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Formulation Development and Evaluation of Lansoprazole Mucoadhesive Microsphere

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ABSTRACT

Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or histamine H2-receptor antagonist properties, but rather suppress gastric acid secretion by specific inhibition of the (H+,K+)-ATPase enzyme system at the secretary surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The aim of the present study was to develop lansoprazole loaded thiolated chitosan microspheres were prepared by emulsifying method using liquid paraffin light and heavy in ratio of 50:50 as a dispersing medium and glutaraldehyde used as a cross-linking agent. The prepared microspheres were evaluated for mean particle size and particle size distribution, drug content, mucoadhesion measurement and in-vitro drug release. FT-IR spectroscopic analysis was performed to ascertain drug polymer interaction. The release profiles showed first order release behavior up to 12 hours where the highest drug release was 88.89 % of the lansoprazole loaded in the thiolated chitosan microspheres, indicating a strong crosslinking between chitosan and glutaraldehyde. From the results of the present investigation it may be concluded that drug loaded chitosan microspheres can be prepared by a simple technique which avoids the use of complex apparatus and special precautions.

Keywords: Lansoprazole, Thiolated chitosan, Microspheres, Glutaraldehyde, Mucoadhesion measurement

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INTRODUCTION

A drug delivery system is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time and place of release of drugs in the body. The efficiency of any drug therapy can be described by providing a therapeutic amount of drug to the proper site of action to achieve the desired concentration of the drug in blood or tissues, for the desired therapeutic response which is therapeutically effective and non-toxic for a prolonged period of time[1]. Recently the novel dosage forms which can control the release rate and target the active drug molecule to a particular site have attained a great formulation interest. Microspheres are one of the novel drug delivery system which possess several applications and are made up of assorted polymers[2]. Microspheres can be defined as solid, approximately spherical particles ranging in size from 1 to 1000 µm range in diameter having a core of drug and entirely outer layers of polymers as coating material. They are made up of polymeric, waxy or other protective materials i.e. biodegradable synthetic polymer and modified natural products such as starches, gums, proteins, fats and waxes. However, the success of these microspheres is limited due to their short residence time at site of absorption[3]. The presence of polymers in sustained release drug delivery systems is important, because almost all of the system using the polymer as a carrier. Some time ago, polymers are divided into three major groups that are soluble polymers, biodegradable polymers or bioerodible, and mucoadhesive polymer[4]. Over time, the presence of polymers today are quite varied, even leading to multifunctional polymers, which can be as mucoadhesive, enzyme-inhibitor, permeation-enhancers, and efflux pump-inhibitor[5]. One of the polymers included in the multifunctional polymer is chitosan. Chitosan has mucoadhesive properties, permeation-enhancers, and enzyme-inhibitor[5]. Chitosan obtained from chitin deacetylation resulting the free amino group that can make it be policationic[6]. Chitosan has been shown to have mucoadhesive properties due to electrostatic interactions between positively charged chitosan and negatively charged mucosal surface. Chitosan has one primary amino group and two free hydroxyl groups for each monomer. Free amino group in chitosan is positively charged subsequently react with the surface/mucus are negatively charged [7]. Various modifications have been made to the existing mucoadhesive polymer resulting in a better mucoadhesvie properties. One modification is done is with the immobilization of thiol groups to mucoadhesive polymer so as to form disulfide bonds with cysteine-rich subdomains of mucus

glycoproteins. Unlike the first generation mucoadhesive polymers attached to the mucus gel layer through noncovalent bonding, the new generation of mucoadhesive polymers capable of forming covalent bonds to the layer of mucus[7]. Modification of the thiol group attachment has also been made to the chitosan. This modification is based on the immobilization of thiol bearing movement on chitosan backbone, thus known as thiolated chitosan. This modification was developed to improve the solubility of chitosan, mucoadhesive property, and/or property of permeation[8]. Improved properties of mucoadhesive thiolated chitosan expected to increase the contact time of the drug in the gastrointestinal tract that it can increase the bioavailability of the drug. Lansoprazole chemical Name 2-[(3-methyl-4-(2,2,2-trifluoroethoxy) pyridin-2-yl) methylsulfinyl]-1*H*-benzoimidazole, Molecular Weight: 369.363 g/mol and half life 1.5hr. Lansoprazole belongs to a class of antisecretory compounds, the substituted benzimidazoles, that do not exhibit ant cholinergic or histamine H2-receptor antagonist properties, but rather suppress gastric acid secretion by specific inhibition of the (H+,K+)-ATPase enzyme system at the secretary surface of the gastric parietal cell[9]. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, lansoprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The stability of lansoprazole a proton pump inhibitor is a function of pH and it rapidly degrades in acidic medium of the stomach, but has acceptable stability in alkaline conditions[10]. To overcome inherent drawbacks associated with conventional dosage forms of lansoprazole, an attempt is being made to develop an alternative drug delivery system in the form of mucoadhesive microspheres.

MATERIALS AND METHODS

Materials

Lansoprazole was obtained as a gift sample from Dr Reddys laboratories, Hyderabad. Thiolated Chitosan was acquired from Sigma-Aldrich (St. Louis, MO, USA). Tween-80 and span-80 from Qualigens, Mumbai. Glacial acetic acids were purchased from Merck Specialities pvt. Ltd., Mumbai, All other chemicals and reagent used were of analytical grade. Ultrapure water was used throughout the study.

Preparation of thiolated chitosan microsphere

Thiolated chitosan was selected for preparing microsphere. Microspheres were prepared by emulsifying method using liquid paraffin light and heavy in ratio of 50:50 as a dispersing medium and glutaraldehyde used as a cross-linking agent. Thiolated chitosan dispersion (1.5% w/v) was prepared by mixing of thiolated chitosan in glacial acetic acid (4%w/v) with Tween 80 (0.5% w/w). Drug was dissolved in chitosan solution. The prepared, 10 ml of thiolated chitosan solution with drug was added dropwise in a beaker containing 100 ml of liquid paraffin light and heavy in ratio of 50:50 containing Span 80 (1.0% w/v). The system was kept under stirring at 3000-4000 rpm using two blade mechanical stirrers. 1.5 ml of glutaraldehyde saturated toluene was added to above solution after 30 min of stirring. Stirring was continued for 4 hr at 40°C at 4000 rpm. The microspheres were separated from dispersion medium by centrifugation and washed two times with petroleum ether to remove liquid paraffin and then washed three times with acetone. Dispersion was poured in petridish to remove acetone. After complete evaporation of acetone, dried drug loaded microsphere were collected and stored in tight container for further evaluation. The compositions of formulation were given in table 1.

Table 1 Formulations of the mucoadhesive microspheres

F. Code	Thiolated chitosan (%w/v)	Tween-80 (%)	Span-80 (%)
F1	0.5	0.5	0.5
F2	1.5	0.5	0.5
F3	2.0	0.5	0.5
F4	1.5	1.0	0.5
F5	1.5	1.5	0.5
F6	1.5	2.0	0.5

Analytical method development

Determination of absorption maxima

A solution of containing the concentration 10 µg/ml was prepared in 0.1N HCl. UV spectrum was taken using Double beam UV/VIS spectrophotometer (Labindia-3000+). The solution was scanned in the range of 200-400nm.

Preparation calibration curve

Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1N HCl solution in 10 ml of volumetric flask. The resulted solution 1000µg/ml and from this solution 1 ml pipette out and transfer into 10 ml volumetric flask and volume make up with 0.1N HCl solution. Prepare suitable dilution to make it to a concentration range of 5-25 µg/ml. The spectrum of this solution was run in 200-400 nm range in U.V. spectrophotometer (Labindia-3000+). Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Evaluation of microspheres

Measurement of mean particle size

Average particles size of prepared microsphere was determined using particle size analyser (Malvern particle size analyser). The microsphere formulation was diluted with deionized water (1:9 v/v) and analysed for average size.

Determination of drug content

The amount of drug entrapped in the microspheres was determined using a UV spectrophotometer. The weighed amount of the microspheres was incubated with 0.1 N HCl, pH 1.2, for 48 h. It was centrifuged at 10,000 g for 30 min and the supernatant was diluted 10 times before analysis into the UV spectrophotometer system at λmax 292nm.

Mucoadhesion measurement study

Mucoadhesiveness of prepared microsphere was determined by taking a 5-6 cm length of piece obtained from freshly cut pig intestine which was procured from a local abattoir within 1 h after sacrificed of animal. It was washed with isotonic saline solution. The pig intestine piece was attached to a polyethylene plate and placed 10 mg of microspheres on the mucosal surface. Plate was positioned at 40° angle relative to the horizontal plane. The time required for shedding all the microspheres from mucosal surface was noted.

In Vitro drug release from microspheres

The drug release was performed in 0.1 N HCl (1.2 pH) for drug loaded thiolated chitosan microsphere. The drug release was performed in 0.1 N HCl (1.2 pH) for prepared microsphere using dialysis bag technique. In this study suspension of microsphere equivalent to 20 mg of drug was taken in dialysis tubing (MWCO, 15KDa, himedia) and placed in a beaker containing 50ml of 0.1 N HCl (1.2 pH). The

dialysis bag retains microsphere and allows passing of free drug into the dissolution media. Temperature was maintained at 37±1^{0}C throughout the study. The samples were withdrawn after specified time intervals that are 0.5, 1, 2, 3, 4, 8, 10 and 12hrs and replaced with the same volume of fresh 0.1 N HCl and analyzed for drug concentration by using UV spectrophotometer a λmax 292nm.

Drug release kinetic data analysis

A number of kinetic models have been planned to explain the release characteristics of a drug from matrix. The next three equations are usually used, because of their simplicity and applicability. Equation 1, the zero-order model equation (Plotted as cumulative percentage of drug released vs time); Equation 2, Higuchi's square-root equation (Plotted as cumulative percentage of drug released vs square root of time); and Equation 3, the Korsemeyer-Peppas equation (Plotted as Log cumulative percentage of drug released vs Log time). To study the release kinetics of stavudine from the mucoadhesive microspheres the release data was fitted to these three equations[11-13].

Zero order equation

When a graph of the cumulative percentage of the drug released from the matrix against time is plotted, zero order release is linear in such a plot, indicating that the release rate is independent of concentration.

$$Q_t = k_0.t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where $Q_{t\ is}$ the percentage of drug released at time t and k_0 is the releaserate constant;

First order equation

$$In\ (100\text{-}Q_t) = In\ 100\text{-}\ k_1.t \quad \ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where k_1 is the release rate constant;

Higuchi's equation

$$Q_t = k_H.t^{1/2} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

Where K_H is the Higuchi release rate constant

Korsemeyer-Peppas

The curves plotted may have different slopes, and hence it becomes difficult to exactly pin-point which curve follows perfect zero order release kinetics. Therefore, to confirm the kinetics of drug release, data were also analyzed using Korsemeyer's equation.

$$Q_t/Q_\infty = k_{KP}.t^n$$

Where Q_t/ Q_∞ is the fraction of drug released at time t, k_{KP}a constant compromising the structural and geometric characteristics of the device and n is the release exponent. The slope of the linear curve gives the 'n' value. Peppas stated that the above equation could adequately describe the release of solutes from slabs, spheres, cylinders and discs, regardless of the release mechanism. The value of 'n' gives an indication of the release mechanism. When n = 1, the release rate is independent of time (typical zero order release / case II transport); n = 0.5 for Fickian release (diffusion/ case I transport); and when 0.5 < n < 1, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when n > 1.0 super case II transport is apparent. 'n' is the slope value of log M_t/M_∞ versus log time curve[14].

RESULTS AND DISCUSSION

λ_{max} of lansoprazole was found to be 292 nm by using U.V. spectrophotometer (Labindia-3000+) in linearity range 5-25µg/ml. Percentage yield of different formulation was determined by weighing the microspheres after drying. The percentage yield of different formulation was in range of 65.56– 85.45%. The Particle size of different formulations was in range of 195.45±0.69- 298.80±0.65nm. This is due to the mucoadhesion characteristics of chitosan that could facilitate the diffusion of part of entrapped drug to surrounding medium during preparation of lansoprazole microspheres Table 2 and Fig 1.

Table 2 Results of percentage yield and particle size analysis of formulation F1-F6

S. No.	Formulation code	Percentage Yield	Particle size
1.	F1	68.98±0.25	298.80±0.65
2.	F2	65.56±0.12	256.21±0.25
3.	F3	85.45±0.25	195.45±0.69
4.	F4	76.54±0.14	269.98±1.25
5.	F5	73.25±0.36	278.85±0.96
6.	F6	72.15±0.14	292.12±0.45

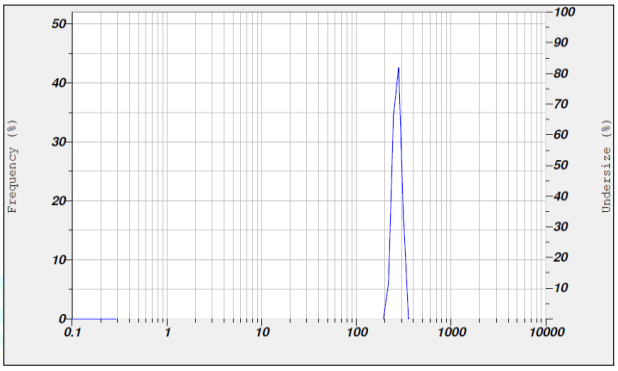

Figure 1 Graph of particle size analysis of optimized formulation F3

The amount of drug entrapped in the microspheres was determined using a UV spectrophotometer. The weighed amount of the microspheres was incubated with 0.1 N HCl, pH 1.2, for 48 h. It was centrifuged at 10,000 g for 30 min and the supernatant was diluted 10 times before analysis into the UV spectrophotometer system at λmax 292nm table 3. The results of mucoadhesiveness of prepared microsphere were given in table 3.

Table 3 Results of Drug content and % Mucoadhesion strength

S. No.	Formulation code	% Mucoadhesion strength	Drug Content
1.	F1	62.36±0.25	68.98±0.95
2.	F2	65.58±0.65	70.23±0.56
3.	F3	79.98±0.52	75.56±0.25
4.	F4	60.23±0.32	65.41±0.32
5.	F5	58.89±0.14	68.41±0.47
6.	F6	63.23±0.48	62.12±0.85

The drug release rate from mucoadhesive microspheres was passed out using the USP type II (Electro Lab.) dissolution paddle instrument. A weighed amount of mucoadhesive microspheres equivalent to 20 mg drug were dispersed in 900 ml of 0.1 N HCl (pH=1.2) maintained at 37 ± 0.5°C and stirred at 55rpm. The release study of optimized formulation F-3 was given in table 4. The kinetics of drug release from the microspheres was studied by mathematical modeling the drug release to zero order, first order kinetics Table 4 and Fig.5 & 6.

Table 4 Release study of formulation F-3

Time (h)	Square Root of Time(h)$^{1/2}$	Log Time	Cumulative* % Drug Release	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
0.5	0.707	-0.301	18.89	1.276	81.11±0.45	1.909
1	1.000	0.000	29.98	1.477	70.02±0.25	1.845
2	1.414	0.301	36.65	1.564	63.35±0.32	1.802
3	1.732	0.477	45.58	1.659	54.42±0.56	1.736
4	2.000	0.602	65.56	1.817	34.44±0.25	1.537
8	2.828	0.903	73.32	1.865	26.68±0.32	1.426
10	3.162	1.000	80.24	1.904	19.76±0.45	1.296
12	3.464	1.079	88.89	1.949	11.11±0.25	1.046

The *In vitro* drug release data of the optimized formulation was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of First order was maximum i.e 0.964 hence indicating drug release from formulations was found to follow First order release kinetics table 5 and fig 2 &3.

Table 5 Comparative study of regression coefficient for selection of optimize batch

	Zero order	First order
r^2	$R^2 = 0.906$	$R^2 = 0.964$

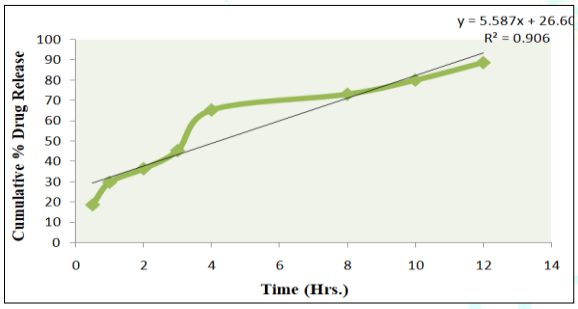

Figure 2 Zero order release Kinetics

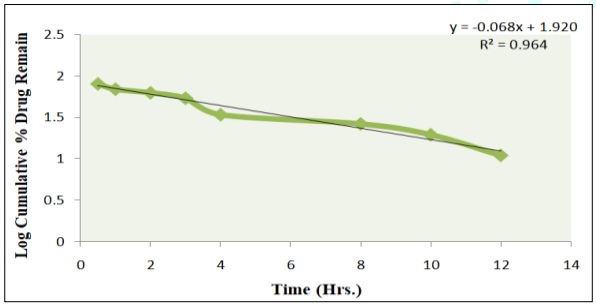

Figure 3 First order release kinetics

CONCLUSION

From the above experimental results, it can be concluded that oral controlled release of lansoprazole from microshere can be achieved by emulsifying method using thiolated chitosan as polymer and glutaraldehyde used as a cross-linking agent. The IR spectra's revealed that, there was no interaction between polymer and drug. The entire polymer used was compatible with the drug. Prepared microspheres exhibited First order release kinetics. From the study, it is evident that a promising controlled release microparticulate drug delivery of Lansoprazole can be developed. Further, *in-vivo* investigation is required to establish efficacy of these formulations.

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