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Formulation and Evaluation of Enteric Coated Sustain Release Tablets of Lansoprazole in a β-Cyclodextrin Complex to Improve the Photostability

Madusudhan RaoYamsani*, Shravan Kumar Y, Architha S, NareshNomula, and Avinash M.

Department of Pharmaceutics, Vaagdevi College of Pharmacy, Naimnagar, Hanamkonda, Warangal-506009, Telangana, India.

ABSTRACT: Enteric coated sustain release Lansoprazoletablets which are proton pump inhibitors in action, are widely used in the treatment of gastric ulcers. The aim of the present study is to improve photostabilityof Lansoprazole. Enteric Coated sustain release tablets of Lansoprazolewere formulates by using enteric polymers like Kollicoat MAE 30DP, and Eudragit L 100. Primary characterization of the drug was done by performing the melting point, identification test by Fourier Transform Infrared Spectroscopy, solubility and assay. To understand the compatibility of the drug with excipients, drug-excipient studies were carried out using Infrared spectroscopy. Using complexation technique different ratios of the drug were complexed with cyclodextrin to improve photostability. The stability test results indicated that the inclusion complex was more stable than raw Lansoprazole in the light. It was observed that inclusion complex of Lansoprazole showed increased the solubility by about 4.5 times. There were no significant differences between 30 min, 6 h and 24 h for either raw material or inclusion complex. Among the four polymers chitosan, xanthum gum, locust bean gum, and guar gum as polymers, chitosan was chosen for further coating process. Physico-chemical and in-vitro drug release studies were performed to all the formulations. F4c formulation was found to be best formulation which showed better resistance in 0.1N HCL, sustained well and with in-vitro release of97.83± 0.39% release in 12hrs.

KEY WORDS: Complexation, FTIR, Beta cyclodextrin, Chitosan, Gastric ulcers, Kollicoat, Lansoprazole, Photostability.

I. INTRODUCTION

The two fundamental issues of importance in drug therapy are safety and efficacy. The properties of the active pharmaceutical ingredients (API) such as physical, chemical, pharmacological and toxicological properties are changed due to instability of pharmaceuticals, thereby affecting its safety and efficacy. Stability is officially defined as time period in which the drug product remains the same properties and characteristics that it possessed it at the time of its manufacturing. The stability of drug product is always expressed in terms of its shelf life. Most valuable attribute for all dosage forms is its expiration period[1-3].

Importance of stability studies:

- Loss of potency of the drug is the most important consequence of the photo instability. Product instability may lead to under medication due to lowering of active drug concentration of dosage form.
- Drug decomposition may leads to formation of toxic products.
- Bleaching ordiscolouration of products is the indicators of photodegradation; the most important consequence of photo degradation is the loss of potency of the product.

The photostability studies are carried out to demonstrate that the appropriate light exposure does not results into unacceptable changes in dosage form. Photostability deals with the effect of light on stability of pharmaceuticals substances/products. Light can influence the active principle in drug formulation, as well as the final product or package. The other effects include cloudy appearance of the product, a loss in viscosity of formulation, Precipitation of active principle, alteration in dissolution rate, Light sensitive drugs can be affected by sunlight (ultraviolet light) or by artificial light (like florescent light)[4,5],

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In recent times, the development of stability-indicating methods has increased enormously using the approach of stress testing as outlined in the International Conference on Harmonization (ICH) guideline Q1B.

To attain optimum therapeutic activity an ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time. To achieve the desired blood concentration for better therapeutic activity multiple dosage is always a choice for the drugs which do not have long sustained activity. Thus sustained release drug delivery system has gained its importance to reduce multiple dosing. Drug administration by conventional dosage form causes poor compliance among the patients and also causes fluctuations in plasma level [5]. Drugs like Lansoprazole are incompatible with gastric juice, for the reason they are enteric coated. Added advantage of sustained release dosage forms is controlled release within narrow therapeutic range which minimizes side effects[6].

II. MATERIALS AND METHODS

MATERIALS

Lansoprazole was gifted from Reddy's laboratories; (Hyderabad, India).The polymers chitosan, Xanthan gum, Guar gum and Locust bean gum were obtained from ChemiPvt.Ltd (Bangalore, India). Eudragit L100 and Kollicoat MAE 30 DP were obtained from BASF chemicals.

METHODS

a. FTIR Studies

The drug Lansoprazole, polymers and other excipients compatibility were studied by BrukerFTIR analysis. The drug interaction with polymers and excipients were studied separately and in combinations to investigate the chemical composition before and after combination. The spectra was analyzed and interpreted in wavelength region ranged from 400 to 4000cm^{-1} after pure drug, mixture was mixed properly and Placed under Bruker FTIR.

b. Preparation of Lansoprazole Complexes

Lansoprazole and βCD are complexed by using complexation technique at different molar ratios and are dissolved under stirring until a clear solution is obtained, sample was evaporated and dried andthen passed through a 60-mesh sieve to carry out photostability studies.

c. Solubility Study

A triplicate study of solubility was conducted forLansoprazole and inclusion complex of lansoprazole-βCD separately, which were dissolved in 100ml of phosphate buffer. Thesamples were sonicated for 30 min, sealed and shook for 24 h to ensure equilibrium. The suspensions were subsequently filtered through a 0.45µ membrane filter. The filtered sample solutions were analyzed using UV spectrophotometer system at a wavelength of 286 nm.

d. HPLC Analysis:

HPLC analysis of the samples were carried out with the Shimadzu High Performance Liquid Chromatography system equipped with a LC 20AT pump and SPD 10 AT UV visible detector and RP C18 column (kromasil, 250mm x 4.6 mm ID, and particle size 5µm). The mobile phase used was a mixture of acetonitrile, phosphate buffer (pH 7) 70:30 v/v, the pH was adjusted to 7 with orthophosphoric acid. The elution was monitored at 286nm, at a flow rate is 0.8 mL/min.

e. Photostability Study

To study the photostability of the drug two solutions were prepared individually. The first solution was pure Lansoprazole was dissolved in the HPLC mobile phase at a concentration of (100ng and 1000ng) respectively. In the second solution the inclusion complex, equivalent to Lansoprazole at a concentration of 100ng and 1000ng was dissolved in the HPLC mobile phase. The solutions were transferred to a cylindrical transparent container and exposed to radiation for 4 days. The irradiation with UV light was performed later. The sample solutions were filtered and analyzed using Shimadzu HPLC system at a wavelength of 286 nm[7-10].

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f. Formulation of Lansoprazole Tablets

Direct compression method was employed to prepare enteric coated sustain release tablets of Lansoprazole or drug-βCD complex with natural polymers using 8 mm concave punches and corresponding dies. A 16 station rotary compression machine (Cemach machineries, Ahmadabad, India) is ueds for this purpose. Polymers used are Chitosan, guar gum, xanthan gum and locust bean gum. Mannitol and MCC pH 102 used as fillers. Magnesium state is used as lubricant. Lansoprazole was first mixed with the polymer mixture for 10 min in a motor and pestle. Filler and lubricant were then added, and mixing continued for another 10 min. The ingredients used in different formulations were shown in table 1. Formulation F4 was selected for further coating as seen in table 2. After core coating, sub-coating as well as enteric coating is done for all F4 formulations (F4a, F4b, F4c, F4d, F4e and F4f).

Sl. No	INGREDIENTS	FORMULATIONS qty./ tab (mg)			
		F1	F2	F3	F4
1	Lansoprazole	30	30	30	30
2	βCD	90	90	90	90
3	Locust bean gum	20	-	-	-
4	Xanthan gum		20	-	-
5	Guar gum	-		20	-
6	Chitosan	-	-		20
7	Mannitol	34	44	44	44
8	MCC pH102	20	70	70	70
9	Magnesium stearate	4	4	4	4
10	Talc	2	2	2	2
	Total Weight	**200**	**200**	**200**	**200**

Table 1: Core tablet formulations.

S.NO	INGREDIENTS	Qty/tab(mg)	Qty/100 tablets
1	Lansoprazole	30	3000
2	BCD	90	9000
3	Chitosan	20	2000
4	Mannitol	34	3400
5	MCC pH102	20	2000
6	Magnesium stearate	4	400
7	Talc	2	200

Table 2: Selected formulation (Core tablets) for enteric coating.

S.No	INGREDIENTS	Qty
1	HPMC 5cps	1.1g
2	Water	20mL

Table 3: Sub-coating for all the formulations (2% weight buildup) .

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S.No	INGREDIENTS	6% wtgain		8% wt gain		10%wt gain	
		F4a	F4b	F4c	F4d	F4e	F4f
1	Eudragit L 100	5	-	5	-	5	-
2	Kollicoat MAE30DP (mL)	-	20		20		20
3	Tri ethyl citrate (mL)	2.5	2.5	2.5	2.5	2.5	2.5
4	Talc (gr)	2	2	2	2	2	2
6	Isopropyl alcohol (mL)	50		50		50	
7	Methanol(mL)	50		50		50	
8	Water		100		100		100
9	Colour	qs	qs	qs	qs	qs	Qs

Table 4: Enteric coating (6, 8 and 10% weight buildup).

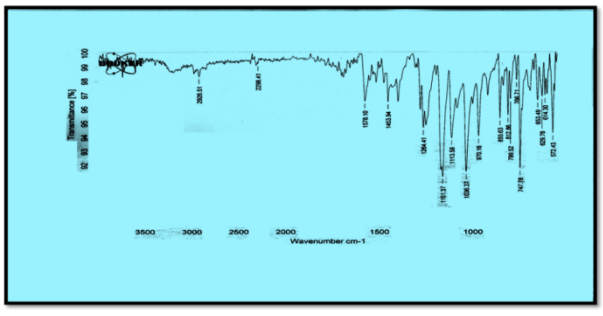
S.NO	INGREDIENTS	FORMULATIONS		
		F4c	F4c1	F4c2
1	Eudragit L 100	5	5	5
2	Tri ethyl citrate	2.5	3	3.5
3	Talc	2	2	2
4	Methanol	50	50	50
5	Isopropyl alcohol	50	50	50

Table 5: Enteric coating (8% weight buildup, Plasticizer effect).

Enteric coated tablets were further evaluated for all parameters.

III. RESULTS

FTIR RESULTS:



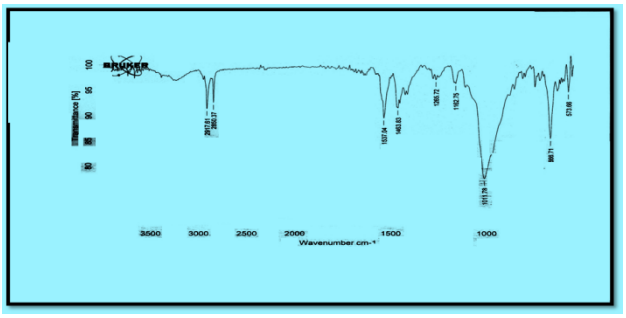


Figure 1:FTIR Spectra of pure Lansoprazole.**Figure 2:** FTIR Spectra of optimized formulation.

The drug-excipient compatibility study was carried out using FTIR. The spectral data obtained from Figure 1 and 2 showed that Lansoprazole is compatible with all the excipients used in the formulation except with Eudragit L100. In order to overcome this problem sub coating was given before enteric coating.

Qualitative determination of Lansoprazole (photostability) by HPLC Analysis:

HPLC analysis were conducted with drugand complexing agent in the ratios 1:1, 1:2, 1:3 in 100ng concentration as shown in figures 3,4,5 and 6. From the HPLC analysis it was found that from all the drug-complexing agent (inclusion complex) ratios prepared 1:3(100ng) ratio was found to be stable. From the graphical representation of HPLC peaks the optimized ratio showed no degrading peaks when compared to the raw Lansoprazole.

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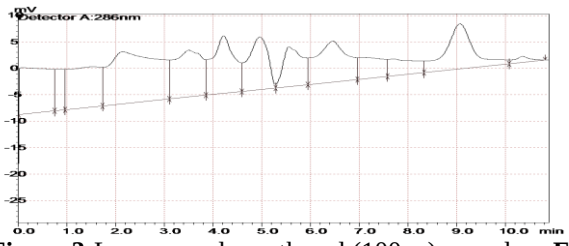


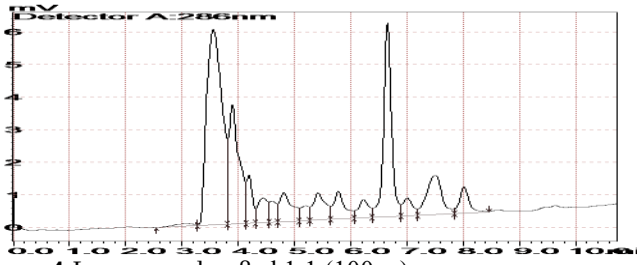
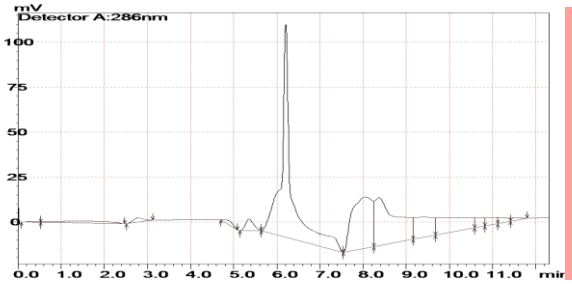


Figure 3: Lansoprazole-methanol (100ng) pure drug.**Figure 4:**Lansoprazole - βcd 1:1 (100ng).



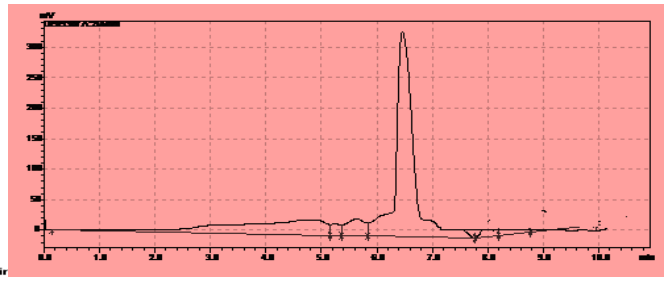


Figure 5: Lansoprazole -βcd 1:2 (100ng).**Figure 6:**Lansoprazole -βcd 1:3(100ng)

Solubility:

Table 6 shows inclusion complex increased the solubility of Lansoprazole by about 4.5 times. There were no significant differences between 30 min, 6 h and 24 h for either raw material or inclusion complex.

Formulation	Solubility 30min	Solubility 6h	Solubility 24h
Lansoprazole	4.23 ± 2.42	4.68 ± 1.22	4.89 ± 1.22
Inclusion complex1:3	16.56 ± 1.22	16.76 ± 1.22	16.79 ± 1.22

Table 6: Lansoprazole solubility in 6.8 pH buffer.

Physical Properties of Enteric Coated Formulations :

The weight variation in all the formulations was found to be 206.40±0.18 mg to 223.60±0.30mg which was in pharmacopoeia limits. The thickness varies between 3.65±0.01 to 4.2±0.06 mm. In all formulations, tablet weight and thickness were within mean ± 7.5% and mean ± 5 % respectively.

Assay was performed and percent drug content of all the tablets were found to be between 98.36 ± 0.38 and 100.82 ± 0.39 of Lansoprazole which was within the acceptable limits (Table 7).

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Formulation code	Weight variation (mg)	Thickness (mm)	Assay %
F4a	206.40 ± 0.18	4.2 ± 0.06	100.01 ± 0.39
F4b	211.52 ± 0.15	4.00 ± 0.10	98.70 ± 0.48
F4c	216.09 ± 0.08	3.65 ± 0.01	99.97 ± 0.26
F4d	218.09 ± 0.20	4.5 ± 0.02	100.82 ± 0.39
F4e	215.47 ± 0.71	4.00 ± 0.04	98.36 ± 0.38
F4f	223.60 ± 0.30	4.00 ± 0.06	99.10 ± 0.38
F4c1	221.09 ± 0.20	3.83± 0.12	99.89±1.20
F4c2	223.60 ± 0.30	3.82±0.16	101.20±0.64

Table 7: Physical properties of enteric coated formulations.

Drug Release:

Formulation Code	Drug Release at 0.1 N HCl (2hrs)	Drug Release time at 6.8 pH phosphate buffer (min)
F4a	Cracking observed after 60 min	8.45 ± 0.42
F4b	Cracking observed after95 min	7.86 ± 0.12
F4c	No drug release in 2hrs	6.93 ± 0.78
F4d	Cracking observed after 105 min	9.75 ± 0.24
F4e	No drug release in 2hrs	9.66 ± 0.41
F4f	No drug release in 2hrs	8.51 ± 0.21

Table 8: Drug Release of Lansoprazole enteric coated tablets in 0.1 N HCl (pH 1.2) followed by 6.8 pH phosphate buffer**.**

The drug release of the tablets formulated is known by Dissolution test.This testis used as a tool to evaluate the functional qualities of the enteric coat during exposure to simulated gastric fluid. Immediately after simulated gastric fluid exposure, each tablet was visually inspected for any evidence, which would indicate improper function of the enteric coat then transferred to a phosphate buffer media as shown in table 8. All the enteric coated tablets readily passed the USP enteric coated testexcept the formulations F4a, F4b & F4d with 6% weight buildup in 0.1N HCl.The amount of drug released was found to be different in different formulations as different polymers were used. Among all formulations F4C showed no drug release in 0.1N HCl during 2hrs and within 6.93min the drug has been released in 6.8 pH phosphate buffer indicating that it is the best formulation.

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	Cumulative drug release (%) ± SD (n=3)			
Sample time(hrs)	**F4c**	**F4d**	**F4e**	**F4f**
0	0	0	0	0
1	28.20 ± 0.63	25.49 ± 0.06	12.36±1.00	23.25 ± 0.18
2	41.41 ± 0.67	30.27 ± 0.10	29.69±1.03	34.05 ± 0.15
3	55.68 ± 0.39	37.84 ± 0.01	40.84±0.36	43.26 ± 0.08
4	59.47 ± 0.82	43.46 ± 0.02	45.84±0.82	49.40 ± 0.20
5	65.53 ± 0.7	52.54 ± 0.04	59.15±0.78	51.26 ± 0.71
6	71.91 ± 0.78	57.04 ± 0.06	62.27±0.85	61.70 ± 0.30
7	77.95 ± 0.78	61.34 ± 0.45	67.46±1.08	68.33 ± 0.36
8	83.53 ± 0.98	68.83 ± 0.34	68.93±1.29	71.24 ± 0.46
9	89.47 ±0.92	76.33± 0.08	70.26±1.23	75.68 ± 0.28
10	91.31 ± 0.85	79.92± 0.12	75.65±1.18	79.25 ± 0.27
11	93.89 ± 0.85	82.25±0.16	77.8±1.32	86.30±0.86
12	97.03 ± 0.39	85.05±1.22	79.56±0.89	90.82±0.16

Table 9: In vitro dissolution studies for F4c, F4d, F4e and F4f.

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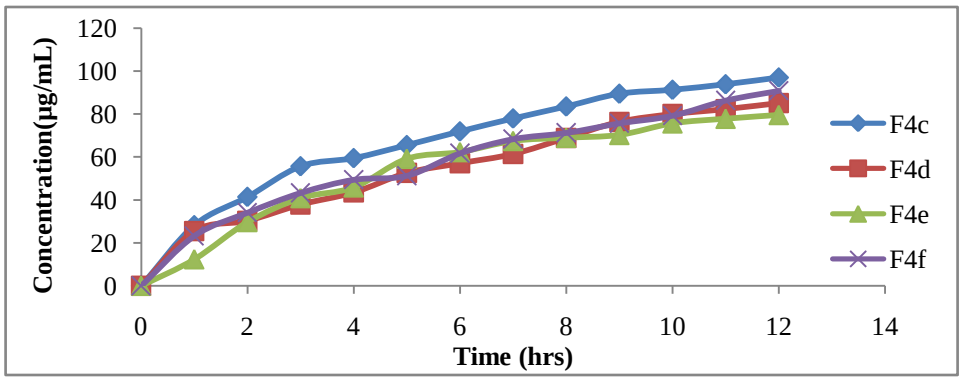

Figure 7: Graphical representation of cumulative percent of Lansoprazole released from Coated tablets.

The in vitro drug release study was performed for F4 formulations. From the in vitro drug release study it was found that from all the formulations of F4, F4c demonstrated excellent physical resistance to the acid medium after 2 hour and the drug release showed good sustain effect when compared to F4d, F4e,and F4f formulations (Table 9) and was found to be within specified limits.

IV. DISCUSSION

Preformulationcharacterization of the drug was done by performing the melting point, identification test by FTIR, solubility and assay. Then drug excipient interaction studies were carried out using IR.
From the photostability test it is revealed that, the inclusion complex was more stable than the raw Lansoprazole in the light. The inclusion complex increased the solubility of Lansoprazole by about 4.5 times. It was observed that there were no significant differences between 30 min, 6 h and 24 h for either raw material or inclusion complex.Out of four formulations of core tablets were prepared, F4 was chosen for further coating process. Because the powder blend showed good flow property and it showed better sustain effect as compared to other formulations. Then F formulation was sub-coated with 2% weight build of HPMC and enteric coated by using different polymers like Kollicoat 30DP and Eudragit L 100.

Among Six formulations prepared (i.e. F4a to F4f), four formulations F4a – F4b 6% weight buildup was given, Formulations F4c- to F4d 8% weight buildup was given and to the next three formulations F4e to F4f 8% weight buildup was given all the formulations were evaluated for their physicochemical parameters like thickness, disintegration time, drug content and dissolution studies. The formulations (i.e. F4a to F4b) with 6%weight buildup in 0.1N HCl could not pass the drug release test. However, formulations with 8% weight buildup (F4c to F4d) showed no drug release in 0.1N HCl for a period of 2hrs.The in vitro drug release study was performed for formulations F4c. From the in vitro drug release study it was found that all the formulations F4c demonstrated excellent physical resistance to the acid medium after 2 hour and the drug release showed good sustain effect and was found to be within specified limits. In phosphate buffer (pH 6.8), formulations F4c (8% weight buildup) drug release was found to be within limits. Among the all formulations F4c showed 97.83± 0.39% release in 12hrs. It was found that formulation F4c showed better release than the other formulations.

V. CONCLUSION

Photostability is the major problem for the drugs like Lansoprazole. Hence the study was undertaken and enteric Coated sustain release tablets of Lansoprazole were formulated by using enteric polymers like Kollicoat MAE 30DP and Eudragit L 100.The in vitro drug release studies infers thatwith the increase in plasticizer there is a decreased drug release in both 0.1 N HCl and 6.8 pH phosphate buffer on the formulations F4c, F4c1 and F4c2. From the above evaluation results of the

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enteric coated sustain release tablets, the formulation F4c was selected as the optimized formulation. To conclude it can be stated that Lansoprazole and βCD complex improves the photostability of the enteric coated sustain tablets of Lansoprazole.

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