in USP XXIII.

50 mg of Esomeprazole loaded microballoons was weighed accurately and gently spread over the surface of 500 mL of dissolution medium. The content was rotated at 100 rpm and thermostatically controlled at 370.5°C. Perfect sink condition was prevailed during the drug dissolution. The release was tested in dissolution medium of pH 1.2 and pH 7.4 phosphate buffer solutions. An aliquot of the release medium was withdrawn at predetermined time intervals and an equivalent amount of fresh medium was added to the release medium. The collected samples were filtered through 0.45µm-syringe filter (Millipore millex HN) and analyzed spectrophotometrically. Drug release profiles were observed for microballoons are recorded in Table 6 and 7 and graphically shown in Figure 2 and 3.

Results and discussion

Eudragit S100-Hyaluronic acid- PVA complexed microballoons were prepared by solvent diffusion method as reported by Kawashima et al., (2001). The Eudragit S100-Hyaluronic acid mixture solution was sequentially dropped into PVA solution and dispersed in external phase. PVA solution was chosen as the external phase because ethanol/dichloromethane (DCM) mixture as an internal phase is not miscible with PVA solution and the Eudragit

Table 1. Effect of Drug concentration on particle size and % drug loading of microballoons

Formulation code	Drug concentration (% of polymer weight)	Particle size (µm)	Percentage drug loading
D1PSXT	20%	75.34±04.15	67.22±01.99 %
D2PSXT	40%	87.33±04.21	69.22±01.67%
D3PSXT	60%	98.42±02.92	75.53±02.96%
D4PSXT	80%	120.95±02.28	79.02±01.88%
D5PSXT	100%	138±03.03	74.22±03.02%

S100-Hyaluronic acid -PVA complex is not soluble in it. As the dispersed droplets of Eudragit S100-Hyaluronic acid solution collided with those of PVA solution, they formed an interpolymer complex. The droplets of Eudragit S100-Hyaluronic acid /PVA complex gradually solidified and hardened as ethanol and DCM diffused out of the internal phase.

It was also observed that Eudragit S100-Hyaluronic acid and PVA aggregated and precipitated out in ethanol-DCM mixture in a relatively short period of time, resulting in the formation of a PVA/ Eudragit S100-Hyaluronic acid interpolymer complex, suggesting that the intensity of hydrogen bonding between Eudragit S100-Hyaluronic acid and PVA is quite strong. It was believed that this strong complexation could be utilized to prepare floating microballoons.

The effect of formulation variables, e.g. drug concentration, solvent ratio of internal phase (ethanol/DCM), surfactant concentration and process variables, e.g. stirring speed and temperature were studied in order to optimize the formulation. The results suggested that these variables influence the shape, size and size distribution, total drug loading efficiency and *in vitro* drug release. Hence, these parameters were optimized to prepare microballoons of small size with narrow size distribution, good drug loading efficiency and good drug release at the gastrointestinal pH.

For the total drug loading efficiency, the microballoons were extracted with PBS (pH 7.4) and extract of drug was determined spectrophotomatrically.

The Esomeprazole floating microballons were prepared by solvent evaporation method and effect of different variables like, drug concentration, polymer concentration, stirring speed, stirring time, and temperature was observed on their average particle size, % drug entrapment and % cumulative drug release. The optimized formulation was evaluated for parameters including average particle size, surface morphology, % cumulative drug release.

The drug entrapment efficiency of prepared microballons was affected by drug: polymer ratio. This drug: polymer ratio also influenced the particle size of the microballons. This was due to the difference in the viscosity of dispersed phase in different ratio of drug and polymer.

As the formulation code D1PSXT, D2PSXT, D3PSXT, D4PSXT, D5PSXT drug concentration as % of polymer weight was initial and optimal according to the matrix

Table 2. Effect of polymer ratio on particle size and drug loading of microballoons

Formulation code	Polymer amount (% of drug weight)	Particle size (µm)	Percentage drug loading
D4P1SXT	10:10 (20)	66.72±02.01	34.15±02.09%
D4P2SXT	20:20 (40)	77.22±02.39	41.13±02.02%
D4P3SXT	30:30 (60)	90.58±02.02	56.66±03.23%
D4P4SXT	40:40 (80)	129.27±02.31	60.31± 03.02%
D4P5SXT	**50:50** (100)	**142.23±02.21**	**79.30±01.99%**
D4P6SXT	60:60 (120)	153.33±03.06	74.11±02.24%

Table 3. Effect of surfactant concentration on particle size and drug loading of microballoons

Formulation code	Surfactant conc. (% W/V)	Particle size (µm)	Percentage drug loading
D4P5S1XT	0.50	158.98±03.03	81.94±02.54%
D4P5S2XT	**0.75**	**144.17±03.29**	**78.92±02.87%**
D4P5S3XT	1.0	131.22±03.13	72.67±02.56%
D4P5S4XT	1.25	122.09±02.58	65.88±02.09%

Table 4. Effect of stirring speed on particle size and drug loading of microballoons

Formulation code	Speed (rpm)	Particle size (µm)	Percentage drug loading
D4P5S2X1T	300	170.02±03.33	73.82±02.98%
D4P5S2X2T	**400**	**142.76±07.65**	**78.05±03.44%**
D4P5S2X3T	500	140.07±03.66	77.76±03.23%

which encapsulated the drug. The optimal concentration of drug was found to be 80 % in respect to the polymer weight. When the concentration of drug increased as in formulation code D5PSXT, the matrix of polymer might has been fully saturated that's why the additional drug was leached out from the matrix. Thus the entrapment efficiency was slightly low (74.22%) as compared to other formulations (79.02%).

Effect of polymer concentration was found to influence the particle size and entrapment efficiency. The polymer concentration was found to be optimal in the 100 mg % of drug weight. The highest entrapment was found in formulation code D4P5SXT. The lower polymer concentration resulted in low entrapment efficiency and exceeding the polymer concentration above 100 mg further reduced the entrapment efficiency from 79.30% to 74.11%. The reason behind this might be that increase in polymer concentration increases matrix density and thus all drug moieties was encapsulated and thus the entrapment efficiency was low due to increase of matrix density.

The surfactant concentration was optimized on the basis of particle size and entrapment efficiency of microballoons. In case of 0.50%w/v surfactant concentration, the particle size was slightly more than that of D4P5S2XT. The reason behind this is that 0.50% w/v surfactant concentration was not sufficient to reduce the surface charge so that the particles were aggregated and resulted in increase in particle size, whereas the entrapment efficiency was high in case of formulation D4P5S1XT. The reason might be due to increase in particle size resulting increase in entrapment efficiency of drug into the increased matrix.

Where as in D4P5S3XT and D4P5S4XT particle size and entrapment efficiency was reduced as compared to D4P5S2XT. The possible reason for this might be the increase in surfactant concentration resulted in reduction in surface charge, so that the particles were unable to aggregate to each other due to sufficient pressure of surfactant on the outer surface of particles, Thus the particle size was found to be smaller than D4P5S1XT and D4P5S2XT and as the particle size reduced the entrapment efficiency was also reduced. The reason has been stated above also i.e unavailability of matrix resulted in low entrapment efficiency as compared to more matrix in D4P5S1XT and D4P5S2XT.

Stirring speed was optimized to get optimum particle size and percent drug entrapment. The results confirmed that stirring speed of 400 and 500 rpm results in approximate same

Table 5. Effect of temperature on particle size and drug loading of microballoons

Formulation code	Optimization of temperature	Particle size (µm)	Percentage drug loading
D4P5S2X2T1	25^0C	147.54±03.11	76.82±03.12%
D4P5S2X2T2	**37^0C**	**121.33±03.45**	**78.02±05.08%**
D4P5S2X2T3	45^0C	160.35±02.77	77.22±02.77%

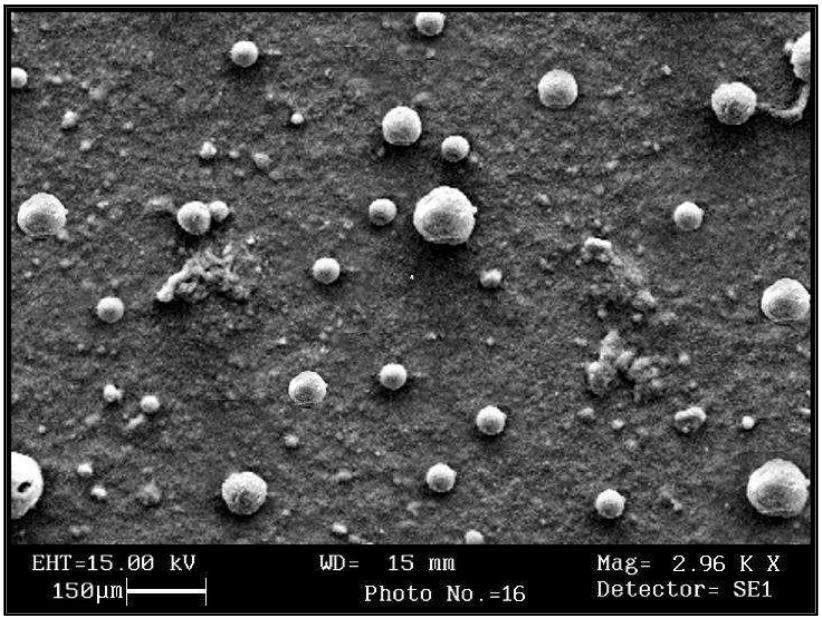

Figure 1: SEM photograph of Esomeprazole microballoons

particle size and entrapment efficiency as that of D4P5S1X1T. In case of D4P5S2X1T, the stirring speed was 300 rpm and it resulted in larger particle size and low entrapment efficiency. The reason might be as the rpm was low, the shearing stress was low and thus resulted in larger particle size as compared to D4P5S2X2T and D4P5S2X3T, whereas the drug entrapment was low in D4P5S2X1T which may be due to, reduction in shearing stress. This resulted in increase in leaching of drug from matrix cavity to external phase and thus entrapment efficiency was low. Therefore, D4P5S2X2T2 was chosen as optimum for further study.

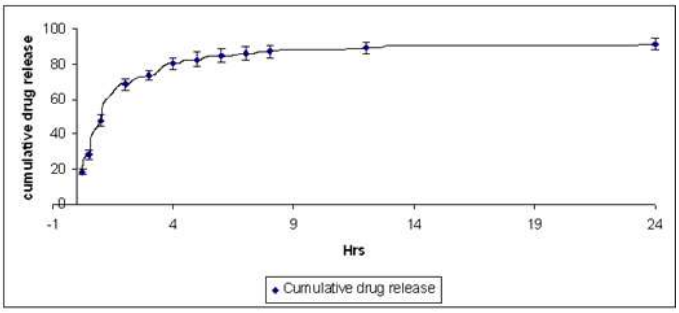

Figure 2. Cumulative % Esomeprazole release from PVA-Eudragit S100 microballoons in SGF pH 1.2; n=3; SD

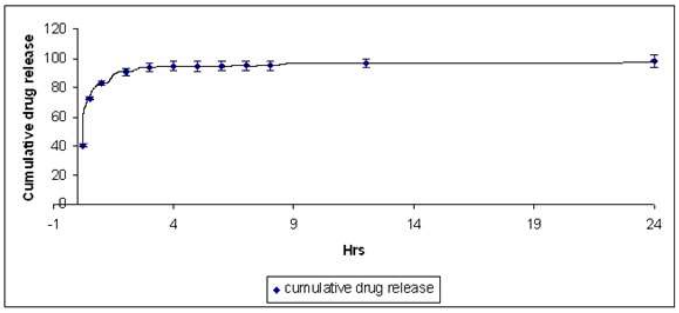

Figure 3. Cumulative % Esomeprazole release from PVA-Eudragit S100 microballoons at pH 7.4; n=3; SD

Table 6. Data for cumulative % Esomeprazole release from PVA-Eudragit S100 microballoons in SFG pH 1.2

S. No.	Time interval (hrs)	Drug release from Eudragit S100-PVA microballoons (%)
1	0.25	17.94±02.08
2	0.5	27.33±01.77
3	1	46.99±02.05
4	2	67.54±03.06
5	3	72.58±02.97
6	4	79.74±03.65
7	5	81.98±02.15
8	6	84.71±02.57
9	7	87.01±02.66
10	8	88.37±02.73
11	12	90.07±03.22
12	24	92.72±03.08

D4P5S2X2T2 37°C was found to be optimum as compared to D4P5S2X2T1 and D4P5S2X2T3. Formulation code D4P5S2X2T1 prepared at 25°C showed larger particle size and low entrapment efficiency than D4P5S2X2T2. In case of D4P5S2X3T1 the particle size was more. This may be due to lower temperature used in preparation which resulted in aggregation of particle size. However, the entrapment efficiency was approximately same at all temperatures.

Further increase in temperature resulted in aggregation of particles due to external charge (temperature) and thus it produced bigger particles (157.02 µm at 45^0C).

The surface and particle morphology (SEM) confirmed the shape and size of microballoons, the particle size was found to be less than 200µm. Similarly surface morphology was found be plain and spherical.

The *in vitro* drug release study performed in all pH, confirmed that floating microballoons resulted in sustained and prolonged release of drug in the GIT fluids. It was found that more than 90 % of entrapped drug was released in 24 hours.

The microscopic examination of microballoons revealed that the mean diameter of Eudragit S100-PVA complexed microballoons varied from 121.56 m to 147.26 m on varying the concentration of all variables. Total drug loading efficiency varied from 68.98 to 80.02%. Thus it may be concluded that the prepared microballoons were of

Table 7. Data for cumulative % Esomeprazole release from PVA - Eudragit S100 microballoons at pH 7.4

S. No.	Time interval (hrs)	Drug release from Eudragit S100- PVA microballoons (%)
1	0.25	44.06±03.07
2	0.5	71.98±01.88
3	1	82.22±02.12
4	2	89.89±02.22
5	3	92.56±01.92
6	4	94.56±02.63
7	5	94.58±03.66
8	6	94.63±01.98
9	7	94.76±02.28
10	8	94.88±02.22
11	12	96.22±02.67
12	24	97.38±02.87

spherical shape with good entrapment efficiency. The optimized formulation D4P5S2X2T2 was selected for further studies.

Conclusion

Microballons were prepared successfully by emulsion solvent evaporation process. The main objective of the preparation was to select the formulation which would provide optimum release for 12 hours.

It is suggested that the work should further be elaborated in the field of targeted drug delivery systems like, binding of molecules (ligands) to the microballons surface, which have to exhibit the ability to recognize cell surface structure such as , lectin, adhesion invasions, antibodies or sugars, which may offer site specific drug delivery. Further, *in-vivo* bacterial clearance and their study with infected animal model also recommended for the future work.

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