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Formulation and *In Vitro* Evaluation of Lansoprazole Delayed Release Capsules

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ABSTRACT

The Present research work is "formulation and evaluation of lansoprazole delayed release capsules 30mg" is a category of proton pump inhibitor (PPI) used in treatment of gastro esophageal reflux disease (G.E.R.D), erosive esophagitis (E.E) and acid – related disorders. Lansoprazole is an acid labile drug. It degrades in the acidic environment of the stomach thus leading to therapeutic inefficacy. Therefore it is necessary to bypass the acidic p^H of the stomach. The present research work emphasis mainly on selection of drug that is lansoprazole and excipients of various like HPC-L and eudragit L30 D55 were used as enteric polymers. The enteric coated pellets were prepared by suspension layering technique in fluidized bed processor (FBP). Ten Formulations (F1 - F10) lansoprazole enteric coated pellets were prepared varying the compositions of drug loading, barrier coating and enteric coating. The prepared pellets were studied for their physico- chemical properties, assay and *in vitro* release studies. The release kinetics was analyzed using zero-order model, first-order model and higuchi's square rot equation. FT-IR was performed to know the compatibility of the drug with various excipients and SEM analysis was performed to know the morphology of the pellet. All the 10 formulations are kept for Stability studies and carried out for 3 months at 40°C/75 %RH and 25°C/60 % RH according to ICH guidelines. The optimized formulation F 10 was shown desirable *in vitro* acid and buffer drug release during the stability period and comparable to the innovator.

Keywords: Pellets, Lansoprazole, Suspension layering method, HPC-L, Eudragit L30 D55.

INTRODUCTION

The term "drug delivery" can be defined as "the techniques that are used to get the therapeutic agents inside the body". The Oral Solid Dosage forms are the preferred route of administration for many drugs and most widely used formulations for new and existing modified release products. As they provides several advantages compared to single- unit dosage forms (e.g.: Pellets, capsules or tablets) and have risks such as spontaneous drug release from a single-unit tablet due to damage coating or its attachment in the stomach or intestine causing an irritation of the gastric or intestinal mucosa, are reduced by the use of multiunit forms. Moreover, such small single units enable a more reproducible dispersion throughout the gastrointestinal tract leading to a reduction of drug release variations and an improved bioavailability. Thus it reduces in drug dose and side effects. The objective of the present study is to develop a pharmaceutically equivalent, low cost quality improved and stable formulation of lansoprazole delayed release capsules comparable to innovator product (Jain NK 2008).

Lansoprazole is a proton pump inhibitor used in treating gastric ulcers and gastro esophageal reflux disease (GERD) and also maintaining of all grades of erosive esophagitis (EE). lansoprazole is highly acid labile and presents many formulation challenges and to protect it from acidic environment of the stomach an enteric coated pellets formulation is tried in the present study. The enteric polymers are becoming very popular due to their property of remaining intact in the stomach, but will dissolve and release the contents. Once it reaches the small intestine. The prime intention is to delay the release of drugs which are inactivated by the stomach contents or may cause bleeding or nausea by the irritation of gastric mucosa. The enteric coated polymer in various proportions was tried in the present study to design the formulation and evaluation of lansoprazole delayed release capsules.

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MATERIALS AND METHODS

Materials: Lansoprazole (Lee pharma ltd), Sugar Spheres (#30/35) (RA Chem), Low substituted-HPC NF

(LH-31) (Merck pvt ltd), HPC-L (Merck pvt ltd), Eudragit L30D55 (Merck pvt ltd).

Preparation of Standard graph of drug in 0.1N HCl

Accurately weighed amount (100 mg) of the lansoprazole was dissolved in methanol in 100 ml volumetric flask and the volume was made up. From this stock solution 10 ml is withdrawn in to volumetric flask, made the volume up to 100 ml with 0.1N HCl. From this second stock solution (100 µ/ml), concentrations of 2, 4, 6, 8, 10, 12 µg/ml solutions were prepared and corresponding absorbance was measured at 330 nm in a UV/Visible spectrophotometer.

Preparation of Standard graph of drug in pH 6.8 Phosphate buffer

Accurately weighed amount (100 mg) of the lansoprazole was dissolved in methanol in 100 ml volumetric flask and the volume was made up to 10 ml. From this stock solution 10 ml is withdrawn in to volumetric flask, made the volume up to 100 ml with pH 6.8 buffer. From this second stock solution (100 µ/ml), concentrations of 2.5, 4, 4.5, 5, 5.5, 6 µg/ml solutions were prepared and corresponding absorbance was measured at 285 nm in a UV/Visible spectrophotometer.

Preformulation study

Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

Preparation of Lansoprazole enteric coated pellets

Lansoprazole enteric coated pellets were prepared by coating the sugar spheres with drug and polymers with varying concentrations by using suspension layering technique in Fluidized bed processor (FBP) (Issac Ghebre *et al*., 2008).

Table.1 Composition of Lansoprazole capsules F1 to F5

S. No.	Ingredients	mg/cap				
		F 1	F 2	F3	F 4	F 5
Drug layering						
1	Sugar spheres (#30/35)	110	110	110	110	110
2	Lansoprazole	30	30	30	30	30
3	Low substituted-HPC NF(LH-31)	18	18	18	18	18
4	Magnesium carbonate heavy	22.4	22.4	22.4	22.4	22.4
5	Sucrose	18.05	18.05	18.05	17.310	18.05
6	Maize starch	20.05	20.05	20.05	20.05	20.05
7	Polysorbate 80	3.52	2.88	3.2	3.2	3.2
8	HPC-L	0.54	0.54	0.54	1.28	2.01
9	Purified water	q.s	q.s	q.s	q.s	q.s
Seal coating						
10	Low substituted-HPC NF(LH-31)	14.180	14.180	14.180	14.180	14.180
11	Sucrose	18.976	18.976	18.976	18.976	18.976
12	HPC-L	9.055	9.055	9.055	9.055	9.055
13	Maize starch	14.488	14.488	14.488	14.488	14.488
14	Titanium dioxide	7.430	7.430	7.430	7.430	7.430
15	Purified water	q.s	q.s	q.s	q.s	q.s
Enteric coating						
16	Eudragit L30 D55	47.567	59.460	59.460	59.460	59.460
17	Talc	4.757	5.946	5.946	5.946	5.946
18	Polysorbate 80	1.780	2.226	2.226	2.226	2.226
19	Macrogol 6000	4.658	5.822	5.822	5.822	5.822
20	Purified water	q.s	q.s	q.s	q.s	q.s
Lubrication						
21	Talc	0.4900	0.4900	0.4900	0.4900	0.4900
22	Silica colloidal anhydrous	0.010	0.010	0.010	0.010	0.010
Capsule fill weight						
23	Hard gelatin capsule shell	345.95	354.05	360.30	360.32	361.05

Table.2 Composition of Lansoprazole capsules F6 to F10

S. No.	Ingredients	mg/cap				
		F 6	F7	F 8	F 9	F 10
Drug layering						
1	Sugar spheres(#30/35)	110	110	110	110	110
2	Lansoprazole	30	30	30	30	30
3	Low substituted-HPC NF(LH-31)	18	18	18	18	18

4	Magnesium carbonate heavy	22.4	22.4	22.4	22.4	22.4
5	Sucrose	18.05	18.05	18.05	18.05	18.05
6	Maize starch	20.5	20.5	20.5	20.5	20.5
7	Polysorbate 80	3.2	3.2	3.2	3.2	3.2
8	HPC-L	1.28	1.28	1.28	1.28	1.28
9	Purified water	q.s	q.s	q.s	q.s	q.s
Seal coating						
10	Low substituted-HPC NF(LH-31)	15.660	17.138	15.660	15.660	15.660
11	Sucrose	20.976	22.936	20.960	20.960	20.960
12	HPC-L	10.00	10.0	10.0	10.0	10.0
13	Maize starch	16.00	17.510	16.0	16.0	16.0
14	Titanium dioxide	8.206	8.980	8.206	8.206	8.206
15	Purified water	q.s	q.s	q.s	q.s	q.s
Enteric coating						
16	Eudragit L30 D55	58.104	60.81	59.460	59.460	59.460
17	Talc	5.810	6.080	7.072	4.872	5.946
18	Polysorbate 80	2.175	2.276	1.100	2.300	3.226
19	Macrogol 6000	5.688	5.954	5.822	5.822	5.822
20	Purified water	q.s	q.s	q.s	q.s	q.s
Lubrication						
21	Talc	0.4900	0.4900	0.4900	0.4900	0.4900
22	Silica colloidal anhydrous	0.010	0.010	0.010	0.010	0.010
Capsule fill weight						
23	Hard gelatin capsule shell	366.10	372.16	367.31	366.77	369.76

Evaluation of capsules

Weight variation test

Individual weights of 20 capsules were taken and the average weight was calculated by using the following formula.

$$\text{Weight variation} = \frac{(\text{Weight of capsule} - \text{Average weight})}{\text{Average weight of capsule}} \times 100$$

Weight variation should not be more than 5 %.

Lock length

It was tested by using vernier calipers.

Water Content by KF / Moisture content

30ml of the methanol was taken into KF titration flask and titrated with KF reagent until the end point to make inside of the flask water free. Finely lansoprazole pellets were transferred quickly and accurately weighed quantity of about 0.5g sample was added to the titration flask and dissolved by continuous stirring and titrated with KF reagent. The % water content was measured by using following formula (Tekade NP *et al*., 2010).

Calculation

$$\textbf{\% Water content} = \frac{\textbf{V X F X 100}}{\textbf{W x 1000}}$$

Where, V = Volume of KF consumed for sample reading

F = Factor for KF reagent

W = Weight of sample in g.

Drug content

Prepared pellets were subjected for the drug content. Weighed and powder 20 capsules. Weighed a quantity of powdered pellets containing 30mg of lansoprazole to 100 ml volumetric flask, add 20 ml of 0.1 M Sodium hydroxide, mix with aid of ultrasound and dilute to volume with 0.1 M Sodium Hydroxide. Centrifuge for 5 minutes and dilute 5.0 ml of the clear supernatant liquid to 50.0 ml with the phosphate buffer pH 6.8. The resultant solution is then analyzed by using UV Spectrophotometer at λ max 285 nm.

$$\% \text{ Drug content} = \frac{\text{Observed value}}{\text{Actual value}} \times 100$$

Dissolution by UV

Acid stage followed by buffer stage

i) Acid Stage:

Dissolution parameters:

Apparatus : USP Type II (Paddle)
Medium : 0.1N Hydrochloric Acid
Volume : 500 ml
RPM : 75
Temperature : 37 ± 0.5 °C
Time : 60 minutes

ii) Buffer stage

Dissolution parameters:

Apparatus : USP-II paddle
Dissolution medium : pH 6.8 buffer
Volume : 900 ml
RPM : 75
Temperature : 37 ± 0.5°C
Time : 60 minutes

Surface characterization

Morphological examination of the surface was

carried out using a SEM (ZEOL JSM-6700). The particles were vacuum dried, coated with thin gold-palladium layer by sputter coater unit and observed microscopically at an accelerating voltage of 10.0 kV.

Particle size distribution

In order to determine the particle size distributions of prepared pellets containing lansoprazole, standard sieve method was used. Mechanical sifter with sieves between apertures 355-2000 µm were used by using all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

FTIR studies

IR spectra was obtained by using the FTIR spectrophotometer (H400-84100, Shimadzu, Japan) using KBR pellets and scanning range was 4400 to 400 cm^{-1} at a scan period of 1 min. The FTIR spectra of pure drug, drug with excipients and only excipients.

Drug release kinetics

To investigate the possible mechanisms of drug release by lansoprazole delayed release capsules, the drug release data were fitted to various models such as zero order, first order, Hixson crowell, erosion model, baker Lonsdale, weibell and korsmeyer model.

Stability study

Storage conditions

Long term: - 25 ºC ± 2 ºC /60% RH ± 5% RH
Accelerated: - 40 ºC ± 2 ºC /75%RH ± 5%RH

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C ± 2˚C / 75%RH ± 5% RH for a period of 6 months. As per the standard protocol the samples must be analyzed at 0, 1, 2, 3 and 6 months time points. Long term and Accelerated stability studies were performed for the final optimized formulation (F10). Samples were analyzed at 1, 2, 3 months' time points.

RESULTS AND DISCUSSION

Fig.1 Standard graph of drug in 0.1N HCl

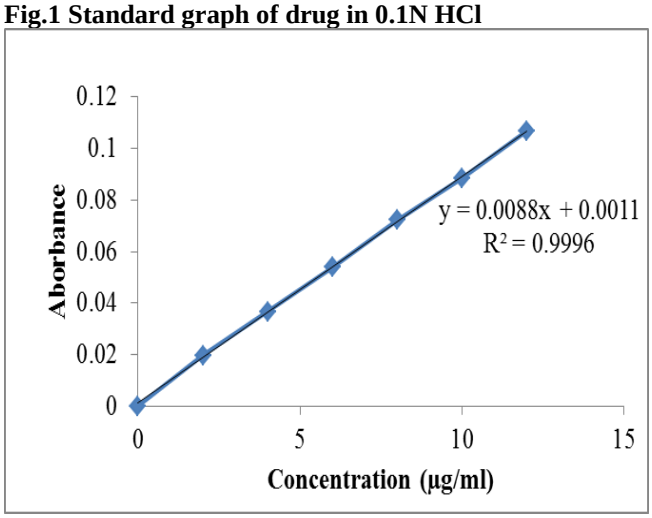

Fig.2 Standard graph of drug in pH 6.8 buffer

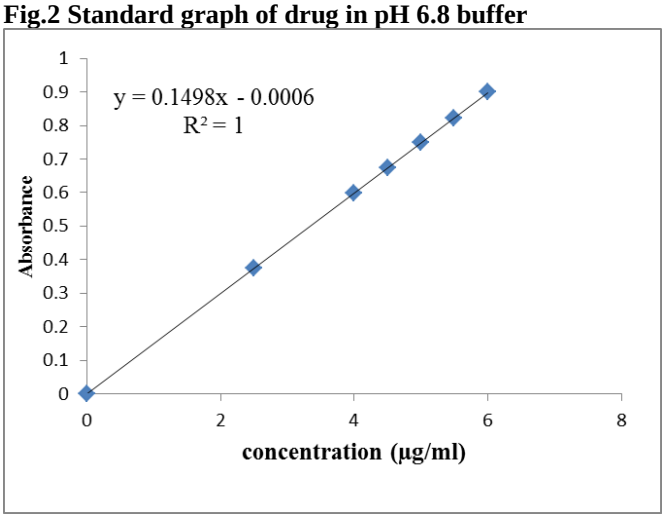

Fig.3 FTIR spectral obtained for pure drug

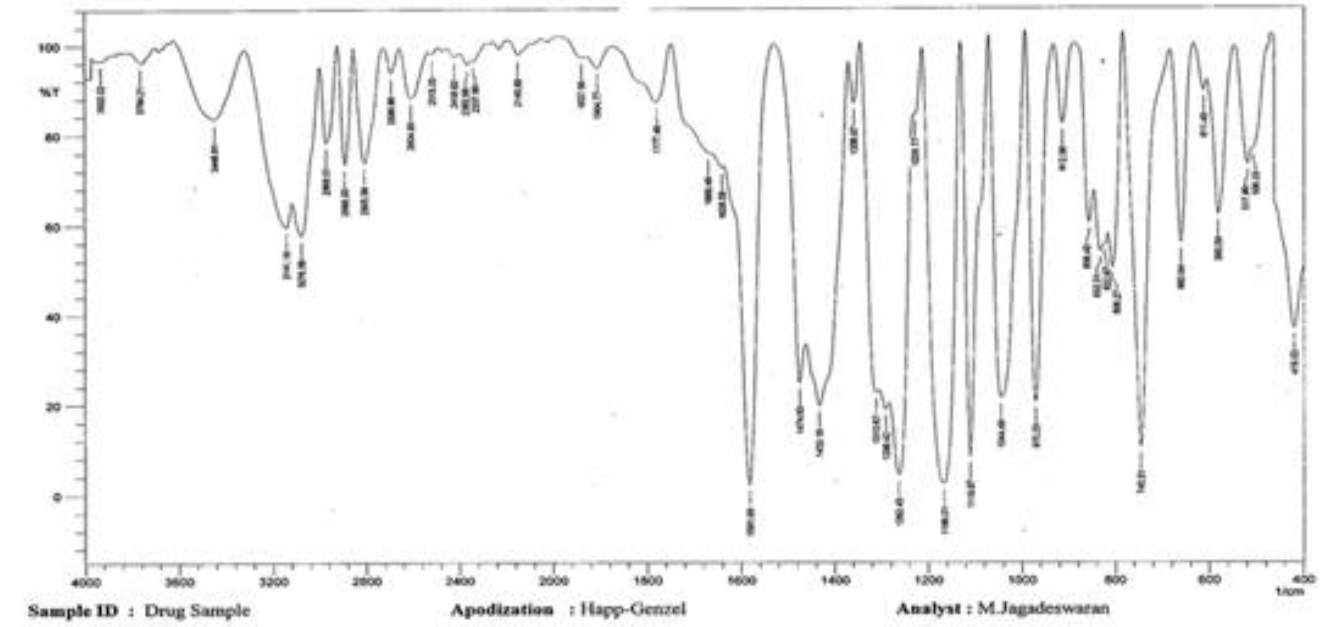

Fig.4 FTIR spectral obtained for blend of Lansoprazole

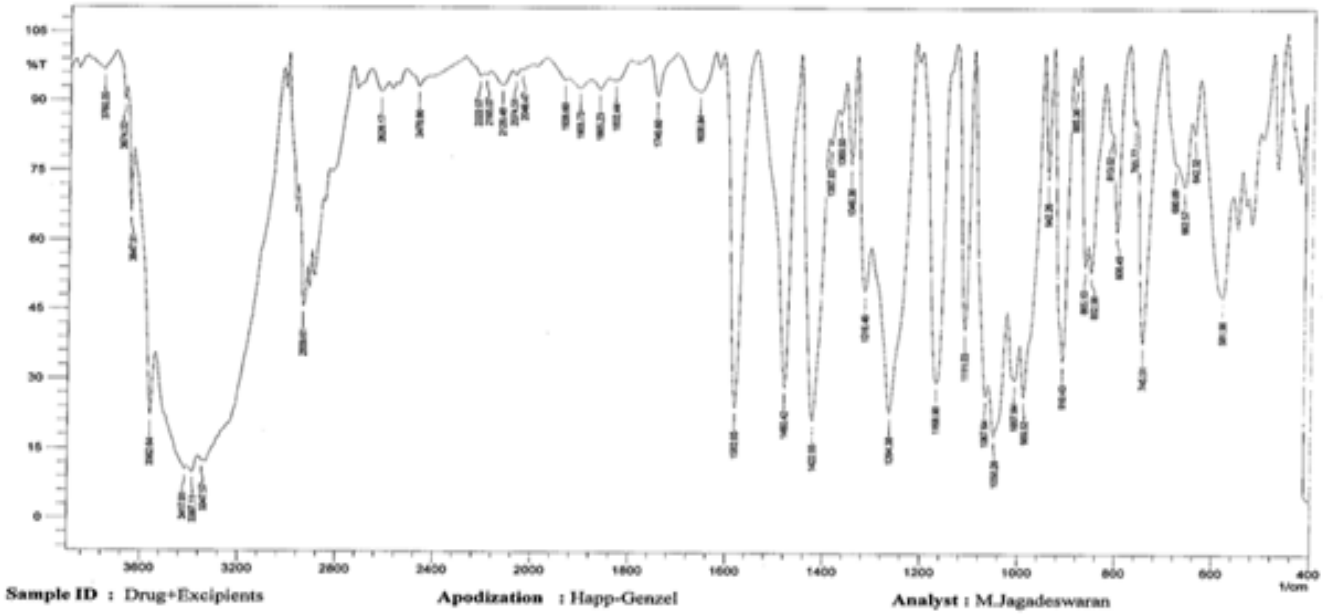

Fig.5 FTIR spectral obtained for excipients of Lansoprazole

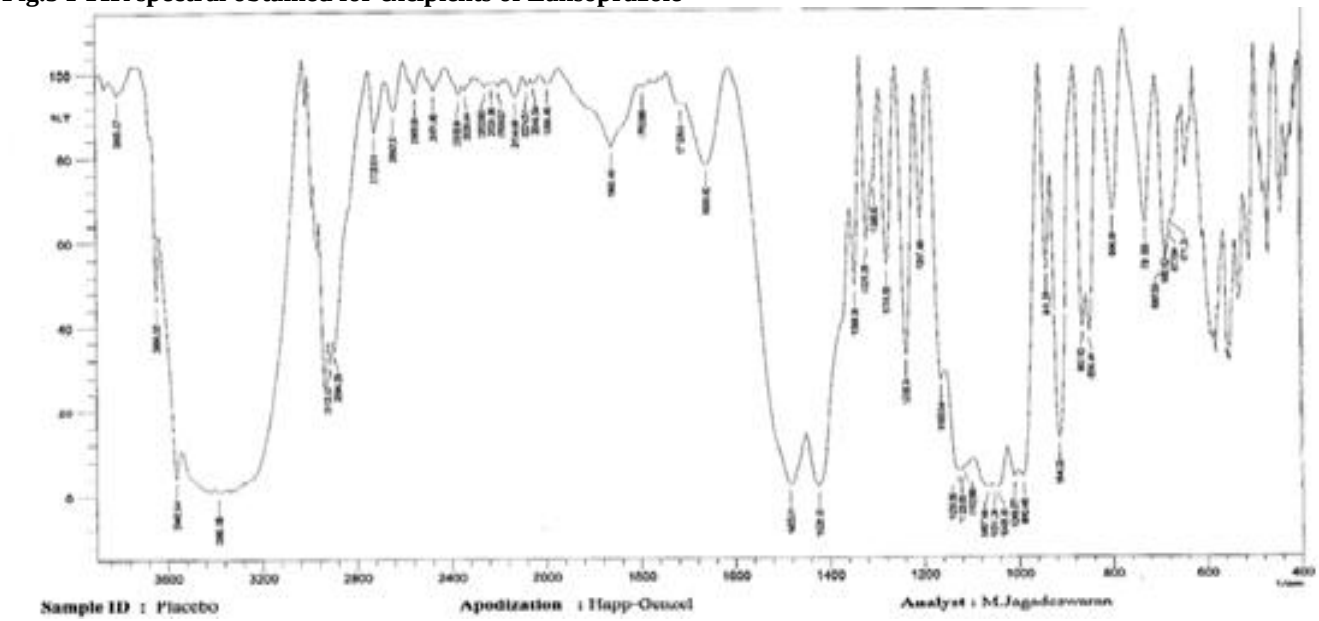

Fig.6 Comparative dissolution profiles of formulations (F1-F10) with innovator

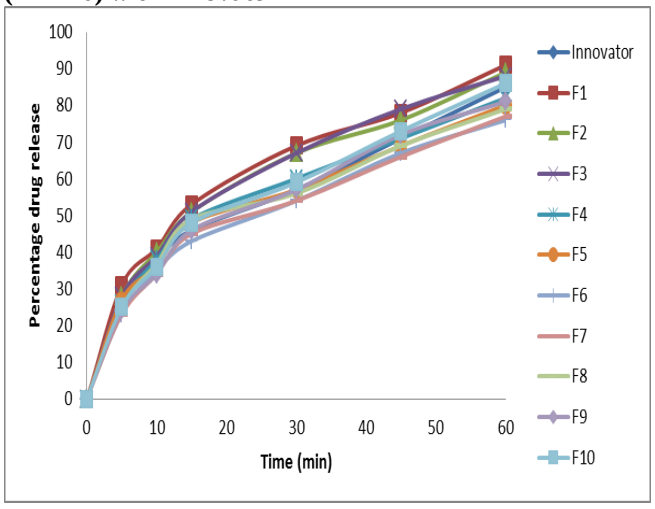

Fig.7 Drug release kinetics

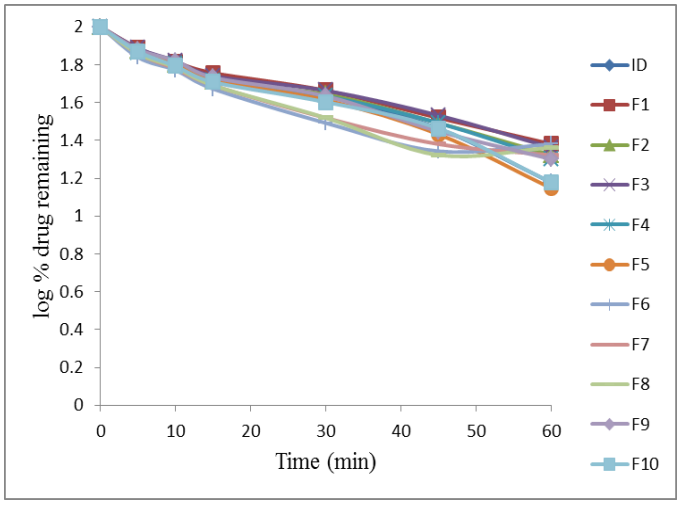

Fig.8 SEM images of enteric coated Pellets of optimized formulation F10

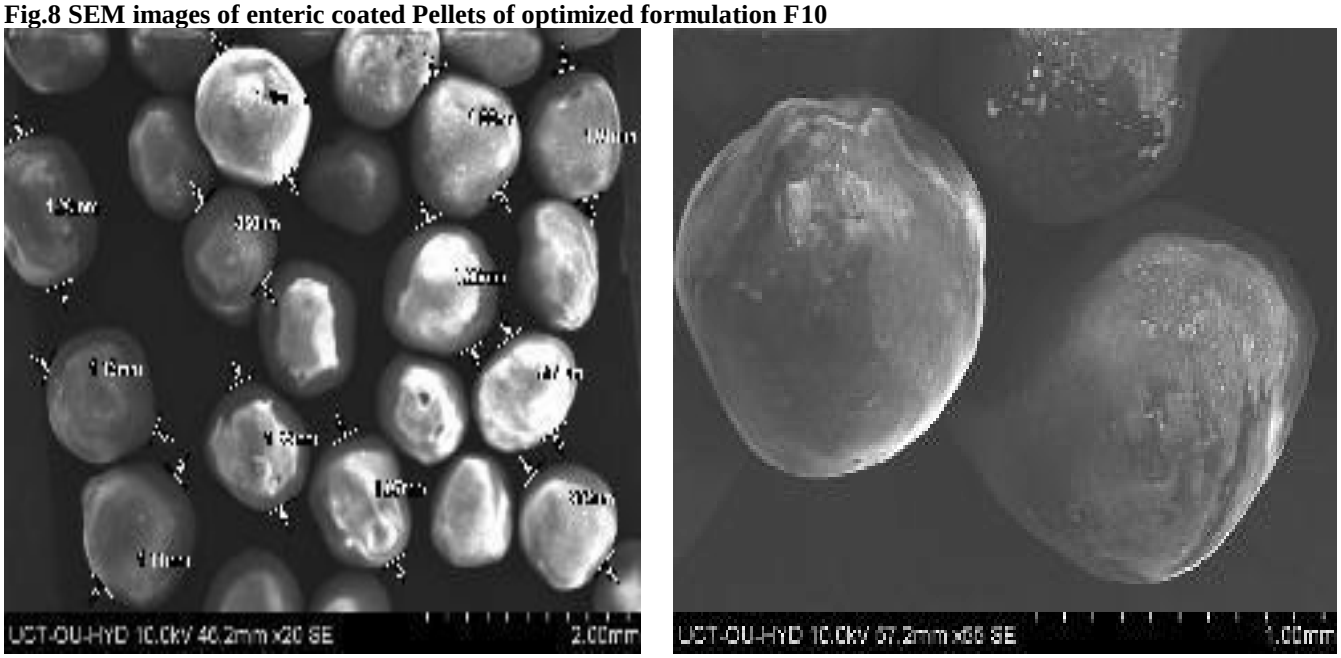

Table.3 FTIR Interpretaton

Wave Number (cm^{-1})	Functional Group
$3448cm^{-1}$	N-H stretching vibrations
1638.58 cm^{-1}	C=N stretching vibrations
$1358.97cm^{-1}$	S=O stretching vibrations
1467 cm^{-1}	C-H bending vibrations
1244 cm^{-1}	C-N stretching vibrations

Table.4 Physico- chemical properties of formulations F1-F10

	Physico- chemical properties of formulations F1-F10									
Parameters	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Bulk density (g/cc)	0.76	0.79	0.75	0.77	0.78	0.76	0.78	0.74	0.76	0.75
Tapped density (g/cc)	0.80	0.82	0.79	0.80	0.81	0.79	0.81	0.78	0.80	0.78
Angle of repose (θ)	22.3	21.6	23.2	22.7	21.4	23.9	22.6	23.0	23.1	23.3
Carr's Index	5	3.65	5.06	3.75	3.07	3.79	3.07	5.12	5.00	3.84
Hauser's ratio	1.05	1.03	1.05	1.03	1.03	1.03	1.03	1.05	1.05	1.04
Moisture content	1.2	1.5	1.8	2.0	1.6	1.6	1.3	1.6	1.9	1.4
Assay	99.6	99.4	99.4	99.4	99.5	100.3	99.7	99.7	99.6	99.3
Weight variation	1.65	1.42	1.53	1.18	1.35	1.44	1.23	1.48	1.62	1.38

Lock length

Empty cap length and width: 9.582 mm, 6.64mm

Empty body length and width: 16.38 mm, 6.24 mm

Lock length of the capsules containing pellets is found to be 19.13 mm

Table.5 *In-vitro* Dissolution data of formulations F1-F10

	Cumulative percent drug release in 0.1 N HCl									
Time(min)	**Innovator**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0	0	0	0	0	0	0
60	3.8	7.9	6.2	5.8	5.9	5.4	5.3	4.8	4.2	4.0	3.6
Cumulative percent drug release in phosphate buffer pH 6.8											
5	27	31	28	28	26	27	23	23	25	24	25
10	38	41	40	39	38	36	35	34	37	34	36
15	46	53	51	51	49	48	43	45	49	46	48
30	57	69	67	67	60	57	54	54	56	57	59
45	71	78	76	79	71	69	67	66	69	72	73
60	85	91	89	88	82	80	76	77	79	81	86

Table.6 Drug release kinetics all formulations

Kinetic model		ID	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
First order	r	0.998	0.996	0.987	0.978	0.996	0.987	0.979	0.986	0.982	0.979	0.992
	k	0.006	0.009	0.031	0.049	0.017	0.035	0.055	0.027	0.041	0.061	0.051
Hixon-crowell	r	0.999	0.997	0.977	0.960	0.992	0.976	0.958	0.973	0.972	0.961	0.970
	k	0.008	0.014	0.045	0.067	0.025	0.050	0.074	0.040	0.057	0.081	0.080
Zero order	r	0.919	0.977	0.947	0.906	0.980	0.940	0.896	0.944	0.929	0.892	0.901
	k	3.406	1.880	2.481	3.470	1.532	2.770	3.762	2.267	3.080	3.999	3.484
Higuchi	r	0.956	0.973	0.998	0.988	0.994	0.997	0.984	0.999	0.995	0.982	0.976
	k	3.764	5.422	8.855	10.46	7.051	9.460	10.892	8.181	10.03	11.32	10.12
Peppas	r	0.929	0.929	0.924	0.918	0.927	0.926	0.924	0.927	0.96	0.925	0.818
	k	0.687	0.537	0.259	0.169	0.388	0.233	0.151	0.285	0.203	0.135	0.110
Erosion	r	0.999	0.996	0.977	0.960	0.992	0.976	0.958	0.973	0.972	0.961	0.760
	k	0.001	0.003	0.009	0.014	0.005	0.010	0.016	0.008	0.012	0.017	0.021
Baker-Lonsdal	r	0.949	0.966	0.993	0.995	0.987	0.993	0.994	0.999	0.994	0.989	0.984
	k	0.0003	0.0006	0.002	0.004	0.0012	0.0024	0.004	0.001	0.003	0.005	0.009
Weibull	r	0.923	0.935	0.972	0.977	0.959	0.970	0.976	0.980	0.971	0.966	0.967
	k	0.155	0.248	0.560	0.813	0.371	0.636	0.902	0.491	0.722	0.993	0.784

Table.7 Stability Study Results of Optimized Formulation F10

Batch number and stability condition	Description	Assay (%)	Drug release in 0.1N HCl (%)	Drug release in pH 6.8 buffer
Room temperature (Initial)	White to beige colored capsules	99.15%	3.67%	87.12%
40° C / 75% RH (1month)	White to beige colored capsules	98.37%	3.78%	86.48%
40° C / 75% RH (2months)	White to beige colored capsules	97.87%	3.83%	86.07%
40° C / 75% RH (3 months)	White to beige colored capsules	97.03%	3.99%	85.78%
25°C/60% RH (1month)	White to beige colored capsules	98.78%	3.72%	87.01%
25°C/60% RH (2month)	White to beige colored capsules	98.36%	3.75%	86.87%
25°C/60% RH (3 month)	White to beige colored capsules	98.07%	3.79%	86.43%

Formulation F1 had shown poor gastro resistant properties, would require high percentage of enter coating for better protection and was having a satisfactory dissolution profile in alkaline p^H. Hence it was decided to proceed with increased percentage of enteric coating.

In F2 and F3 the concentration of enteric coating was increased to decrease the release in 0.1 N HCl and also concentration of polysorbate 80 in drug layering stage also changed for optimization of polysorbate 80. Polysorbate 80 with concentration of 3.2 mg/ capsule had shown desirable dissolution profile in buffer stage. So it was decided to proceed with 3.2 mg/ capsule concentration as optimum. But the drug release was compared to be more compared to that of innovator.

In F4 and F5 the concentration of binder in drug layering stage was changed to optimize the release in buffer stage. Increase in binder concentration retards the drug release from initial to end points. Hence it was decided to proceed with a binder concentration of 1.28 mg/ capsule as optimum. But the drug release in acid and buffer stage was not comparable to the innovator.

In F6 and F7 the composition seal coating and enteric coating was changed to decrease the release in acid stage and also to improve the stability of the drug from acidic p^H of the enteric coating polymer. At all level of seal coat, the pellets found to be satisfactory. The stability data with respect to impurity profile also shown satisfactory results on formulation F6. Hence it was decided to proceed with seal coating in the range of 30.76 to 32.75% m/m of core drug layered pellets with targeted weight buildup of 31.76% m/m. But the release was less compared to the innovator product.

In F8, F9 and F10 the concentration of polysorbate 80 in enteric coating composition was changed to increase the release in buffer stage. In F10

polysorbate 80 with a concentration range of 3.226 mg/ capsule shown desirable dissolution profile in acid stage and buffer stage and comparable to the innovator. So it was decided to proceed with 3.226 mg/ capsule concentration of polysorbate 80 as optimum at enteric coating stage.

The results indicated that the finished product formulation F10 fulfilled all the specifications of the physico - chemical properties and *in vitro* release and is comparable to the innovator product. Formulation F1 to F9 was failed due to various reasons like less acid resistance compared to innovator or increased impurities profiles during the course of stability or less *in vitro* drug release compared to the innovator. Even though all the formulations are releasing the drug but those are not comparable to the innovator product.

In, formulation F10 drug release in 0.1N HCl and 6.8 phosphate buffer releases were found to be very close to that of innovator (85%).Hence formulation F10 was considered to be the optimized formulation.

Surface characterization

The optimized formulation F10 pellets were found to be spherical as indicated by SEM. Surface of the coated pellets were found to be uniform and smooth.

Particle size distribution

Pellets particle sizes in all formulations were ranged from 710µm to 850µm.

Average pellets particle size in optimized formulation F10 was found to be 710µm.

The dissolution data was treated with various kinetic models and it was found that the drug releases from the pellets follow first order kinetics. This release patterns are evident with the correlation coefficient "r" values which were nearer to 1.

In Formulation 10 the assay of the capsules was found to be 99.15% initially, after 1 month it was decreased to 98.37% and 98.78%, after 2 month it was found to be 97.87 % and 98.36% later it was found to be 97.03% and 98.07% after 3 months at 40^0C/75%RH and 25^0C/60%RH respectively.

In Formulation10 the acid release of the drug from capsules was found to be 3.67% initially, after 1 month it raises to 3.78% and 3.72%, after 2 month it raises to 3.83% and 3.75% later it was found to be 3.99% and 3.79% after 3months at 40^0C/75%RH and 25^0C/60%RH respectively. This indicates that there is little change in the acid resistance of lansoprazole delayed release capsules for batch 10.

Formulation F10 fulfilled all the specifications prescribed for lansoprazole delayed release capsules and was comparable to the innovator product.

CONCLUSION

The study was undertaken with an aim to develop an optimized formulation of lansoprazole enteric coated pellets drug delivery system by using Eudragit L30D55, low subsstitued- HPC as retarding agents.

The active pharmaceutical ingredient, lansoprazole was selected and formulated as enteric coated pellets comparable to the innovators product. Based on the drug excipient compatibility data and prototype formulations, the formula that found to be giving the desired drug release pattern was considered as the optimized formulation and further studies was conducted on this formulation F10 to have a detailed study over that formulation. By the observations made, it was concluded that the formulation F10 shows better resistant to 0.1 N HCl and better release at phosphate buffer p^H 6.8. Then the optimized formulation F10 was compared with innovator product by an *in vitro* study, it shows that the formulation F10 was good as compared with the innovator product.

The optimized formulation F10 was kept for Stability studies and carried out for 3 months at 40°C/75 %RH and 25°C/60 % RH according to ICH guidelines. The optimized formulation F 10 was shown desirable *in vitro* acid and buffer drug release during the stability period and comparable to the innovator.

REFERENCES

Aulton ME. International student Edition, Pharmaceutics-The Science of Dosage form design, Churchill Livingston, 2001:129-191.

British pharmacopeia, 2010

Drug delivery, 1991. Available from: URL: www.wikipedia.org

Ghebre-sellasssie. A general overview of Pharmaceutical Pelletization Tecnolgy, 1981: 1-13.

Hand book of pharmaceutical excipients, 6 ^{h} edition, 2003.

Howard C Ansel, Loyd V Allen, Nicholas G Popovich. Ansel's Pharmaceutical Dosage forms and Drug Delivery Systems, 2000:268.

http://www.ema.europa.eu/docs/en_GB/document_lbrary/Referrals_document/Agopton_30/WC500009199.pdf.

Issac Ghebre, Sellassie, Pharmaceutical Pelletization Technology, Marcel Dekker, Inc. 1989:37:1-13, 49

Jain NK. Advances in controlled and Novel Drug Delivery, CBS publications, New Delhi, 2000:268-269.

Lee TWY, Robinson JR., 20th edition, Remington: The Science and Practice of Pharmacy, Lippincott Williams and Wilkins, Maryland, 2000:1069-70.

Loyd V Allen J, Nicholas G Popovich, Howard C Ansel, 8th edition, Ansel: Pharmaceutical Dosage Forms and Drug Delivery System, Lippincott Williams and Wilkins, Philadelphia, 2006:260-275.

Robinson JR, Lee VH. 2nd edition, Controlled Drug Delivery: Fundamentals & Application, Marcel Dekker, New York (NY), 1987:36.

Saptarshi D, Mukul S. Modified release dosage form and drug delivery. *J pharm research*. 2009;2(11):1728-29.

Tekade NP, Bhajpale NS, Ganesan V, Dewade DR. Orodispersible Tablets of Lansoprazole: Formulation, Characterization and *In-vitro* Evaluation. Int J Chem *Tec Res*. 2010;2(1):400-05.

The Merck index, thirteenth edition

Yue Cui, Yu Zhang, Xing Tang. *In vitro* and *In vivo* evaluation of ofloxacin sustained release pellets. *Int J of Phar*. 2008;47-52.