To Developed and Optimized Formulation of Lansoprazole Enteric Coated Pellets Drug Delivery System by Using Polymer

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ABSTRACT: Lansoprazole is a proton siphon inhibitor utilized in treating gastric ulcers and gastro esophageal reflux Disease (GERD) and furthermore keeping up with of all grades of erosive esophagitis (EE). Proton pump inhibitors are corrosive labile medications. These medications will debase in acidic climate of stomach and will prompt restorative inefficacy. lansoprazole is profoundly corrosive labile and presents numerous plan difficulties and to safeguard it from acidic climate of the stomach. It is important to sidestep the acidic pH of the stomach, which can be accomplished by planning postponed discharge measurement structures (single unit or numerous units) by utilizing different intestinal polymers. Lansoprazole and excipients of different like HPC-L and eudragit L30 D55 were utilized as intestinal polymers. The intestinal covered pellets were ready by suspension layering strategy in fluidized bed processor (FBP). Nine Definitions of lansoprazole intestinal covered pellets were arranged differing the syntheses of medication stacking, boundary covering and intestinal covering. Corrosive protections concentrate on shows that the advanced definition F9 is more steady in the acidic media for example 96.73% of medication was delivered in an hour. The point of the current review was to create a chemically same, stable, cost of powerful and quality superior definition of lansoprazole deferred discharge pellets. The pre-arranged pellets were read up for their physico-compound properties, examine and in vitro release studies.

Keywords: Lansoprazole, Enteric Coated Pellets, eudragit, Accelerated stability

INTRODUCTION:

Lansoprazole is one of the classes of proton siphon inhibitors, which diminish gastric acridity, a significant calculate recuperating corrosive related problems like gastric ulcer, duodenal ulcer and reflux oesophagitis. It is utilized to treat gastro-oesophageal reflux illness, ulcers, corrosive related dyspepsia and as an adjuvant in the destruction of H. pylori1, 2,3 .

Deferred discharge frameworks discharge a bolus of the medication after a foreordained time in a foreordained area, for example they don't deliver the medication following ingestion, for instance intestinal covered tablets, pulsatile discharge containers Postponed discharge dose forms1 are intended to give spatial position or fleeting designated conveyance of a medication to the distal human stomach. Spatial position connects with focusing on a medication to a particular organ or tissue, while fleeting conveyance alludes to wanted pace of medication delivery to target tissue over a predetermined time of treatment. The essential point of utilizing postponed discharge items is to safeguard the medication from gastric liquids, to diminish gastric trouble brought about by drugs especially disturbing to the stomach or to work with gastrointestinal travel for drugs that are better consumed from digestive tract The medications contained in such a framework are those that are:

- Obliterated in the stomach or by digestive proteins.
- Known to cause gastric misery.
- Ingested from a particular digestive site.

Pellets:

Pellets are small, freely flowing, spherical or semi-spherical solid units that are usually intended for oral administration and range in size from approximately 0.5 mm to 1.5 mm. They are produced by agglomerating fine powders or granules of bulk drugs and excipients using the right processing tools. To obtain nonpareils/pellets that are drug-loaded, employ the following methods.

a. A method of loading powder onto the surface of non-perils that involves alternating the dosing of powder (containing the drug material) and binder liquid until the necessary dose of the drug has been loaded.

b. Spraying a medication onto the surface of the non-perils that is either suspended or dissolved in a suitable solvent (often water) and contains a polymer (such as hydroxyl propyl methyl cellulose or polyvinyl pyrrolidone) as a binder. 5, 6.

Advantages [7,8,9]

- It enhances the safety, efficacy, and flow property of medicines while also improving the product's appearance and core.
- Compared to reservoir type single unit formulations, pellets are less prone to dose dumping when designed as modified release dosage forms.
- Pelletization decreases variances in gastric emptying rates and total transit times, which in turn minimises intra- and inter-subject variability of plasma profiles.
- Different medications can be combined and formed into pellets in a single unit dose form, making it easier to deliver two or more medications that are chemically compatible or incompatible at the same or different sites in the GI tract.
- Dissimilar medications can be processed separately and then combined, or pellets with various release mechanisms can be combined to provide a new, modified release profile.
- Pellets spread out easily in the GI tract and hence greater absorption of the active drug occurs.

MATERIAL AND METHOD:

Material:

Lansoprazole (Cedilla Healthcare Limited, Ahmedabad), sugar spheres (Sanmour pharma pvt.ltd, Mumbai), starch (Loba chemie, pvt. Ltd. Mumbai), sucrose (Loba chemie, pvt. Ltd. Mumbai), Hydroxy Propyl Methyl Cellulose E5 (Himedia laboratories, pvt. Ltd.Mumbai) , talc (Loba chemie, 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 u to 80-85ºC. 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^{0C}. 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 screens 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 Density[13]:

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 become more spherical in shape, bulk density is increase. 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 Density[13]:

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. Hauser's Ratio[13]:

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.

$$\textbf{Hauser's ratio} = v_i / v_t$$

Were,

v_t = Tapped volume

v_i = untapped volume

4. Angle ofRepose[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,

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

Were,

θ= angle of repose

h= height of the heap

r = radius of the base of the heap

5. Friability[15]: 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 steal balls to increase stress. The friability was calculated as percentage weight loss according to the following equation: -

% Friability = Initial weight - Final weight / Initial weight ×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 Study[18]:

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 (chromeleon) 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 0f 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 40^0C/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.

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 as retarding agents. Pellets were prepared by using suspension layered 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 the pharmacopeia specification. From the results it was observed that the average particle sizes of the pellets were nearly 100 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 resistances study shows that the optimized formulation F9 is more stable in the acidic media i.e. 96.73% of drug was released in 60 minutes. Result of acid resistances 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 resistant to 0.1N HCL as compared to their formulations because formulation F9 contains high concentration of sugar sphere. As sugar sphere used in high concentration It giving a thin layer of drug on each pellets and HPMCK5 used in high concentration forming a thick layer between drug and enteric polymer, so It prevent the interaction between the drug and enteric polymer. Therefore, formulation F9 showed the better resistant 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 the formulations. Because it may be in formulation F9 Eudragit L30D55 was used in low concentration, there for the drug release from pellet occurs fatly in phosphate buffer pH6.8. While keeping in 6.8pH buffer, 70.35cumulative percent drug release occur at 75 minutes, after 120 minutes 96.9 cumulative percent drug release was attained, when compared to the 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 months 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 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 Water	qs	qs	qs	qs	qs	qs	qs	qs	qs
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±0.0 2	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±0.0.1	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					
Sr. No.	Time (min)	Cumulative percent drug release			
		Initial	1 month	2 months	3 months
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

TableNo.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		
TIMEINMIN.	**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.

Figure No.1: Cumulative Percentage of Release of Lansoprazole in 0.1 NHCL

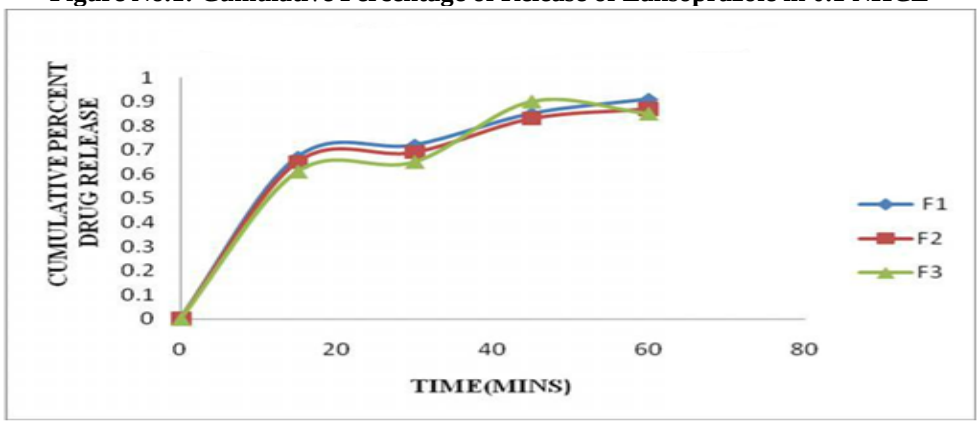


Figure No.2: Cumulative Percentage of Release of Lansoprazole in 0.1 NHCL

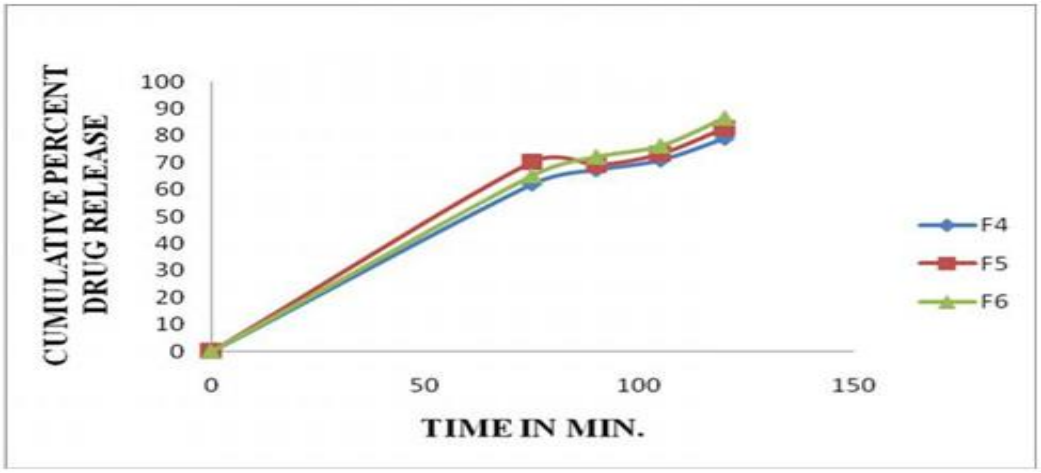


Figure No.3: Cumulative Percentage of Release of Lansoprazole in 0.1 NHCL

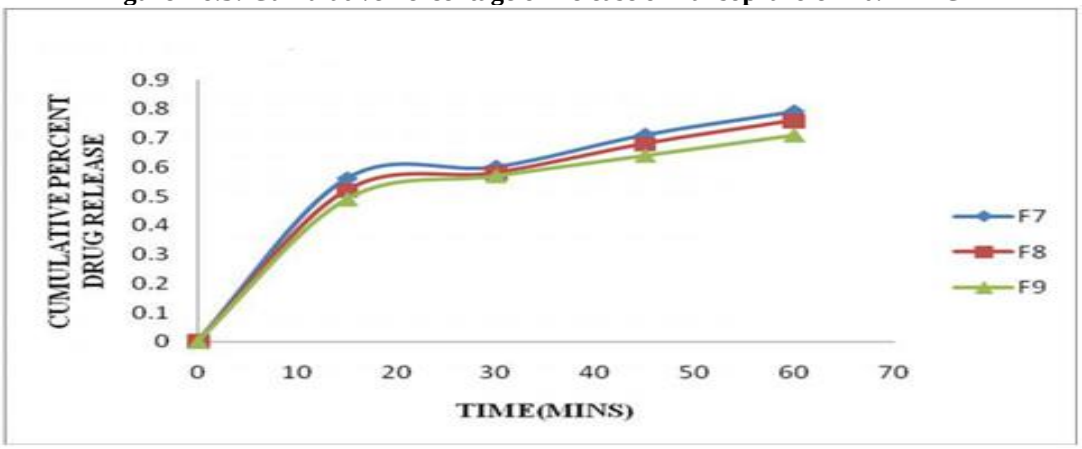


Figure No.4: Cumulative Percentage of Drug Release of Lansoprazole in Phosphate Buffer pH 6.8

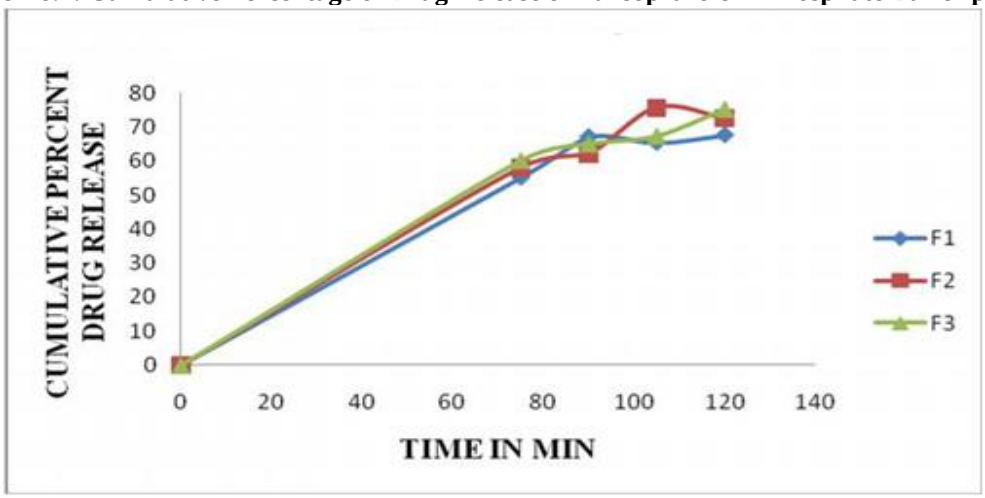


Figure No.5: Cumulative Percentage of Drug Release of Lansoprazole in Phosphate Buffer pH 6.8

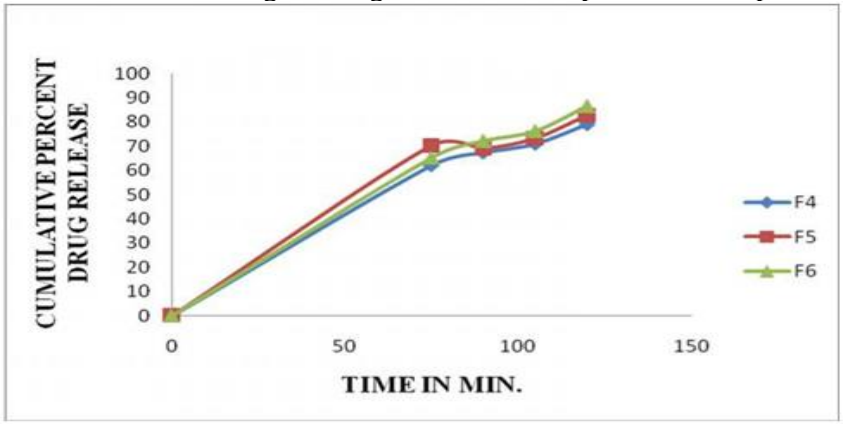
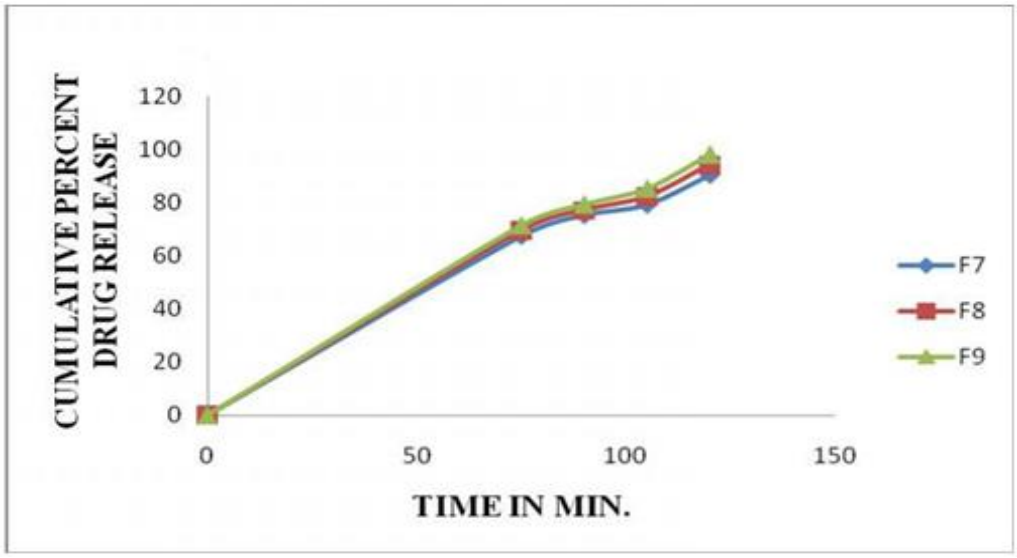


Figure No.6: Cumulative Percentage of Drug Release of Lansoprazole in Phosphate Buffer pH 6.8



Conclusion-

The study was undertaken with an aim to develop an optimized formulation of Lansoprazole Enteric Coated Pellets drug delivery system by using Eudragit L-30D-55, HPMC K5 as retarding agents. The active pharmaceutical ingredient, Lansoprazole was selected and formulated as Enteric Coated Pellets comparable to the innovator's product. Based on the results, suitable excipients were selected for formulation development. Pellets were prepared by using Suspension layered method. Finished products were evaluated for friability test, assay, and In-vitro release studies performed for 1hr in acidic media at 0.1N HCL, after that 1 hr in 6.8 pH Phosphate buffer. From the evaluation it was concluded that percent friability and percent assay for all formulations from F1 to F9 were found within the limit. Invitro dissolution study showed that Formulation F9 having the better resistance in 0.1 N HCL and good release in phosphate buffer pH 6.8. From the above results and discussion, it might be concluded that the formulation F9 of enteric coated pellets of Lansoprazole was found to be stable in acidic medium and shows better drug release in basic medium. Therefore, it was an ideal and optimized formulation of enteric coated pellets. Then the optimized formulation F9 was compared with marketed product by an invitro study, it shows that the formulation F9 was good as compared with marketed one.

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