

Enhancing Lansoprazole Formulations: Addressing Acid Labile Challenges via Enteric Coating Techniques to Improve Therapeutic Efficiency

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ABSTRACT :

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). Proton pump inhibitors are acid labile drugs. These drugs will degrade in acidic environment of stomach and will lead to therapeutic inefficacy. Lansoprazole is highly acid labile and presents many formulation challenges and to protect it from acidic environment of the stomach. It is necessary to bypass the acidic pH of the stomach, which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers. 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). Nine Formulations of lansoprazole enteric coated pellets were prepared varying the compositions of drug loading, barrier coating and enteric coating. The aim of the present study was to develop a pharmaceutically equivalent, stable, cost of effective and quality improved formulation of lansoprazole delayed release pellets. The prepared pellets were studied for their physico-chemical properties, assay and in vitro release studies.

I. INTRODUCTION :

Lansoprazole is one of the classes of proton pump inhibitors, which reduce gastric acidity, an important factor in healing acid-related disorders such as gastric ulcer, duodenal ulcer and reflux oesophagitis. It is used to treat gastro-oesophageal reflux disease, ulcers, acid-related dyspepsia and as an adjuvant in the eradication of *H. pylori*^{1,2,3}.

Delayed release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the

drug immediately after ingestion, for example enteric-coated tablets, pulsatile release capsules. Delayed release dosage forms are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of treatment. The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to the stomach or to facilitate gastrointestinal transit for drugs that are better absorbed from intestine. The drugs contained in such a system are those that are⁴:

- Destroyed in the stomach or by intestinal enzymes.
- Known to cause gastric distress.
- Absorbed from a specific intestinal site.

Pellets :

Pellets can be defined as small, free flowing, spherical or semi-spherical solid units, typically from about 0.5 mm to 1.5 mm, and intended usually for oral Administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment. Following techniques can be used to get drug loaded non-pareils/pellets.

- a. A powder-dosing technique involving alternate dosing of powder (containing drug substance) and binder liquid onto the surface of the non-pareils until the required dose of the drug has been loaded.
- b. Spray application of drug, either suspended or dissolved in a suitable solvent (usually water) containing a polymer (such as hydroxyl propyl methyl cellulose or polyvinyl pyrrolidone) as a binder onto the surface of the non-pareils^{5,6}.

Advantages^{7,8,9}

- Improved appearance of the product and the core is pharmaceutically elegant.
- It improves safety, efficacy and flow property of drugs.
- When formulated as modified release dosage forms, pellets are less susceptible to dose dumping than reservoir type single unit formulations.
- Pelletization reduces intra and intersubject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times.
- Pellets composed of different drugs can be blended and formulated in single unit dosage form that facilitates delivery of two or more chemically compatible or incompatible drugs at the same or different site in GI tract.
- Incompatible drugs processed separately and mixed later, or pellets with different release mechanisms can be mixed to give a new modified release profile.
- Pellets disperse freely in the GI tract and hence greater absorption of the active drug occurs.

II. MATERIAL AND METHOD :

Material :

Lansoprazole (Cadila Healthcare Limited, Ahmedabad), sugar spheres (Sanmour pharma pvt.Ltd, Mumbai), starch (Lobachemie, pvt. Ltd. Mumbai), sucrose (Lobachemie, pvt. Ltd. Mumbai), Hydroxy Propyl Methyl Cellulose E5 (Himedia laboratories, pvt.Ltd.Mumbai), talc (Lobachemie, pvt. Ltd. Mumbai), Polyethylene Glycol 6000 (Himedia laboratories, pvt.Ltd.Mumbai), Eudragit L30 D-55 (Sanmour pharma pvt.Ltd, Mumbai), Polysorbate 80 (Himedia laboratories, pvt.Ltd.Mumbai).

Method of Formulations^{10,11,12}:

STAGE- I : Drug Loading:

Took weighed 1/3rd of the total quantity of purified water in stainless steel vessel and heat the water up to 80-85°C. Sucrose, poly-ethylene glycol 6000, polysorbate 80 was weighed and added one by one in the water and dissolved with continuous stirring. Hydroxyl propyl methyl cellulose was weighed and transferred in hot purified water under stirring and slurry was prepared. Required quantity of starch added into purified water and these was again added in the hot slurry under stirring to dissolve HPMC. Cooled the solution up to room temperature under stirring. Lansoprazole USP was weighed and added in above solution slowly under

stirring; stirred until uniform slurry to be formed. Finally mixed properly for 10 minutes, and passed solution through 100 meshes.

STAGE-II: Seal Coating:

Took weighed 1/3rd of quantity of purified water in stainless steel vessel and heat the water up to 80-85°C. Hydroxyl propyl methyl cellulose, starch and sucrose were weighed and added one by one in the water and dissolved. Remaining quantity of purified water was added to the above solution under stirring. Cooled the solution up to room temp under stirring. Purified talc was added under stirring. Finally mixed for 10 minutes, and pass the solution through 100 meshes.

STAGE-III: Enteric coating:

Purified water was taken in a stainless steel vessel. PEG 6000, polysorbate 80 was weighed and added one by one in the above mentioned water and dissolved. Purified talc was weighed and added under stirring. Eudragit L 30 D55 was weighed and added to the above solution under mild stirring. An ordinary propeller stirrer suffices. Continue stirring for another 15-20 mins. Filtered the final dispersion through 100 mesh screen only. The dispersion was now ready for use. The dispersion was kept under mild stirring during the coating operation.

CHARACTERIZATION OF API AND FORMULATIONS :

1. Bulk Density¹³:

Bulk density is defined as the mass of the powder divided by the bulk volume. Bulk density largely depends on particle shape, as the particle becomes more spherical in shape, bulk density increases. In addition as the granule size increases bulk density decreases.

Method: A given quantity of the Lansoprazole pellets was transferred to a measuring cylinder and tapped mechanically either manually or using some tapping device till a constant volume is obtained. This volume is bulk volume and it includes the true volume of the powder and the void space among the powder particles.

Bulk Density = Bulk Mass / Bulk Volume

2. Tapped Density¹³:

Tapped density was determined by using Electrolab density tester, which consists of a graduated cylinder. An accurately weighed 5gm sample of pellets was carefully added to the cylinder with the aid of a funnel. The initial volume

was noted, and the sample was then tapped (500,750 or 1250 tapping) until no further reduction in volume was noted or the percentage of difference is not more than 2%. A sufficient number of taps should be employed to assure reproducibility for the material in question. Volume was noted and tapped density was calculated using following formula.

Tapped density = Wt. of sample in gm / Tapped volume

3. Hausner's Ratio¹³:

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is the determined by the ratio of tapped density and bulk density.

Hausner's ratio = v_i / v_t

Where,

v_t = Tapped volume

v_i = untapped volume

4. Angle of Repose^{13,14}:

Angle that can be obtained between the free surface of a powder heap and horizontal plane. The angle of repose was measured by allowing the pellets to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height. The height of the heap was measured and then circumference of the base of heap was drawn on a graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = angle of repose

h = height of the heap

r = radius of the base of the heap

5. Friability¹⁵:

There was no standard method established for evaluating friability of pellets. The friability of pellets was determined by using Roche friabilator. But due to the low weight of the pellets the mechanical stress applied is less. This can be corrected by adding glass or steel balls to increase stress. The friability was calculated as percentage weight loss according to the following equation:-

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

6. Particle Size Determination^{16,17}:

In order to determine the particle size distributions of the 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.

7. Assay Study¹⁸:

Equivalent weights to equivalent to 30mg of Lansoprazole into a dry 100 ml volumetric flask added about 50 ml of 0.1 M NaOH and sonicate to dissolve. The volume was made up to the mark with 0.1 M sodium hydroxide and mix. 20 to 30 ml of solution was transferred into dry stoppered test-tube and it was centrifuge at 5000rpm for 5 minutes. Samples were analyzed using HPLC Dionex (chromleon) at a wavelength of 285nm. The drug content was determined by diluting 5 ml of the supernatant solution to 50ml with mobile phase.

8. Gastric Acid Resistance Test^{19,20}:

Acid resistance test is a significant index of drug dissolution performance of enteric coated formulations. Model fraction of coated pellets was subjected for acid resistance test in USP dissolution test apparatus –II (SR-8, Hanson Research, and Chatsworth, USA). Weighed amount of pellets were placed in the vessel and test was carried out in 0.1N HCl for 1hr at 75 rpm. Lansoprazole released at 1hr in 0.1 N HCl was estimated as per method specified in USP. Minimal amount of drug release in this test is indicative of gastric acid resistance.

9. In-vitro Dissolution Test^{19,20,21,22}:

Method:

Dissolution studies were carried out for all the formulations, employing USP-II paddle method 500 ml of 0.1 N HCL for first 1 hr and 900 ml of phosphate buffer pH-6.8 for next 1 hr were used as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C + 0.5°C. Pellets were placed in the vessel and the vessel was covered and operated for 1 hr in 0.1 N HCL at 75 rpm and next 1 hr pH-6.8 phosphate buffer at 100 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 281 nm using UV-spectrophotometer.

Preparation of 0.1 N HCL:

Transferred 8.5 ml of HCL into a suitable container containing water, dilute to 10,000 ml with purified water and mixed.

Dissolution Parameters.

Medium	- 0.1N HCL
Volume	- 500 ml
Apparatus	- USP type II (paddle)
Speed	- 75 rpm
Temperature	- 37.0°c ± 0.5°c
Sampling point	- 15,30,45 and 60 min

Preparation of buffer:

Weighed and transferred 1.41 grams of disodium hydrogen phosphate anhydrous into a beaker containing 1000 ml of water. Filtered through 0.45µ membrane filter.

Dissolution Parameters:

Medium	- PH 6.8 phosphate buffer
Volume	- 900ml
Apparatus	- USP type II (paddle)
Speed	- 100 rpm
Temperature	- 37.0°c ± 0.5°c
Sampling points	- 75, 90,105 and 120 min

10. Accelerated Stability Study^{21,22}:

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retesting for the drug substance or a shelf-life for the drug product and recommended storage conditions. The ICH Guidelines have established that accelerated stability testing should be done at 40°C/75%RH for 3 months. Stability study was carried out for the optimized formulation. Tablets of optimized formulation were packed in strip and kept in stability chamber for 3 months on above mention temperature. Samples were analyzed at 1, 2, 3 months for invitro dissolution study.

III. RESULTS AND DISCUSSION

The study was under taken with an aim to develop an optimized formulation of Lansoprazole Enteric Coated Pellets drug delivery system by using Eudragit L30 D-55, HPMCE5 asretarding agents. Pellets were prepared by using suspension laye red method.

Physical characterization:

Formulations were evaluated for physical characterization such as bulk density, tapped density, angle of repose, particle size analysis, etc. Solution properties solubility evaluated, results were complied with thepharmacoepia

specification. From the results it was observed that the average particle sizes of the pellets were nearly 1100 µm for all 9 formulations. Loss on drying was within the British Pharmacopeia limit. Flow properties and flow rate of different formulations were excellent as compare to pure lansoprazole drug .

Assay study :

Assay of Lansoprazole was carried out using HPLC and it was found to be 98.20 %.

Gastric Resistance study:

Acid resistance studies show that the optimized formulation F9 is more stable in the acidic media. 96.73% of drug was released in 60 minutes. Results of acid resistance studies are correlated in table no. 5.

In Vitro Dissolution Studies :

From the result (Table no. 6 and figure no. 1, 2 and 3) it was observed that the formulation F9 had better resistance to 0.1N HCL as compared to other formulations because formulation F9 contains high concentration of sugars. Assugars were used in high concentration in a thin layer of drug on each pellets and HPMCK5 used in high concentration for forming a thick layer between drug and enteric polymer, so it prevents the interaction between the drug and enteric polymer. Therefore formulation F9 showed the better resistance to 0.1N HCL. From the result (Table no. 6 and figure no. 4, 5 and 6) it was observed that the formulation F9 has better cumulative percent drug release as compared to other formulations. Because it may be in formulation F9 Eudragit L30 D55 was used in low concentration, therefore the drug release from pellets occurs fastly in phosphate buffer pH 6.8. While keeping in 6.8pH buffer, 70.35 cumulative percent drug release occur at 75 minutes, After 120 minutes 96.97 cumulative percent drug release was attained, when compared to other formulation F9 showed better release, so F9 was selected as optimized formulation.

Accelerated stability studies :

The stability study was carried out for formulation F9 at 1, 2, 3 month for invitro dissolution study and from this it was observed that there were no changes and clearly showing that the optimized formulation F9 was stable.

Comparison of In-vitro dissolution data of Optimized Formulation with Marketed Product:

Results for comparison of in-vitro dissolution data of optimized formulation with marketed formulation were given in table no. 8.

Table No. 1: Formulas for drug loading process:

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ingredients	mg/unit	mg/ unit	mg/unit	mg/unit	mg/unit	mg/unit	mg/ unit	mg/unit	mg/unit
Sugar Spheres	110	112	114	116	118	120	122	124	126
Lansoprazole	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00	30.00
Starch	20	20	20	20	20	20	20	20	20
Hydroxy Propyl Methyl Cellulose E5	35	35	35	35	35	35	35	35	35
Sucrose	16	19	22	25	28	31	34	37	40
Polyethylene Glycol 6000	6	6	6	6	6	6	6	6	6
Polysorbate 80	3	3	3	3	3	3	3	3	3
Purified water	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total	220	225	230	235	240	245	250	255	260

Table No. 2 : Formulas for seal coating:

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lansoprazole layered pellets	220	225	230	235	240	245	250	255	260
Hydroxy Propyl Methyl Cellulose E5	15	15	15	20	20	20	25	25	25
Sucrose	15	15	15	15	15	15	15	15	15
Talc	7	7	7	7	7	7	7	7	7
Starch	13	13	13	13	13	13	13	13	13
Purified Water	qs	qs	qs	qs	qs	qs	qs	qs	qs
Total	270	275	280	290	295	300	310	315	320

Table No. 3 : Formulas for enteric coating :

	F1	F2	F3	F4	F5	F6	F7	F8	F9
Eudragit L30 D-55	50	50	50	45	45	45	40	40	40
Polyethylene Glycol 6000	4	4	4	4	4	4	4	4	4
Talc	13	13	13	13	13	13	13	13	13
Polysorbate 80	3	3	3	3	3	3	3	3	3
Purified	qs	qs	qs	qs	qs	qs	qs	qs	qs

Water									
Total	340	345	350	355	360	365	370	375	380

Table No. 4: Characterization of API and formulations.

Formulation codes	Bulk Density (g/ml)	Tapped Density(g/ml)	Hausner Ratio	Angle of Repose
Lansoprazole	0.90	1.10	1.22±0.05	36.20
F1	0.924±0.03	0.991±0.02	1.07±0.02	26.99
F2	0.929±0.02	1.004±0.04	1.07±0.04	27.15
F3	0.923±0.01	0.987±0.01	1.07±0.02	27.92
F4	0.931±0.02	0.999±0.02	1.06±0.01	28.44
F5	0.925±0.3	0.980±0.03	1.04±0.02	28.81
F6	0.953±0.03	1.025±0.04	1.05±0.04	26.86
F7	0.949±0.02	1.015±0.01	1.08±0.05	28.73
F8	0.938±0.01	1.009±0.02	1.04±0.03	28.15
F9	0.937±0.03	1.010±0.3	1.06±0.06	28.53

All values represent mean ± standard deviation (SD) n=3.

Table No. 5: Characterization of API and formulations.

Formulation codes	Particle Size (µm)	Loss on Drying(%)	Friability (%)	% Assay	%Acid Resistance
Lansoprazole	300	0.39	-	97.72±0.02	-
F1	1243.10	2.11	0.66±0.02	96.82±0.04	89.88±0.03
F2	1026.46	2.23	0.73±0.01	98.43±0.02	91.25±0.01
F3	1120.41	2.34	0.55±0.02	89.58±0.04	95.98±0.02
F4	1020.40	2.44	0.63±0.05	91.79±0.04	87.95±0.02
F5	1219.51	2.56	0.71±0.02	94.78±0.03	92.19±0.01
F6	1102.39	2.61	0.56±0.01	93.49±0.01	89.29±0.01
F7	1019.35	2.74	0.45±0.01	94.90±0.03	90.10±0.04
F8	1187.78	2.79	0.63±0.02	95.51±0.02	95.96±0.01
F9	1142.45	2.75	0.76±0.03	98.20±0.02	96.73±0.02

All values represent mean ± standard deviation (SD) n=3.

Table No.6: Cumulative percentage of lansoprazole release in 0.1N HCL and phosphate Buffer pH 6.8

Cumulative percent drug release in 0.1 N HCL									
Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
15	0.66	0.64	0.60	0.69	0.72	0.57	0.55	0.51	0.48
30	0.73	0.68	0.64	0.70	0.65	0.60	0.61	0.59	0.56
45	0.86	0.84	0.91	0.79	0.75	0.73	0.72	0.69	0.64
60	0.93	0.88	0.87	0.81	0.95	0.80	0.78	0.75	0.70
Cumulative percent drug release in phosphate buffer ph 6.8									
75	54.03	57.01	59.21	61.81	69.95	64.92	66.83	69.25	70.35
90	66.04	61.91	64.99	66.91	68.85	71.88	74.93	76.93	78.40
105	64.84	74.75	66.95	70.97	72.79	75.64	78.86	81.88	84.10
120	66.77	71.86	74.64	78.02	81.77	85.66	89.90	93.75	96.97

All values represent mean ± standard deviation (SD) n=3.

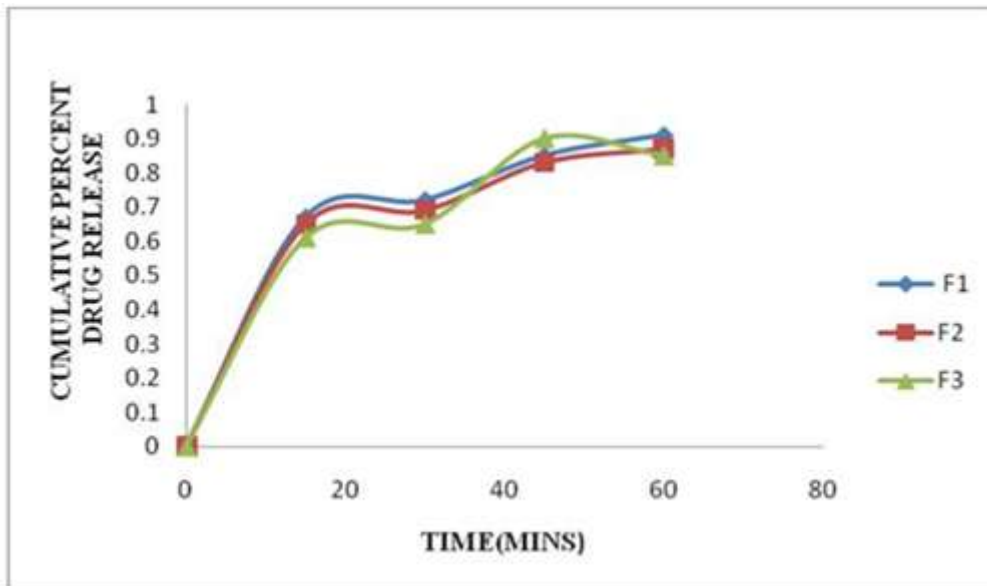
Table 7. Accelerated stability study

In 0.1 N HCL					
Sry. No.	Time (min)	Cumulative percent drug release			
		Initial	1 month	2 month	3 month
1	0	0	0	0	0
2	15	0.48	0.45	0.43	0.42
3	30	0.56	0.54	0.56	0.52
4	45	0.63	0.61	0.62	0.59
5	60	0.70	0.68	0.69	0.67
In Phosphate buffer pH 6.8					
6	75	69.15	69.15	69.10	69.04
7	90	78.24	78.16	78.15	78.09
8	105	84.17	84.06	84.00	83.92
9	120	98.86	98.73	98.55	98.44

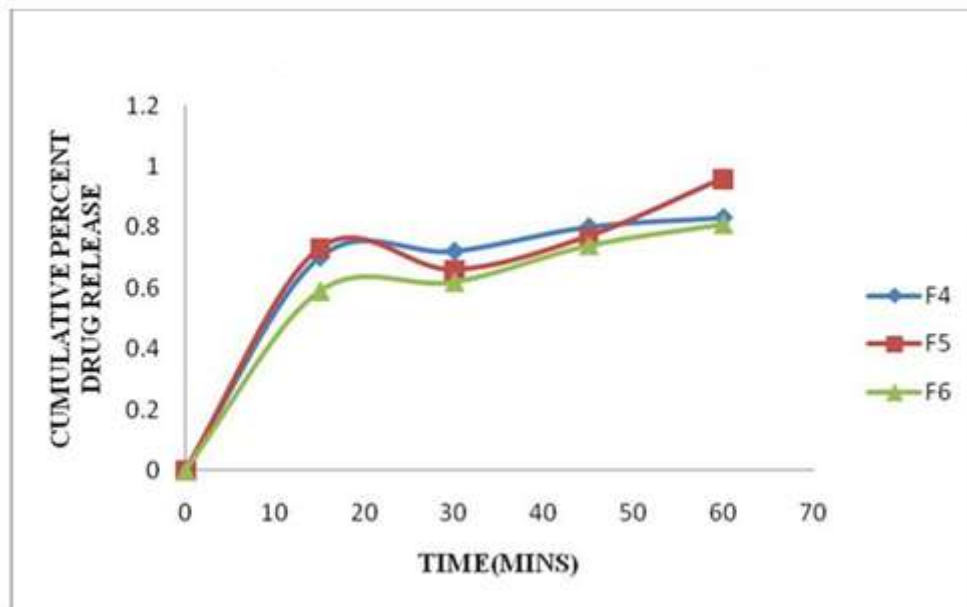
Table No.8: Comparison of Cumulative % Drug Release in 0.1N HCL and Phosphate Buffer pH 6.8 of Optimized Formulation with Marketed Product.

In 0.1N HCL		
TIME IN MIN.	F9	MARKETED
0	0	0
15	0.48	0.50
30	0.56	0.58
45	0.64	0.65
60	0.70	0.72
In Phosphate Buffer pH 6.8		
75	70.35	70.15
90	78.40	78.05
105	84.10	83.98
120	96.97	96.61

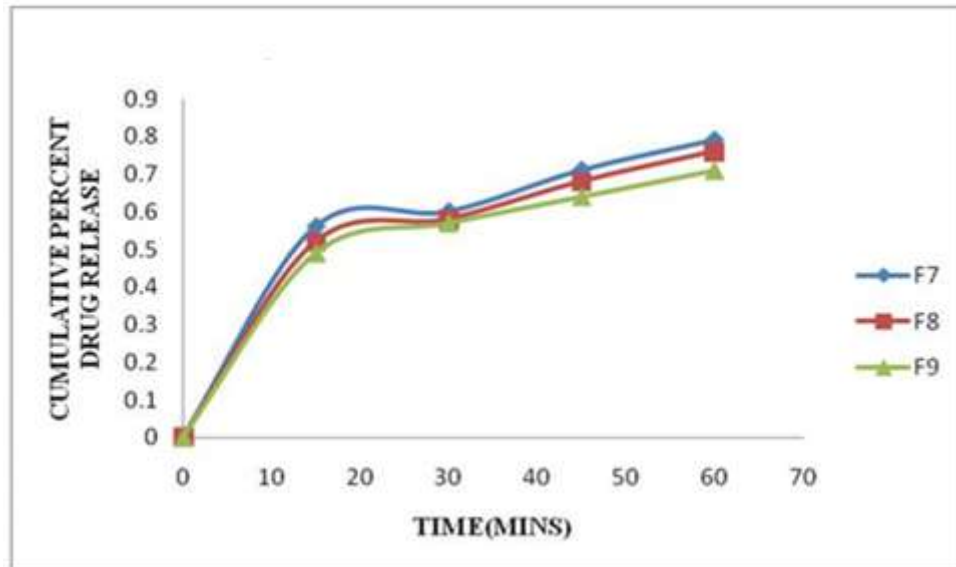
All values represent mean (n)=3.



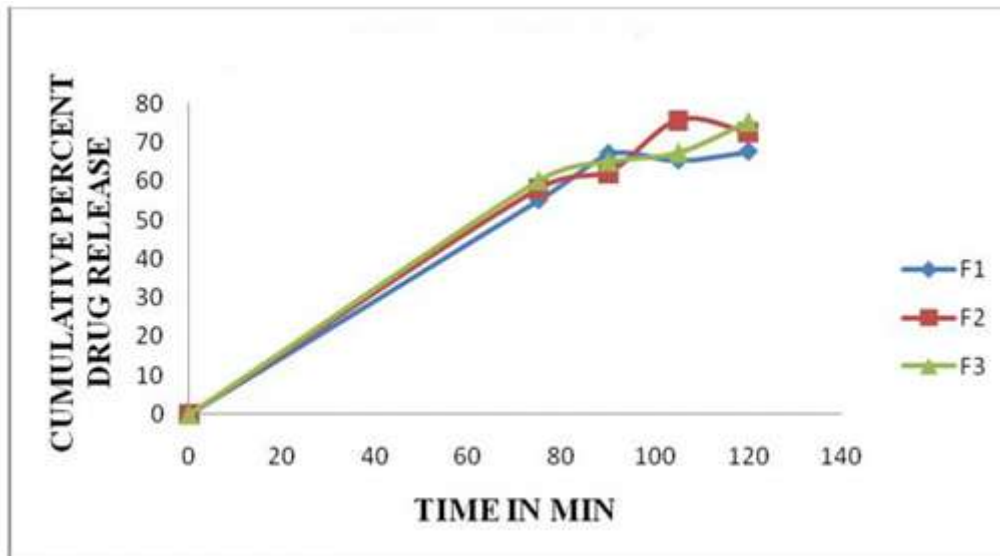
FigureNo.1:CumulativePercentageofReleaseofLansoprazolein0.1NHCL



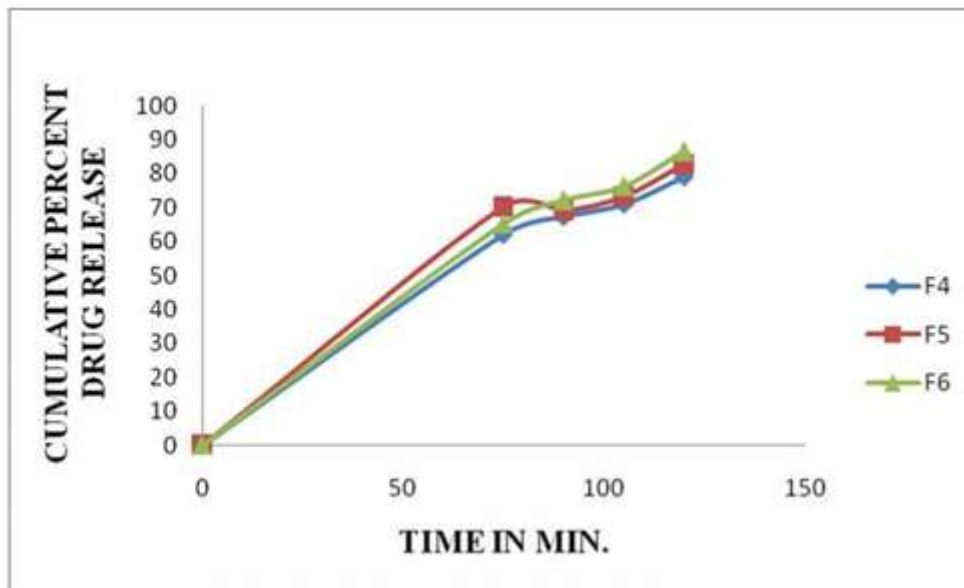
FigureNo.2:CumulativePercentageofReleaseofLansoprazolein0.1NHCL



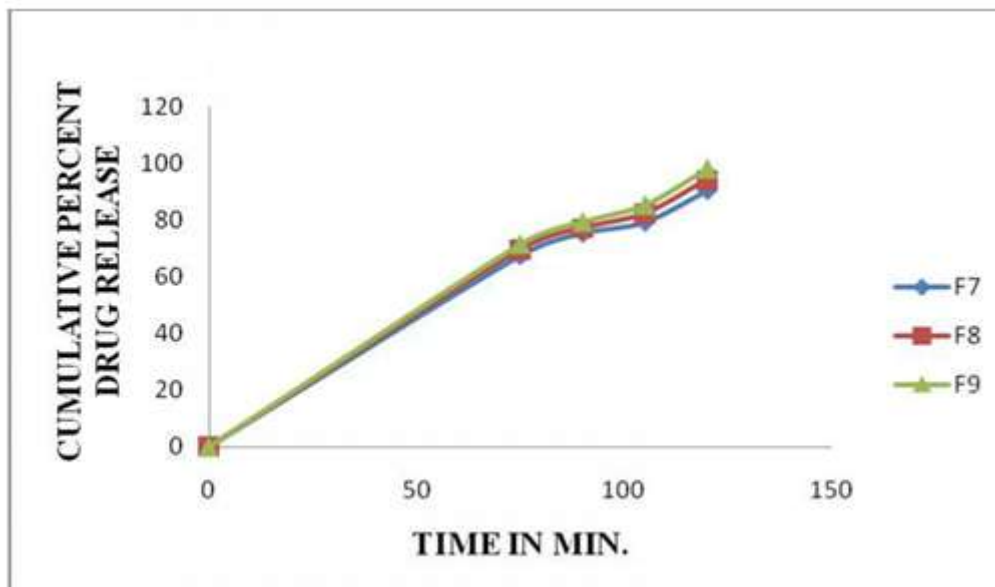
FigureNo.3:CumulativePercentageofReleaseofLansoprazolein0.1NHCL



FigureNo.4:CumulativePercentageofDrugReleaseofLansoprazoleinPhosphateBufferpH6.8



FigureNo.5: Cumulative Percentage of Drug Release of Lansoprazole in Phosphate Buffer pH 6.8



FigureNo.6: Cumulative Percentage of Drug Release of Lansoprazole in Phosphate Buffer pH 6.8

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