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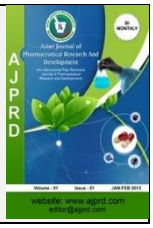

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Research Article

Design, Development and Evaluation of Gastro- Retentive Mucoadhesive Microballons of Lansoprazole for Management of Peptic Ulcer

Jitendra Kumar *, Dharmendra Singh Rajput, Naveen Gupta, Neeraj K Sharma

School of Pharmacy, Madhyanchal Professional University, Bhopal, M.P

A B S T R A C T

A major problem for gastric delivery is the attainment of an optimal concentration at site of action with maximum bioavailability of drugs. The problem is associated with the conventional dosage form for peptic ulcer diseases is frequent dosing due to the low half life. The bioavailability of an instilled compound is generally low from 1.5 – 3.0 h and low solubility, with only a small fraction reaching the target site. In the present study an attempt was made to develop a mucoadhesive Microballons of Lansoprazole with variation in polysaccharide polymeric combination with different ratios to increase mucoadhesion at gastric mucosa, which increase the gastric residence time, thus increase the bioavailability.The result indicated that the drug have maximum solubility water, and also soluble in 0.1 N HCl. The partition coefficient of Lansoprazole HCl was found to be (0.2442). The FTIR spectrum is shown in Figure. The characteristic peaks of Lansoprazole HCl were observed at 3290, 3220, 3127, 3084, 2975, 2820, 2819, 2781, 1621, 1517, 1420, 1418, 1425, 1412, 1317 and 1319 cm^{-1}.The prepared mucoadhesive microballons were determine for percentage yield and the range of percentage yield is 89.2 % - 95.9. The Shape and surface morphology of prepared mucoadhesive microballons was shown by photograph by scanning electron microscope in Figure.

Keyword: Lasnoprazole, Preformulation, In vitro, Peptic ulcer, Microballona

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*Address for Correspondence:
Jitendra Kumar, School of Pharmacy, Madhyanchal Professional University, Bhopal, M.P

INTRODUCTION

The stomach and duodenum, two areas of the gastrointestinal tract (g.i.t.) that are exposed to gastric acid and pepsin, are where peptic ulcers develop. The exact cause of a peptic ulcer is unknown. It is most likely the result of an imbalance between the defensive (high mucosal blood flow, innate resistance of the mucosal cells, gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide) and the offensive (acid, pepsin, bile, and H. pylori) components. Numerous psychological, humoral, and vascular abnormalities have been linked, and it is now known that Helicobacter pylori infection plays a significant role in the development and recurrence of ulcers. Acid secretion is often normal or low in gastric ulcers, although defective mucosal defense (mostly impaired mucus and bicarbonate secretion) is more important. About half of patients with duodenal ulcers have high acid secretion, while the other half has normal acid secretion. Acid production, whether it is low or high, does contribute to ulceration as an aggressive factor, and reducing it is the primary ulcer therapy strategy. The targets of antisecretory medication action will become clearer with a better understanding of the process and regulation of stomach acid secretion. An ulcer is a 2 to 4 cm in diameter round or oval hole with smooth, perpendicular margins and a base. It is also known as a parietal defect. An ulcer in the digestive tract known as a "peptic ulcer" is characterised by its intense pain and acidity. It is also known as peptic ulcer disease or peptic ulcers (PUD). Contrary to general belief peptic ulcers happen more often in the duodenum first part of the small intestine than in the stomach. Duodenal ulcers are usually benign whereas about 4% of stomach ulcers are caused by a malignant tumor. The borders of the Peptic ulcer are not well-known in the acute form but elevated and

inflammatory in the chronic form. In the ulcerative form of gastric cancer the borders are uneven. Microballons are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000µm or 1mm). Microballons are sometimes referred to as microparticles. Microballons are defined as "the monolithic spheres or therapeutic agents distributed throughout the matrix either as a molecular dispersion of particles". Microballons are small spherical particles with diameter in the micrometer range and sometimes referred as microparticles. When adhesion is restricted to the mucous layer lining of the mucosal surface it is termed as mucoadhesion. Mucoadhesion offers prolonged residence time at the site of absorption, localization of the drug delivery system at a given target site, increase in drug. Development of adhesive bond between polymer and biological membrane or its coating can be achieved by two ways: initial contact between the surfaces or formation of secondary bonds due to non covalent interaction. Mucoadhesives must interact with mucin layer during the process of attachment. Mucins are synthesized by globet cells and special exocrine glands with mucin cells acnini. There are atleast two main targets which could be used for anchoring of delivery system through mucoadhesive in the GIT, the mucosal tissue and mucosal gel layer. The mucos layer is the first surface encountered by particulate system and its complex structure offers many opportunities for the development of adhesive interaction with small polymeric particles either through non specific or specific interaction between complimentary structures. Due to all above advantages Microsphere delivery is an better choice for drug delivery in colon [33].

The objective of the present investigation was to develop a formulation gastroretentive Lansoprazole mucoadhesive microballons for treatment of peptic ulcer mainly at gastric part of GIT, to improve gastric residence time and increase bioavailability.

MATERIAL & METHODS

Analytical and Validation studies

Determination of absorption maxima (λ_{max})

The absorption maxima of drug (Lansoprazole HCl) were determined by scanning drug solution in ultraviolet spectrophotometer between 200 to 400 nm wavelengths.

50 mg of drug was dissolved in 50 ml of dissolution medium (0.1 N HCl) in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. The resulting solution was labeled as **Stock-I**. 1 ml of this solution was diluted up to 100 ml with same solvent separately with sonication for 20 min to obtain 10 µg / ml solution. The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan).

Preparation of calibration curve of Lansoprazole HCl in 0.1N HCl

Procedure: 50 mg of drug was dissolved in 50 ml of dissolution medium (0.1 N HCl) in 50 ml volumetric flask with the help of sonication in bath sonicator for 20 min to obtain 1000 µg/ml solution. The resulting solution was labeled as **Stock Solution-I**. From the above stock solution 10 ml was again diluted with 100 ml of dissolution medium to obtain 100 µg / ml solution. The resulting solution was labeled as **Standard Stock Solution-II**.

From above standard **stock solution-II** 1 ml, 2.0 ml, 3.0 ml upto 5.0 ml aliquots were withdrawn and diluted up to 10 ml with respective solvent in 10 ml volumetric flasks to get concentration of 10 µg / ml, 20 µg / ml, 30 µg / ml, upto 50 µg / ml respectively. The absorbance of each solution was measured separately at 228 nm for

0.1 N HCl. The absorbance was measured and standard curve was plotted between absorbance vs. concentration.

Evaluation of mucoadhesive microballons:

Percentage yield determination: The prepared mucoadhesive microballons were weighed after drying for the determination of actual yielding after preparation process. The percentage yield of prepared mucoadhesive Microballons were calculated using following Formula:

Percentage Yield = (Actual weight x 100)/ Theoretical Weight

Shape and surface morphology: Scanning electron microscopy (SEM, JealJX 840- A, Tokyo, Japan) was performed to characterize the surface of formed mucoadhesive Microballons. Samples for SEM were prepared by lightly sprinkling the powder on a double adhesive tape stuck to an aluminum stub. The stubs were then coated with gold film under reduced pressure. This film acts as a conducting medium on which a stream of electron was allowed to flow and then photograph was taken with scanning electron microscope.

Particle size analysis: Mucoadhesive microballons were studied microscopically for their size and size distribution using calibrated ocular micrometer.

Drug Entrapment Efficiency: Mucoadhesive microballons were studied for determination drug entrapment efficiency 500mg of microballons containing a drug were taken, crushed by trituration and suspended in a minimal amount of dichloromethane (10ml) for dissolving the coat shell of the Microballons. The suspension was suitably diluted with 0.1N HCl buffer (100mL) for 1hr and filtered to separate the shell fragments. Then Drug entrapment efficiency was analyzed after suitable dilution by spectrophotometrically with a UV-detector (Shimadzu, UV-1800) at 228 nm. The drug entrapment efficiency was calculated as follows:

Drug entrapment efficiency = Calculated drug concentration ×100

Theoretical drug content

Degree of Swelling of microballons: For estimating the degree of swelling 1gm of microsphere were suspended in 5 mL of simulated gastric fluid USP (pH 1.2). The particle size was monitored by microscopy technique every 1 hour using an optical

microscope (Labomed CX RIII). The increase in particle size of the Microballons was noted for up to 8 hours.

In vitro Wash-off Test for microballons: The mucoadhesive properties of the Microballons were evaluated by in vitro wash-off test. For this 1 cm piece of rat stomach mucosa was tied onto a glass slide using thread. About 100 Microballons was spread onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movements in a beaker containing the simulated gastric fluid USP (pH 1.2). At the end of 1 hr, 5 hr and 10 hr intervals and the number of Microballons still adhering onto the tissue was measured.

In-vitro buoyancy percentage: Mucoadhesive microballons (0.3 g) were spread over the surface of USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 N hydrochloric acid containing 0.02 % Tween 80. The medium was agitated with paddle rotating at 100 rpm for 24 h. the floating and the setteled portion of mucoadhesive Microballons were recovered separately. The mucoadhesive Microballons were dried and weighed. The buoyancy percentage was calculated as the ratio of the mass of the Microballons, that remained floating and the total mass of Microballons.

In vitro drug release studies in simulated gastrointestinal fluids: The dissolution test of Lansoprazole Hcl mucoadhesive microballons was carried out by the paddle type-II dissolution apparatus specified in USP XXIII. 500 mg of Lansoprazole loaded microballons was weighed accurately and gently spread over the surface of 900 mL of dissolution medium. The content was rotated at 100 rpm .

RESULT AND DISCUSSION

The absorption maxima (λ-max) of Lansoprazole HCl (10 µg / ml) in 0.1 N HCl solution were found to be at **298 nm**.

Lansoprazole HCl drug was estimated in-vitro by reported UV spectrophotometric methods. The reported UV spectrophotometric methods were slightly modified and optimized according to the existing laboratory conditions.

The drugs were estimated in the dissolution medium (0.1 N HCl). The calibration curves in the various dissolution medium (0.1 N HCl) were prepared with drug solutions of known concentrations. The absorbance was measured and plotted against drug concentration.

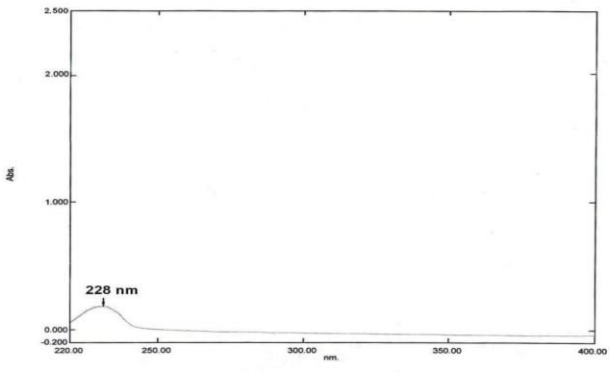

Figure 1: Absorption maxima (λ-max) of Lansoprazole HCl in 0.1N HCl solution (10 µg/ml)

The calibration curves show excellent linearity of data as evidenced by the values of correlation coefficients that were found to be greater than 0.99. The curves were found to be recti-linear in the concentration range **0 µg / ml to 80 µg / ml** for the drug.

Evaluation of mucoadhesive microballons:

The prepared mucoadhesive Microballons were determine for percentage yield and the range of percentage yield is 89.2 % - 97.8. The Shape and surface morphology of prepared mucoadhesive microballons was shown by photograph by scanning electron microscope in **Figure 5.5 – 5.6**. The particle size of prepared mucoadhesive microballons were studied microscopically and the result was shown in **Table**. All the formulations were shown in good flow ability and the particle size in the range of d_{avg} is 362.55 µm – 384.56 µm.

The Drug Entrapment Efficiency of prepared mucoadhesive Microballons were studied for determination drug entrapment efficiency and the result was shown in Table 5.15. The drug entrapment efficiency was in the range of 82.82 % - 94.29 %.

The Degree of Swelling of Microballons was shown in **Table.** The Swelling rate and percent mucoadhesion of mucoadhesive Microballons of Lansoprazole HCl was in the range of 76.23 % - 89.24 %. The in-vitro buoyancy percentage of mucoadhesive Microballons was shown in **Table** for determination of floating ability of all formulations. All the prepared formulations was floated more than 7 h - 12 h.

The in vitro drug release studies in simulated gastrointestinal fluids of SGF (pH 1.2) and the observations are recorded in **Table.**

The in-vitro Release profile of tablets was characterized for release percentage and release rate **k**. Release data within the linear range were selected and fitted to a zero- order mathematical model:

$$Q = C + kt$$

Where Q is the release percentage at time t; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of plumbagin release and calculated here from the fitted equation, setting Q=0:

$$T_{lag} = - C / k.$$

The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable. Floating mucoadhesive microballons B2 is the best formulations containing naturally occurring polysaccharide polymeric blend as Drug : HPMC: Carbopol 934 (1:1:1) that release more than 98.13 % of the drug in gastric environment in controlled and sustained manner upto 24 h.

Regression analysis was performed and the r^2 values suggested that the curves were fairly linear and slope values were computed from the graph. For all of the batches the value of release exponent "n" was > 0.89 indicating Super-case II transport mechanism.

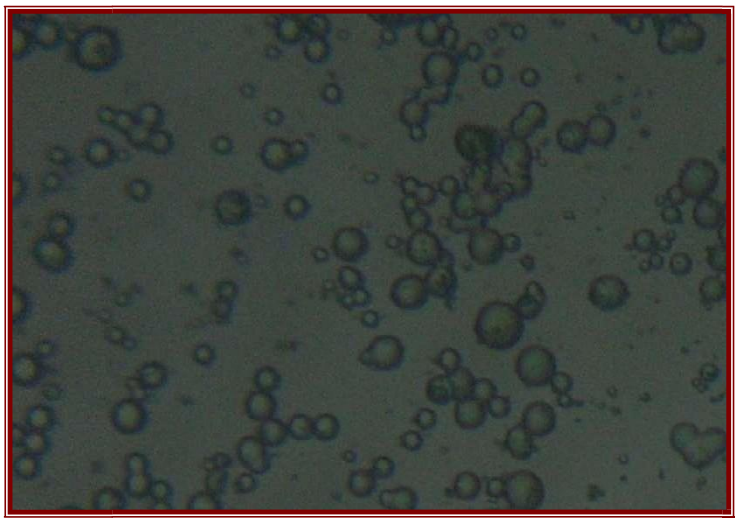

Figure 2: Photograph of microspheres (100X)

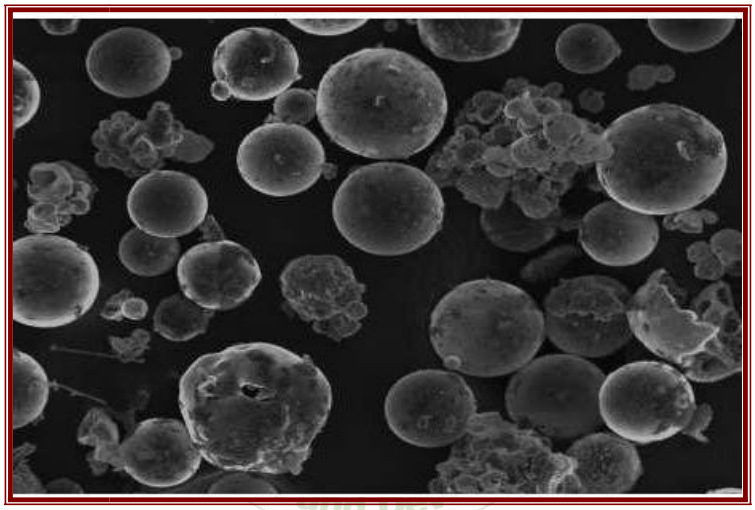

Figure 3: SEM photomicrograph of microspheres (650X)

Table 1: Percentage yield of mucoadhesive microballons of Lansoprazole HCl (A1 – B3)

S. No.	Code	Ingredients	Drug:Polymer	Theoretical yield (gm)	practical yield (gm)	percentage yield (%)
1	A1	Drug : HPMC	1:1	3	1.987	78.2
2	A2	Drug : HPMC	1:2	3	1.786	81.6
3	CH1	Drug : Chitosan	1:1	3	1.769	82.3
4	CH2	Drug : Chitosan	1:2	3	1.987	78.3
5	CA1	Drug : Carbopol 934	1:1	3	1.876	79.1
6	CA2	Drug : Carbopol 934	1:2	3	1.987	81.2
7	B1	Drug : HPMC:Chitosan	1:1:1	3	1.876	83.2
8	B2	Drug : HPMC:Carbopol 934	1:1:1	3	1.895	86.5
9	B3	Drug : Chitosan:Carbopol 934	1:1:1	3	1.745	81.5

Table 2: Particle size of mucoadhesive microballons of Lansoprazole HCl (A1 – B3)

S. No.	Code	dmean (µm)
1	A1	351.45±0.640
2	A2	382.86±0.736
3	CH1	381.15±0.795
4	CH2	387.10±0.772
5	CA1	372.12±0.536
6	CA2	371.95±0.218
7	B1	371.17±0.535
8	B2	373.24±0465
9	B3	371.86±0.732

Table 3: Drug entrapment efficiency of mucoadhesive microballons of Lansoprazole HCl (A1 – B3)

S. No.	Code	Drug content (mg./gm. of microspheres)	Encapsulation efficiency (%)
1	A1	410.2	84.69
2	A2	304.4	83.78
3	CH1	441.5	87.24
4	CH2	281.5	84.44
5	CA1	415.5	86.56
6	CA2	288.6	87.72
7	B1	312.2	97.44
8	B2	335.4	96.51
9	B3	391.8	90.23

Table 4: In-Vitro dissolution data of mucoadhesive microballons of Lansoprazole HCl (A1)

Time	√Time	Log time	Cummula tive drug released	Cummula tive % drug released	Log cummulat ive % drug released	Cummula tive % drug retained	Log cummulati ve % drug retained
0	0	#NUM!	0	0	#NUM!	100	2
2	1.39	0.38	7.23	7.71	0.68	94.29	1.99
4	2.22	0.66	18.82	17.21	1.42	87.79	1.95
6	2.89	0.88	27.12	19.68	17	85.32	1.90
8	2.66	0.99	54.51	38.67	1.95	68.33	1.85
10	3.65	1.21	68.91	49.27	1.86	59.73	1.78
12	3.99	1.20	79.88	58.25	1.83	49.75	1.64
14	3.75	1.24	98.51	69.34	1.82	38.66	1.57
16	4.15	1.27	124.81	75.54	1.85	29.46	1.30
18	4.18	1.29	153.11	88.74	1.89	6.26	1.10
20	4.19	1.30	163.06	99.37	1.96	6.63	0.67
22	4.60	1.39	167.18	98.12	1.99	1.88	0.20
24	4.95	1.37	179.99	99.99	2.00	0.01	-1

Table 5: In-Vitro dissolution data of mucoadhesive microballons of Lansoprazole HCl (A2)

Time	√Time	Log time	Cummula tive drug released	Cummula tive % drug released	Log cummulat ive % drug released	Cummula tive % drug retained	Log cummulati ve % drug retained
0	0	#NUM!	0	0	#NUM!	100	2
2	1.39	0.38	3.01	3.01	0.48	96.99	1.99
4	2.22	0.66	8.23	8.23	0.92	91.77	1.96
6	2.89	0.88	10.34	10.34	1.01	89.66	1.95
8	2.66	0.99	19.87	19.87	1.30	80.13	1.90
10	3.65	1.21	31.23	31.23	1.49	68.77	1.84
12	3.99	1.20	41.34	41.34	1.62	58.66	1.77
14	3.75	1.24	53.37	53.37	1.73	46.63	1.67
16	4.15	1.27	65.78	65.78	1.82	34.22	1.53
18	4.18	1.29	77.45	77.45	1.89	22.55	1.35
20	4.19	1.30	87.32	87.32	1.94	12.68	1.10
22	4.60	1.39	97.51	97.51	1.99	2.49	0.40
24	4.95	1.37	99.24	99.24	2.00	0.76	-0.12

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