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FORMULATION, DESIGN AND OPTIMIZATION OF ORALLY DISINTEGRATING LANSOPRAZOLE TABLET BY EFFERVESCENT METHOD

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ABSTRACT

Lansoprazole a proton pump inhibitor used in the treatment of gastric and duodenal ulcer, reflux esophagitis. In the present investigation enhance the solubility and dissolution profile of lansoprazole by using solid dispersion technique. Effervescent method can be used as alternative to develop dosage form which can accelerate drug disintegrating and dissolution, is usually applied in quick release preparation. Lansoprazole is insoluble in water, improved the solubility by using the solid dispersion technique. Solid dispersion prepared by the solvent evaporation method was further used in formulation as active API. Then Effervescent tablet was prepared by using Direct Compression method. Design using the excipient such as alkalizing agent sodium bicarbonate and acidifying agenttartaric acid. Drug- excipient compatibility checked by FTIR method also micromeritics properties were performed such as Bulk density, Tapped density, Hausner's ratio, Carr's index, Angle of repose. Among 7 batches F4 batch was optimized batch with drug release, Hardness, Friability, Weight variation, Drug content uniformity, Disintegration time and pH of solution, Dissolution study were evaluated. The dissolution data subjected to drug release kinetic fit in Higuchi model of regression coefficient of correlation R^2 =0.809.

Keywords: Lansoprazole, Gastroretentive dosage form, Effervescent Tablet, Solid Dispersion Method (PEG S600), Direct Compression Method, Drug Release Kinetic, Higuchi Model

INTRODUCTION

Oral drug delivery is the most popular of taking medicines and easy administration route among all the route having some disadvantages like slow absorption and thus onset action is prolonging drug delivery profile in the gastrointestinal tract is to control the gastric residence time using gastroretentive dosage form that will be improved as the new and attributed therapeutic options so effervescent act as an alternative dosage form **[1]**.

Effervescent is defined as the evaluation of bubbles of gas from a liquid as a result of a chemical reaction. The reaction starts at the presence of water, even with a very small amount as a catalyzing agent, and because water is one of the reaction products, it will accelerate the rate of reaction lading to difficulty in stopping the reaction. The whole manufacturing and storage of effervescent product is done by minimizing contact with water in controlled in suitable container **[6]**. Formulation of effervescent preparation include of three components Active ingredient ,acid source and alkaline source **[5]**.

Lansoprazole is aproton pump inhibitor used in the treatment as gastric and duodenal ulcers and gastroesophageal reflux disease. It reduced the acid produced in the stomach. Lansoprazole also effective in combination with different regimen for H. Pylorieradication. Lansoprazole is a BCS II drug classification which has poor solubility and high permeability **[1]**. Lansoprazole insoluble in water. Inhaced solubility by using the solid dispersion method in which select the solvent evaporation method. After solid dispersion done then this mixture used in the formulation. Formulation is design by choosing the various excipient and check Compability by FTIR method **[15]**. For better result used the direct compression method. During compression of tablet humidity of room temp must below 35% because moisture may cause effervescent reaction. To achieve high level safety, low moisture should be presented in ventilated air **[8]**.

Solid Dispersion: [3, 5]

Solvent evaporation method: [3, 5]

Solid dispersion of Lansoprazole drug prepared by melting the weighed accurately amount of time of tablet and carrier as PEG600. Then the mixture is heated under controlled temperature. Preparation was transferred to porcelain tile to solidify and cooled in an ice bath. The solid dispersion was kept for pulverized and the sifted from #80 sieve.

Evaluation of solid dispersion: [3, 5]

Solid dispersion prepared by using solvent evaporation method was evaluated solubility, particle size determined by

particle size analysis. And drug content by UV. Visible spectrophotometric Method.

Formulation method: [5]

1. Solid dispersion of lansoprazole and excipient weight accurately in polyethene bag.
2. Then Super disintegrant sodium bicarbonate, Crospovidone and lansoprazole sifted through #40 then acidifying agent citric acid and tartaric acid are passing through the sieve No. #40.
3. All the excipient mixed properly in polythene bag. Weight accurately 700mg tablet weight and then direct compression done by using single punch compression machine.
4. Compressed tablet was kept in the air tight container.
5. For the evaluation take one full glass of water one tablet are transferred in glass and check the effervescent time and pH of solution **(Table 1)**.

Table 1: Formulation table of Lansoprazole Effervescent Tablet

Ingredient	F1	F2	F3	F4	F5	F6	F7
Lansoprazole	60	60	60	60	60	60	60
Crospovidone	200	200	200	200	200	200	200
Sodium Bicarbonate	215	190	165	190	140	175	185
Citric acid + Tartaric acid	100:75	100:100	100:120	100:75	100:150	100:115	100:105
Mannitol	50	50	50	50	50	50	50
Flavor (Strawberry)	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

PRE-FORMULATION STUDY -

1. **Melting point determination:** The melting point determine by introducing small amount and the capillary attached to graduated thermometer.
2. **Determination of solubility:** Qualitative solubility analysis of drugs was done by dissolving 5mg of drug in 5ml freely soluble in organic solvent such as dimethyl formamide, soluble in methanol.
3. **UV.SPECTROPHOTOMETER DETERMINATION: [15]**

50mg of Lansoprazole was weighed accurately and transferred it into 50ml volumetric flask with 50ml Methanol (1000ug/ml). It was sonicated for 5minutes, and then 5ml pipette out from first stock and transferred into 50ml volumetric flask the volume was made upto the mark with distilled water to get the stock solution (100ug/ml). This solution is further dilution were made by using this stock solution and Standard solution will be prepared at five concentrations.

Further calibration curve of Solifenacin Succinate was plotted by measuring absorbance of 2 µg/ml, 4 µg/ml, 6 µg/ml,8 µg/ml and 10 µg/ml solutions scanned in the range 400-200nm using U.V. spectrophotometer (SHIMADZU1800).

Spectrophotometric data for the estimation of Lansoprazole at 282 nm.

4. **COMPABILITY STUDY: [15]**

The compatibility of solifenacin succinate with excipient was studied by FTIR spectroscopy. The method used for study is pressed KBr pellet method and the ratio of sample is should be 1:100, where 1 is a part of drug sample and 100 is a part of KBr. The scanning range was 4000-400cm^{-1} at ambient temperature. (Perkin Elmer spectrum-65).

CHARACTERIZATION OF EXCIPIENTS:

The excipients were evaluated for their appearance, Colour. Citric acid, sodium bicarbonate, and the additives were used in the formulations.

1. **Angle of repose (θ): [6, 7]** Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$\tan \theta = H / R$

$\theta = \tan\text{-}1 (H/R)$

Where, θ is the angle of repose

H - height of pile

R - radius of the base of pile

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (H). The angle of repose was then calculated by measuring the height & radius of the heap of powder formed. Care was taken to see that the powder particles slip & roll over each other through the sides of the funnel. Relationship between angle of repose and powder flow property.

2. **Bulk Density: [6, 7]** The bulk density was obtained by dividing the mass of a powder by the bulk volume in cm3. The sample of about 50 cm3 of powder, previously been passed through a standard sieve no. 20, was carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface three times from a height of 1 inch. The bulk density of each formulation was then obtained by dividing the weight of sample in grams by the final volume in cm3 of the sample contained in the cylinder.

3. **Tapped density: [6, 7]** The tapped density was obtained by dividing the mass of a powder by the tapped volume in cm3. The sample of about 50 cm3 of powder previously been passed through a standard sieve no. 20, is carefully introduced into a 100 ml graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation was then obtained by dividing the weight of sample in grams by the final tapped volume in cm3 of the sample contained in the cylinder.
4. **Carr's Index: [6, 7]** An indirect method of measuring powder flow from bulk densities was developed by Carr's. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below

$$\textbf{Carr's index} = \frac{\textbf{Tapped density} - \textbf{Bulk density}}{\textbf{Tapped density}} \times 100$$

5. **Hausner's ratio: [6, 7]** Hausner's ratio was determined by following equation. Hausner's ratio = tapped bulk density/ bulk density A Hausner's ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

.**EVALUATION OF LANSOPRAZOLE EFFERVESCENT TABLET:**

1. **Tablet Thickness and Diameter: [6, 7]** Thickness and diameter of tablets are important for uniformity of tablet size. Thickness and diameter were measured using digital Vernier calipers.
2. **Tablet Hardness: [6, 7, 13]** The resistance of tablets to shipping or breakage under condition of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Erweka Hardness Tester. The hardness was measured in terms of kg/cm2.11 Hardness or tablet crushing strength is the force required to break a tablet in a diametric compression. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets.
3. **Weight Variation: [6, 7, 13]** Weight variation was determined to know whether different batches of tablets have uniformity. Twenty tablets were selected randomly. Tablets were weighed individually and average weight was calculated.

4. **Disintegration Time: [6, 7, 13]** The disintegration time is indicating the time required to disintegrate the tablet in 120 ml of water at 37°C. By using the ECLTROLAB Disintegration apparatus.
5. **Friability: [6, 7, 13]** Take 650mg weight of tablet. Place the tablet in Roche friabilator. The friability was operated at 25rpm at 100 revaluation then removes loose duct from then weights them accurately. The % friability was calculated by using following equation.

$$\% \text{ Friability} = \frac{\text{Initail weight} - \text{final weigth}}{\text{Initial weight}} \times 100$$

6. **Dissolution of Lansoprazole: [6, 7]**

   In-vitro dissolution studies for Aspirin was carried out in USP dissolution test apparatus-II, employing a paddle-type apparatus at 50 rpm using 900ml 6.8pH phosphate buffer solution and test carried out for the 5min. One tablet was used in each test. At predetermined time intervals 5ml of the samples were withdrawn by using a syringe. The volume withdrawn at each interval was replaced with the same quantity of fresh dissolution medium maintained at37±0.5ºC. The withdrawn samples were filtered through membrane filter 0.45µm & analyzed byusing a UV spectrophotometer at λmax of 282.00nm respectively.
7. **Drug Content Analysis of lansoprazole: [6, 7]** Accurately weighed the quantity of the tablet powder equivalent to 100mg of the drug was transferred to 100ml volumetric flask. 50 ml of buffer solution of pH – 7.2 was added. Mix with the aid of ultrasound for 10min,and then the volume was made upto 100ml with the same buffer solution mixed solution was filtered through filter paper,5ml of the filtrate was diluted to 100ml with same buffer solution and examined under UV-spectro-photometer at 282 nm.

RESULT AND DISCUSSION

Pre-Formulation Study:

The absorption maximum of Lansoprazole was found to be 282nm in Distilled water taken as blank **(Figure 1, 2)**. FTIR of Lansoprazole **(Figure 3)**, Compatibility study of lansoprazole with excipients **(Figure 4)**.

FTIR of Solid Dispersion of Lansoprazole **(Figure 5),** Compatibility study of Solid

Dispersion of Lansoprazole with excipients **(Figure 6)**.

Pre-formulation evaluation of powder:

The effervescent tablet of Lansoprazole was evaluated for various pre-Compression evaluation parameters. This includes Angle of repose, Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio **(Table 2)**.

Post- compression parameter of Lansoprazole Effervescent Tablet:

Various post-compression evaluations were performed such as weight variation, Hardness, Thickness, Friability and uniformity of weight. The weight uniformity is indicative of the degree of uniformity of active drug. The Thickness of the tablet is important aspect considered during packaging disintegration and dissolution of the tablet. Vernier caliper used to measure the Thickness of the tablet. Hardness is important as it maintains the integrity of the tablet during its transportation, storage, handling of the tablet. The Friability of the tablet must be less than 1%. Dissolution and Drug content uniformity is measured as per USP guidelines **(Table 4)**.

In-vitro drug release was studied for effervescent Lansoprazole Tablet:

The dissolution was carried out by USP-II type apparatus (Electrolab tdt-08L) using 900ml phosphate buffer pH 6.8 at 50rpm and 37°C temp. At predetermined time (1min) interval upto 5min, 5ml of the sample withdrawn by syringe fitted with pre-filter the volume interval was replaced with same quantity of fresh dissolution medium (phosphate buffer pH 6.8). The resultant sample were analyzed by measuring the absorbance at 282nm using UV. Visible spectrophotometer and calculate the percentage drug release. The F4 batch has shown cumulative percent drug release of about 103.8 in 5min. in shown **Figure 7**.

Drug Release kinetic (Table 6)

Kinetic Model: [6, 7] The F4 batch dissolution was found the Higuchi drug release pattern. The mechanism drug release is determined by Higuchi equation. The graphical representation of cumulative % of drug release against time represent that drug release of lansoprazole is Higuchi model value of regression coefficient of correlation R^2 =0.809 **(Figure 8)**.

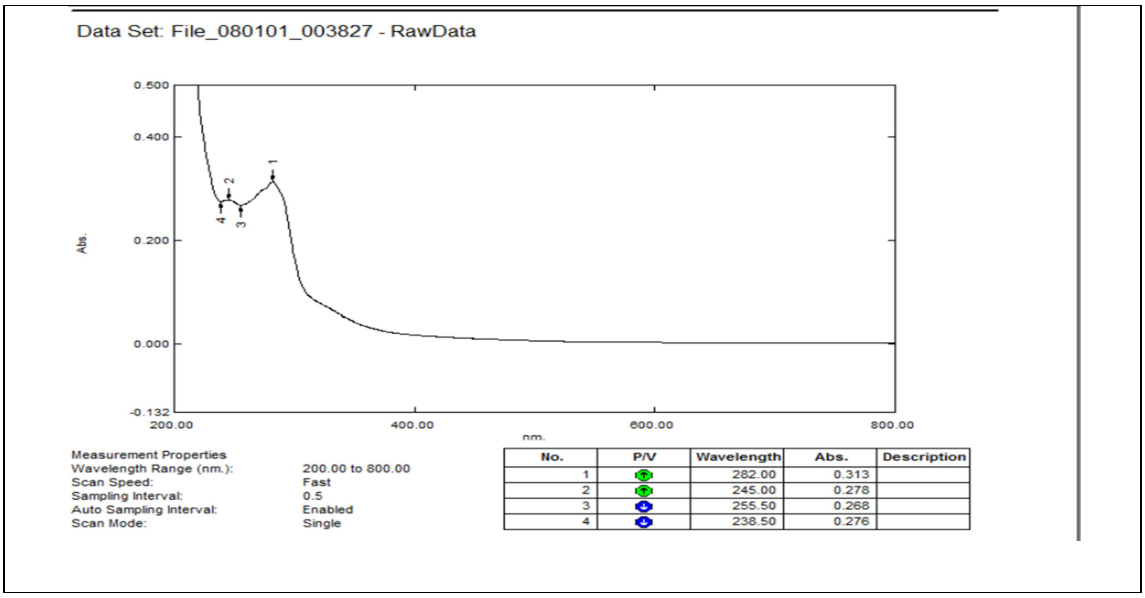

Figure 1: Absorbance of Lansoprazole

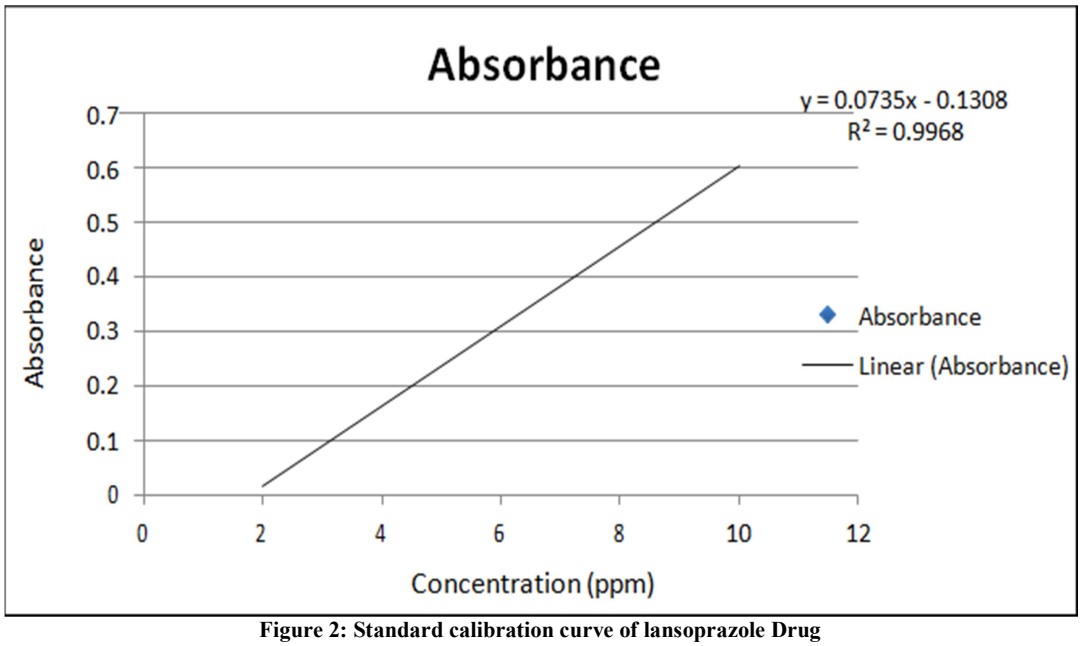

Figure 2: Standard calibration curve of lansoprazole Drug

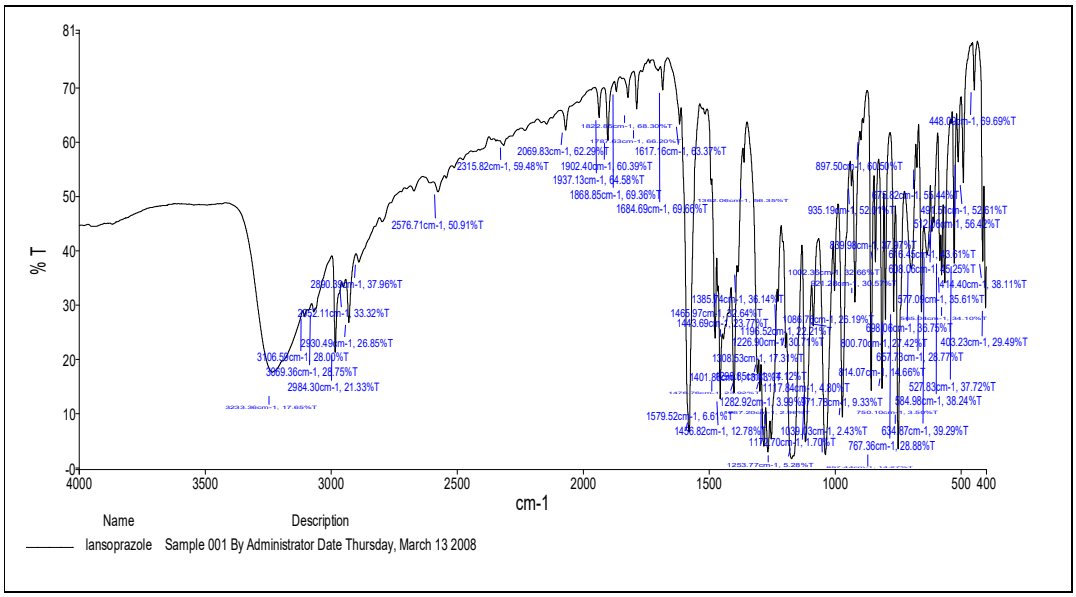

Figure 3: FTIR of Lansoprazole

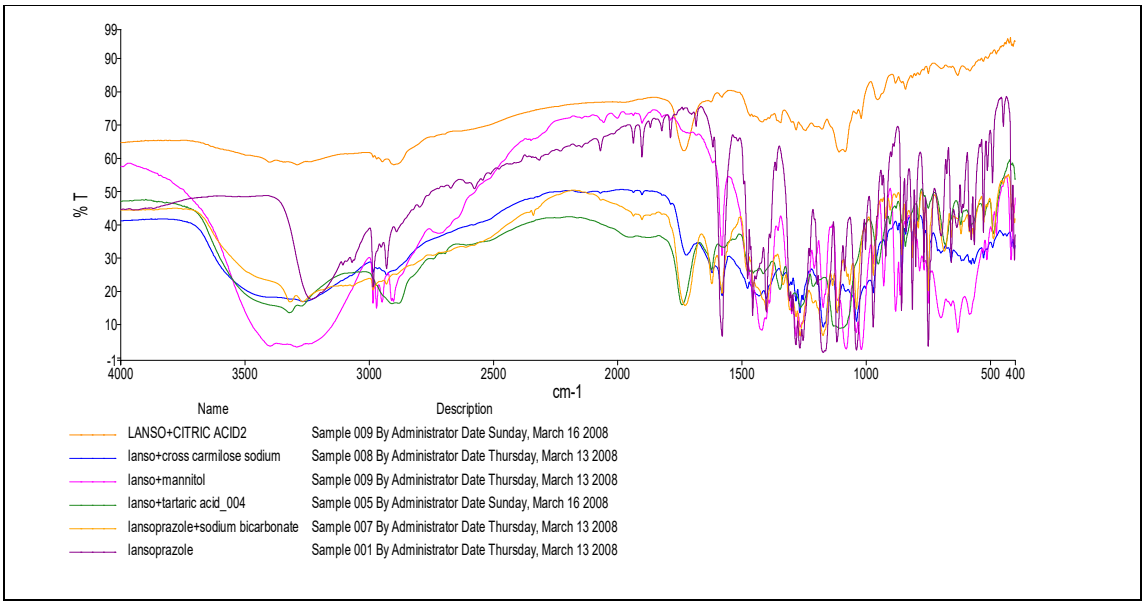

Figure 4: Compatibility study of lansoprazole with excipients

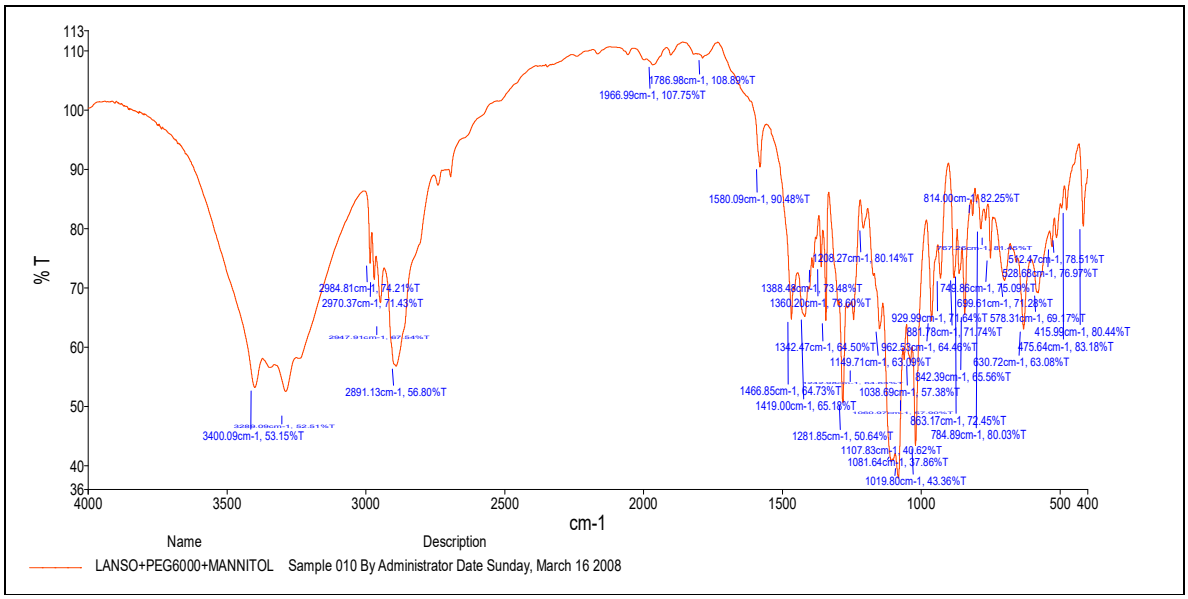

Figure 5: FTIR of Solid Dispersion of Lansoprazole

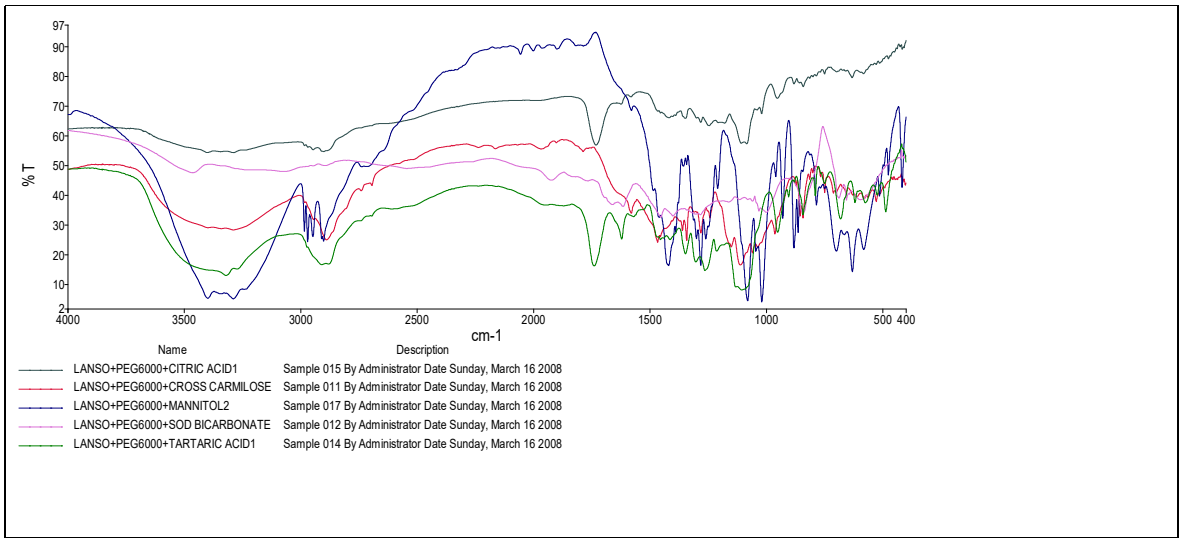

Figure 6: Compatibility study of Solid Dispersion of Lansoprazole with excipients

Table 2: Pre-Formulation result

S. No.	Parameter	Lansoprazole
1.	Identification of U.V. spectrophotometer	282 nm
2.	Melting point	166-167°C
3.	Solubility	Freely soluble in organic solvent such as Dimethyl formamide, soluble in methanol.
4.	Compatibility study	Compatible.

Table 3: Pre-compression parameter of Lansoprazole Effervescent Tablet

Formulation	Angle of repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
F1	25.56	0.849	0.903	5.58	1.063
F2	25.64	0.852	0.906	5.96	1.063
F3	25.76	0.854	0.909	6.05	1.064
F4	25.84	0.857	0.914	6.23	1.066
F5	25.78	0.859	0.917	6.32	1.067
F6	26.08	0.854	0.911	5.7	1.06
F7	25.70	0.857	0.909	6.05	1.065

Table 4: Post-compression parameter of Lansoprazole Effervescent Tablet

Formulation	Tablet weight (mg)	Hardness (kg/cm^3)	Thickness (mm)	Friability	Drug content	PH of solution	D.T. (sec)
F1	700.1	3.15	2.54	0.50	103.14	6.2	57.19
F2	700.1	3.16	2.53	0.52	100.1	6.3	53.04
F3	700.3	3.33	2.16	0.47	103.04	6.1	43.64
F4	700.0	3.30	2.43	0.40	103.8.35	6.5	13.51
F5	700.2	3.45	2.33	0.43	103.01	5.9	22.35
F6	700.4	3.51	2.73	0.46	102.1	6.4	25.09
F7	700.1	3.24	2.47	0.49	102.9	6.5	17.65

Table 5: Dissolution of Lansoprazole Effervescent Tablet

Time	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	89	88	88	89	88	89	89
2	101.01	98.9	100.08	101.02	100.06	101.06	100.4
3	102.21	101.02	101.07	102.05	1010.9	102.03	101.6
4	103.02	102.05	102.06	102.9	102.04	102.06	102.9
5	103.03	103.01	103.02	103.8	103.03	103.7	103.6

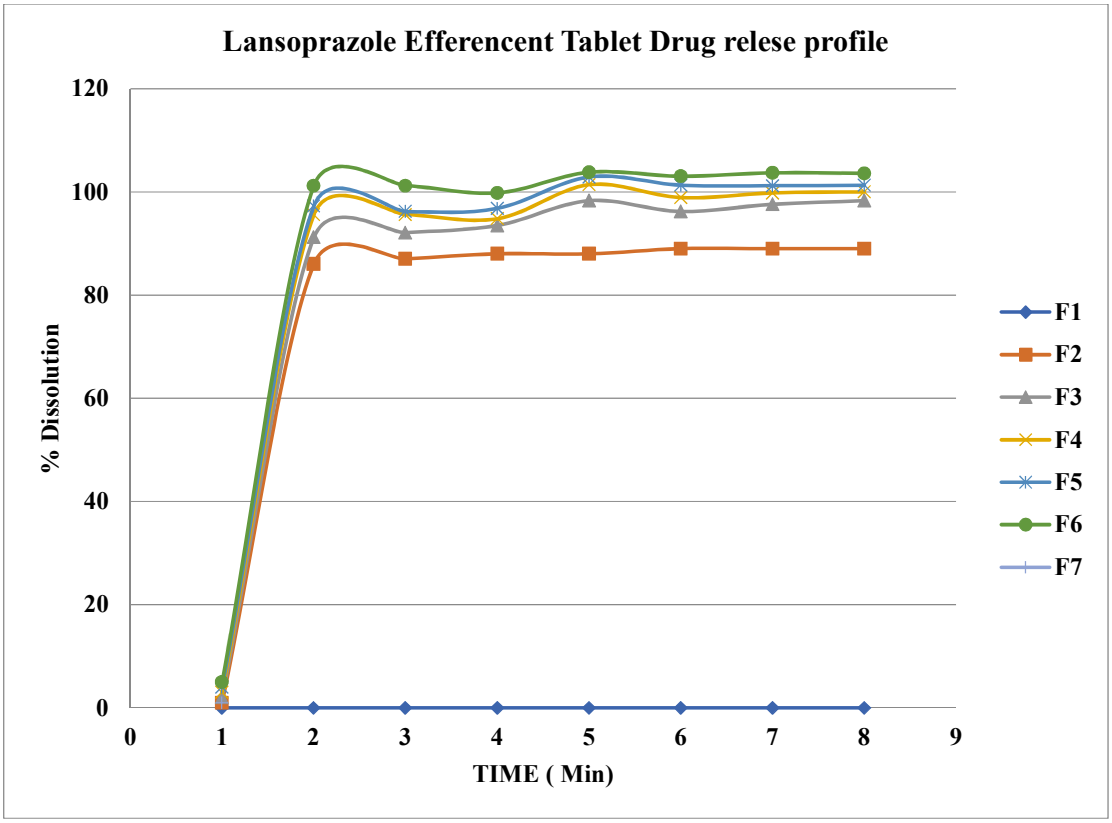

Figure 7: Drug Release profile of Lansoprazole Effervescent Tablet

Table 6: Drug release Kinetic of optimized batch

Time(min	cumulative % drug released	% drug remaining	Square root time	log Cumu % drug remaining	log time	log Cumu % drug released	% Drug released	Cube Root of % drug Remaining(Wt)	Wo-Wt
0	0	#REF!	0.000	#REF!	0.000	0.000	100	#REF!	0.000
1	89	100	1.000	2.000	0.000	#NUM!	#REF!	4.642	0.000
2	100.02	11	1.414	1.041	0.301	1.949	89	2.224	2.418
3	101.6	-0.02	1.732	#NUM!	0.477	2.000	11.02	-0.271	4.913
4	102.5	-1.6	2.000	#NUM!	0.602	2.007	1.58	-1.170	5.812
5	103.8	-2.5	2.236	#NUM!	0.699	2.011	0.9	-1.357	5.999
30		-3.8	5.477	#NUM!	1.477	2.016	1.3	-1.560	6.202
0	0	100	0.000	2.000	#NUM!	#NUM!	-103.8	4.642	0.000
0	0	100	0.000	2.000	#NUM!	#NUM!	0	4.642	0.000
0	0	100	0.000	2.000	#NUM!	#NUM!	0	4.642	0.000
0	0	100	0.000	2.000	1.000	#NUM!	0	4.642	0.000
0	0	100	0.000	2.000	#NUM!	#NUM!	0	4.642	0.000
0	0	100	0.000	2.000	#NUM!	#NUM!	0	4.642	0.000
0	0	100	0.000	2.000	#NUM!	#NUM!	0	4.642	0.000

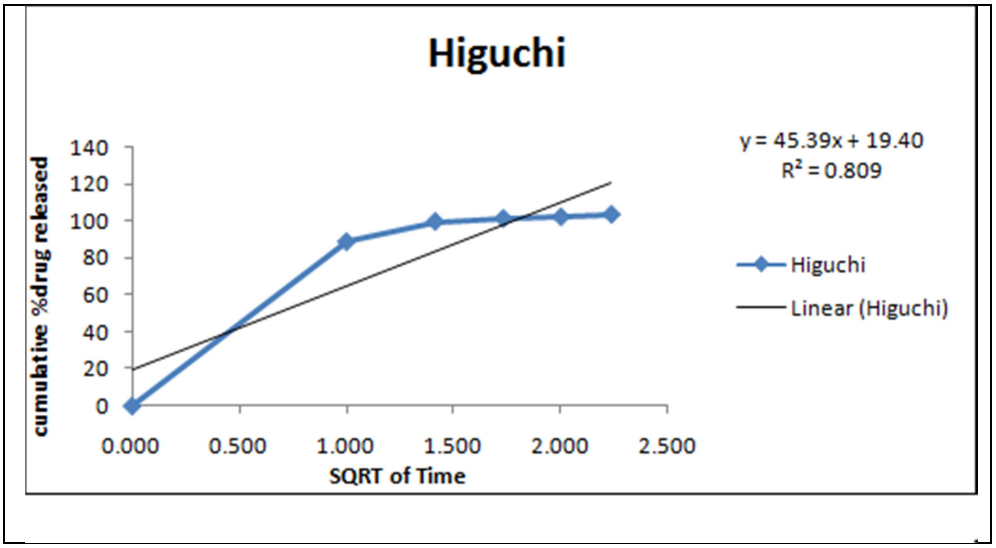

Figure 8: Drug Release kinetic of Lansoprazole found Higuchi Model

CONCLUSION

In the present study of lansoprazole 700mg effervescent tablets were prepared by using citric acid, tartaric acid, and sodium bicarbonate, as an effervescent composition. The lansoprazole are less soluble in water for enhancing the solubility used the solvent evaporation method. Then this solid dispersion of lansoprazole is used in formulation as a API to prepared the effervescent tablet. Lansoprazole is gastroretentive dosage form used in the treatment of gastric and duodenal ulcer, reflux esophagitis. The

seven batches were prepared by using OFAT design to minimize the error and get optimized batch. All pre-formulation parameter such as melting point, solubility, identification by UV Visible spectrophotometer, compatibility by FITR spectroscopy conducted and their results were found within limit. The micromeretic property of the blend of effervescent tablet was performed and all the values were found to be within acceptable limit of pharmacopeia specification. The all physical parameters such as weight variation, Thickness, Hardness, Friability, result found to be satisfactory. In –vitro drug release study carried using 6.8 phosphate buffer upto 5min. and among all the batches, sF4 batch was found to be optimized batch the drug release was found 103.8%. And F4 batch the drug release kinetic fit in Higuchi model and the value of regression coefficient of correlation R^2 =0.809.

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AUTHORS CONTRIBUTION:

All authors contributed equally.

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