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Stalin reddy Challa

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Research Article

Gastric Ulcer Prevention by Lansoprazole

Stalin reddy Challa*, Prasad Garrepally
Department of Pharmaceutics, Jangaon Institute of Parmaceutical Sciences, Jangaon,India

***Corresponding Author : Stalin reddy Challa, Department of Pharmaceutics,Jangaon,India.**

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Abstract

The objective of the current investigation is to formulate ethyl cellulose and hydroxypropyle methyle cellulose based sustained release microspheres, containing lansoprazole as model drugs. lansoprazole is type II anti-ulcer agent when administered shows synergetic effect in their action. Microspheres were prepared by W/O/O double emulsion solvent evaporation method with different stabilizer concentration and at different speeds of emulsification while maintaining constant amount of lansoprazole. Drug excipient compatibility study was performed prior to formulation development and only compatible excipients were used in the fabrication of microspheres. Prepared microsphere formulations were characterized by percentage yield, particle size analysis, entrapment efficiency, invitro release behavior, differential scanning colorimetry (DSC) and scanning electron microscopy (SEM). SEM studies showed that the microspheres were spherical with rough surface morphology. The drug loaded microspheres showed 10.4-57.9% entrapment capacity for lansoprazole and The invitro release profile showed a slow and steady release pattern for lansoprazole. A 95-98% was releases within a period of 12 hrs . The drug release was found to be diffusion controlled mechanism. The n value of Korsmeyer Peppas equation indicated non Fickian type of diffusion.

Keywords: microspheres; lansoprazole; hydroxypropyle methyle cellulose; ethyl cellulose; double emulsion solvent evaporation method; FTIR;SEM; DSC

Introduction

Sustained Release Formulation

For decades an acute or chronic illness is being clinically treated through delivery of drugs to the patients in form of some pharmaceutical dosage forms like tablets, capsules, liquids, creams, pills, aerosols, injectable, and suppositories with their main discrepancy to maintain drug levels within the therapeutic range. However, these conventional dosage forms have some drawbacks. Multiple daily dosing is inconvenient to the patient and can result in missed doses, made up doses and patient incompliance with the therapeutic regimen. When conventional immediate release dosage forms are taken on schedule and more than once daily, there are sequential therapeutically blood peaks and valley associated with taking each dose. It should be emphasized that the plasma level of a drug should be maintained within the safe margin and effective range.For this, proper and calculated doses of the drug need to be given at different time interval by conventional dosage form.[1]

This is possible through administration of conventional dosage form in a particular dose and particular frequency to provide a prompt release of drug. Therefore to achieve as well as to maintain the concentration within the therapeutically effective range needed by the treatment by repeated administration a day, results in a significant fluctuation in a plasma drug level, leads to several undesirable toxic effects, and poor patient compliance.[2]The loopholes of the conventional dosage forms lie in their inability:

Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms. Various terms like 'smart', intelligent', 'novel', therapeutic have been assigned to controlled release systems.

Methods and Materials

The following materials of Pharma grade or the best possible Laboratory Reagent grade were used as supplied by the manufacturer.

S.No	CHEMICAL NAME	SOURCE	PURPOSE
1	Lansoprazole	MSN Laboratories, Hyderabad, India	Drug
2	Ethyl Cellulose	SD Fine chemical Ltd, Mumbai, India	olymer
3	Dichloro Methane (DCM)	SD Fine chemical Ltd, Mumbai, India	Polymer
4	Paraffin Liquid (light)	SD Fine chemical Ltd, Mumbai, India	Solvent
5	Span 80	SD Fine chemical Ltd, Mumbai, India	Stabilizer
6	N- Hexane	SD Fine chemical Ltd, Mumbai, India	Solvent
8	Potassium dihydrogen Phosphate	SD Fine chemical Ltd, Mumbai, India	Buffer ingradient
9	NAOH pellets	SD Fine chemical Ltd, Mumbai, India	Buffer ingradient

Table 1: List of materials used and supplier

Lansoprazole

Lansoprazole belongs to class of antisecretory compounds, the substituted benzimidazoles that donot exhibit antocholinergic or histamine H2 receptor antagonist properties but rather supress gastric acid secretion by inhibition of the H+, K+ ions.

Lansoprazole has been charecterised 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.

Analytical method development

Preparation of buffer pH 6.8

50ml of the potassium dihydrogen phosphate (0.2M) was placed in 200ml volumetric flask and to it 22.4ml of sodium hydroxide solution (0.2M) was added and the volume was made upto 200ml with distilled water.

Preparation of standard solution of lansoprazole:

Procedure: Accurately weighed 100 mg of lansoprazole drugwas dissolved in 100 mL of (Conc. 1000 µg/mL). From this solution, 10 mL was pipetted out into 100 mL volumetric flask and volume was made up to with methanol (Conc. 100 µg/mL). Further 10ml aliquot was taken from this solution (100µg/ml) and diluted to 100ml with methanol to give 10µg/ml standard solution of drug.

Similarly, standard stock solution was prepared in phosphate buffer pH 6.8 and methonol.

Preparation of microspheres

For the preparation of microspheres the double emulsion method was used as suggested by Rama Rao et al. (2005) with slight modifications. The polymer was dissolved in a mixed solvent system (MSS) of acetonitrile and dichloromethane. To this polymer solution glipizide was added and mixed. Then metformin was dissolved separately in 3 ml of distilled water and added to the polymer solutionwhile stirring to form a primary emulsion. This primary emulsion wasstirred at 450 rpm for 15 min using a mechanical stirrer. Then, this w/o emulsion was poured into liquid paraffin containing Span180 as the surfactant. This was stirred using a mechanical stirrer for 3 h, for the complete evaporation of the solvent. 10 ml of n-hexane was addedas the non solvent after 2 h of the stirring process. [47]

Treatment and randomization

All patients who met the inclusion and exclusion criteria received a 1 week course of antihelicobacter therapy containing lansoprazole 30 mg, amoxicillin 1 g and clarithromycin 500 mg, given twice daily. This was followed by treatment with lansoprazole 30 mg, given daily for 4 weeks. Repeat endoscopy was performed at the end of treatment to check for healing of ulcers and eradication of H. pylori using the methods described above. Patients with unhealed ulcers would be given 30 mg of lansoprazole daily for another 4 weeks. Patients who failed H. pylori eradication, defined as a positive rapid urease test or histology, would receive another 1 week course of triple therapy containing ranitidine bismuth citrate 400 mg, amoxicillin 1 g and metronidazole 400 mg, given twice daily. Patients with unhealed ulcers and two unsuccessful eradication treatments of H. pylori were taken out of the study.

Results and Discussion

In the present investigation an attempt has been made to formulate microspheres of lansoprazole by using biocompatible polymer like ethyl cellulose and hydroxypropyle methyle cellulose as carrier for sustained release. Microspheres were prepared by double emulsion solvent evaporation method. Prepared microspheres are subjected for characterization and evaluation studies.

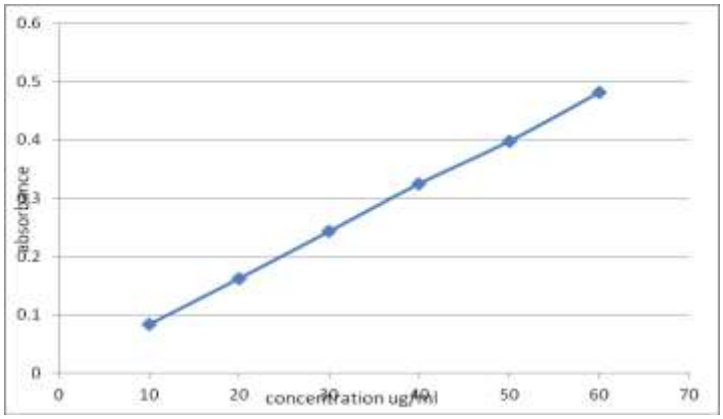
Characteristics of patients

Among 102 patients screened during the study period, 45 were suitable for entry into the trial and were given a 1 week course of triple therapy, followed by treatment with lansoprazole. Reasons for exclusion are given in Figure 1. Two patients had persistent H. pylori infection after the first course of eradication therapy; they received the second antihelicobacter therapy and H. pylori was eradicated in both patients. Two patients had persistent ulcers after repeated anti- ulcer treatment and were excluded from the study. The remaining 43 patients were given naproxen 750 mg daily and randomly assigned to receive lansoprazole treatment (n = 22) or no treatment (n = 21).

	No treatment group (*n* = 21)	Lansoprazole group (*n* = 22)
Mean age, years (range)	67.1 (41–78)	70.2 (43–78)
Age ≥ 65 (%)	13 (59.1)	12 (57.1)
Female gender (%)	8 (36.4)	11 (52.4)
Diagnosis (RA/OA/other)	6/15/2001	4/17/2000
Smoking (%)	3 (13.6)	2 (9.5)
Alcohol (%)	2 (9.1)	2 (9.5)
Co- morbid illnesses (%)	8 (36.3)	9 (42.9)
Location of ulcer (gastric ulcer/duodenal ulcer)	18/4	15/6
Ulcer size	11.2 ± 4.0	10.3 ± 4.3
Bleeding on presentation (%)	17 (77.3)	13 (61.9)
Characteristics of ulcer bleeding		
Admission haemoglobin, g/dL	9.5 ± 1.5	9.3 ± 1.2
Transfusion required, units	1.1 ± 1.3	1.4 ± 1.2
Before endoscopy	0.76 ± 1.03	1.0 ± 1.0
After endoscopy	0.29±0.47	0.38 ± 0.51
Median ulcer size, mm (range)	10.0 (5–20)	10.0 (5–20)
Admission pulse ≥ 100 beats/min (%)	4 (23.5)	3 (23.1)
Admission systolic BP < 100 mmHg (%)	4 (23.5)	2 (15.4)
Shock at presentation * (%)	4 (23.5)	2 (15.4)
Serum urea > 10 mmol/L	10 (58.8)	10 (76.9)
Location of ulcer (gastric ulcer/duodenal ulcer)	14/3	3-Oct
Endoscopic haemostasis (%)	7 (41.2)	3 (23.1)

Data of standard graph of lansoprazole in ph.6.8 phosphate buffer

Concentration (ug/ml)	Absorbance in phosphate buffer
10	**0.083**
20	**0.162**
30	**0.243**
40	**0.325**
50	**0.398**
60	**0.482**



Standard graph of lancoprazole in phosphate Buffer of Ph

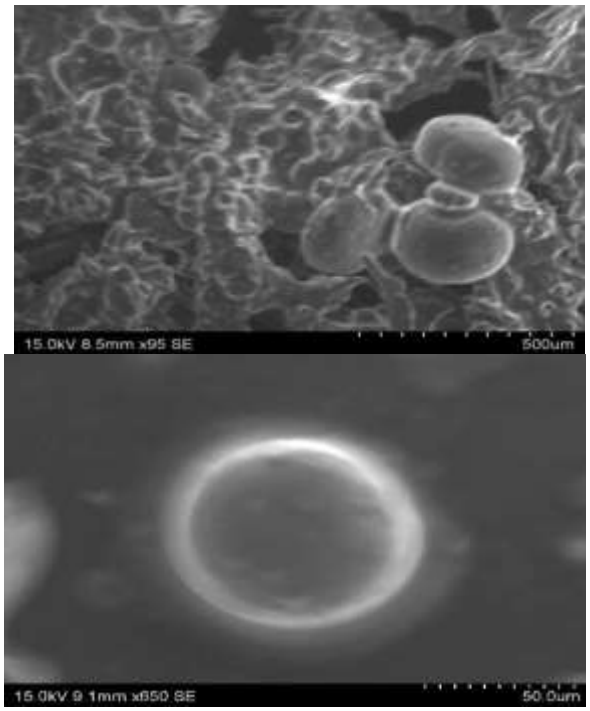
Preformulation Studies

Preformulation study for lansoprazole has been performed to know the drug physical properties so as to design it to a suitable formulation.

Physical property	lansoprazole
Empirical Formula	$C_4H_{11}N_5.HCl$
Molecular Weight	369.36 daltons
Color and odour	White brownish colour powder
Taste	Slightly bitter in taste
Appearance	Crystalline powder

Table: Description data of lansoprazole

Surface Morphology By Sem



Particles in spherical shape

Conclusion

From the study it is evident that promising sustained release microspheres of lansoprazole may be developed by W/O/O double emulsion solvent diffusion technique by using ethyl cellulose and hydroxyl prople methyle cellulose polymer.

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