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Formulation & Evaluation Of Pantoprazole Enteric Coated Tablet For The Treatment Of Peptic Ulcer

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Abstract

The purpose of this study was to prepare Pantoprazole enteric coated modified release formulation by using various super disintegrates and by keeping optimum physical parameters like hardness, thickness, disintegration and weight variation of the tablets so as to control the disintegration of the tablets which ultimately gives effect on dissolution of tablets which is having direct impact on drug release. The uncoated tablets were further enteric coated by using dipping method. The enteric coated tablet were again evaluated for hardness, Thickness, Friability, Weight Variation and Drug Content Uniformity, in-vitro dissolution testing and stability study was performed for optimized batch and further anti-ulcer activity was also performed. The average hardness increased to 2.97 Kg/cm^2, Average thickness also increased to 2.27 and average friability also decreased to 0.52% due to enteric coating. The Weight Variation was again under 5%. The Drug Content uniformity was found to be between 97-102%. In in-vitro dissolution testing, in initial 2 hours maximum drug release was of 2.10% in 0.1N hydrochloric acid and showed maximum of 92.45% drug release in phosphate buffer pH 6.8 over the period of total 12 hours for F8 batch. Therefore F8 batch was considered to be optimized batch and selected for anti-ulcer activity on animals. The study was conducted on 12 subjects and eleven subject showed maximum subjects revealed that the plasma drug concentration of test was quite similar to that of reference.

1. Introduction:

In the treatment of stomach and duodenal ulcers, as well as gastroesophageal reflux disease (GERD) and Zollinger Ellison syndrome, the proton pump inhibitor pantoprazole sodium has found widespread application.[1] Pantoprazole sodium is a member of the benzimidazole group of drugs.[2]The proton pump inhibitor prodrug pantoprazole, sometimes known simply as pantoprazole, shown in Figure 1; it plays a significant role in the treatment of disorders associated to excess acid in the body.[3]
This study concerns the development of enteric coated modified release formulations of Pantoprazole Sodium.[4] Enteric-coated medications pertain to the "delayed action" dosage form category.[5] The primary

treatment goals in patients with ulcer and gastroesophageal reflux disease are relief of symptoms, prevention of complications related to the disease and healing of ulceration.[6] Inhibition of the gastric proton pump is gaining acceptance as the treatment of choice for severe gastrooesophageal reflux disease, and for treatment of duodenal and gastric ulceration.[7]

Recently, delayed release tablets have been received much attention by the pharmaceutical scientists as it is useful for delivering the drugs, which causes gastric mucosal irritation and gets degraded by gastric enzymes well as acidic environment of the stomach, in the intestine.[8] As it is said earlier pantoprazole gets degraded by the gastric enzymes and the acidic environment of the stomach. Hence, a delayed release formulation of pantoprazole as an enteric coated tablet may solve the stability problem of drug in the stomach and release the drug in the intestine. So that drug absorption begins only after the tablet leaves the stomach. Pantoprazole is a substituted benzimidazole that works by specifically blocking the proton pumps found in the parietal cells of the stomach. This stops the stomach from producing hydrochloric acid.[2]

The IUPAC name of Pantoprazole is 6-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-1H-benzimidazole.[9]

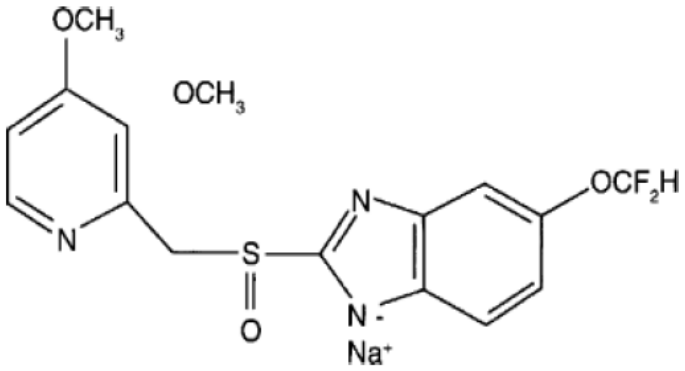

Figure 1. Chemical structure of Pantoprazole sodium[9]

2. Materials

2.1. Chemicals and Reagents

A complimentary sample of Pantoprazole was purchased from Aadhaar Life Sciences Pvt. Ltd., Solapur, MH, India. Hydrochloric acid, Potassium dihydrogen Phosphate, Sodium Hydroxide, Sodium Carbonate, calcium Stearate were purchased from Thomas Baker (Chemicals) Pvt. Ltd., India; Klucel KF, Polyplasdone XL 10 were purchased from Ashland Speciality Ingredients, U.S., Mannitol (Pearitol SD200) wss purchased from Roquette; Instacoat IC-S-329was purchased fromwas Ideal cures Puvt. Ltd. and Sheffcoat ENT 5Y was purchased from Kerry groups. All weighing was done using calibrated NABL scales. Samples were produced in Type A glassware and the analytical balance.

3. Method

A. Preformulation Studies:

1. Construction of Calibration Curve:

The calibration curve of Pantoprazole was constructed in 0.1 N Hydrochloric acid and Phosphate buffer pH 6.8. The samples were measured by UV- visible spectrophotometer at 283.5 nm (pH 1.2) and at 288.5 nm (pH 6.8) against a blank. Stock solution of 1000 µg/ml of Pantoprazole was prepared in each medium and series of dilution were prepared to make up the concentration of 5-25 µg/ml.

B. Optimization by Risk assessment and QbD:

Proper selection & optimization of formulation, equipment & process related variable in coating. Thus, risk assessment tools were used to identify and rank parameters with potential to have an impact on In Process/ Drug Product Critical Quality Attributes (IP/DP CQAs), based on prior knowledge and initial experimental data which were refined further to determine the significance of individual variables and interactions through DOE that lead to mechanistic understanding to achieve a higher level of process understanding.

C. Preparation of granules[10]

Pantoprazole sodium sesquihydrate granules for tableting were prepared by wet granulation method. Specified quantity of pantoprazole, super disintegrant, binding agent, glidants, lubricants were weighed according to the formula and mixed thoroughly by using appropriate sifter, blender. The granules prepared were dried in suitable drier and lubricated by using lubricants in blender.

D. Preparation of pantoprazole sodiumses quihydrate tablets[11]

An ideal mixture of granules were directly punched into tablets weighing about 200 mg containing 40 mg of pantoprazole sodium sesquihydrate, using rotary tablet compression machine by using 8 mm diameter concave punches. The [11] different batches of pantoprazole tablets were collected and stored in airtight containers.

E. Characterization of pantoprazoles odiumsesquihydrate Granules:[12]

i. Percentage yield

The prepared pantoprazole sodium sesquihydrate granules were completely collected and weighted. The percentage product yield was calculated from its theoretical and practical product yield.

$$\text{Percentage Yield} = \frac{\text{Practical Product Yield}}{\text{Theoretical Product Yield}} \times 100$$

ii. Mean granule size analysis by optical microscopy

In the present study the granules particle size was determined by the optical microscopy.1mm of the stage micrometer scale is equal to 89 eyepiece division. Therefore 1 eyepiece division is equal to (1/89) ×1000 Microns i.e. 11.2 µm. The dry granules were uniformly spread on the slide. Granules particle sizes were measured by using Sieve analyzer, along the longest axis and the shortest axis (cross shaped measurement). Average of these two reading given was mean diameter of particles. The diameter of a minimum number of 50granulesin each batch was calculated.

iii. Bulk density(Db)

Accurately weighed granules were carefully transferred into graduated measuring cylinder. The granules bed was then made uniform and the volume occupied by the granules was noted as per the graduation marks on the cylinder as ml. It is expressed in gm/ml and is calculated using the following formula.

$$Db = \frac{M}{Vb}$$

Where, M -Mass of the powder

V_b- Bulk volume of the powder

iv. Tapped density(D_t)

It is the ratio of total mass of granule to the tapped volume of granule. The graduated measuring cylinder containing accurately weighed granule was manually tapped for 50times. Volume occupied by the granule was noted. It is expressed in gram/m land is calculated by following formula.

$$Dt = \frac{M}{Vt}$$

Where, M-Mass of the powderV_t-Tapped volume of the powder

v. Compressibility index(I)and Hausner' sratio

Carr' sindex and Hausner' sratio measure the propensity of granuletobe compressed and the flow ability of granule. Carr's index and Hausner' sratio were calculated.

vi.Angle of repose(θ)

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole granules were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula.

$$\text{Angle of repose}(\theta) = \tan^{-1}(h/r)$$

Where, h –Height of the pile in cm r –Radius of the pile

F. In process compression parameters[13]

i. Hardness test

The prepared tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in kg/cm^2.

ii. Friability test

The friability was determined using Roche friabilator and expressed in percentage (%). 20tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability(F) was calculated for each batch by using the following formula.

$$F=\frac{(Winitial)-(Wfinal)}{(Winitial)}x100$$

iii. Weight variation test

20 tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%. IP limit for weight variation in case of tablets weighing more than 80 mg but less than250mgis ± 7.5 %.

iv. Uniformity of drug content by content uniformity test.

The prepared pantoprazole sodium sesquihydrate tablets were tested for their drug content. Three tablets of each formulation were weighed and finely powdered. About 40mg equivalent of pantoprazole sodium sesquihydrate was accurately weighed and complete lydis solved in pH 6.8 phosphate buffer and the solution was filtered. 1 ml of the filtrate was further diluted to 100 ml with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured by UV-Visible spectrophotometer at 288.5 nm.

G. Coating of compressed Pantoprazole sodium 40 mg tablets[14]

i. Preparation of enteric coating solution

Table 1: Composition of coating solution

Ingredients	Quantity(%w/w)
Cellulose acetate phthalate /EudragitL100/DrugcoatL100	6.0
Titanium dioxide	2.6
Diethyl phthalate	2.0
Acetone	59.4
Isopropyl alcohol	30.0

The enteric coating solution was prepared by solution method. It was prepared by 6% w/w of Eudragit L100 or cellulose acetate phthalate or Drug coat L100 as an enteric polymer,2.6% w/w of titanium dioxide as opacifier, diethyl phthalate 1.2% w/w as plasticizer and acet one and isopropyl alcohol mixture was used as solvent.

ii. Enteric coating of pantoprazole sodium sesquihydrate compressed tablets by dipping method

The compressed tablets were coated with enteric coating polymer (EudragitL100or cellulose acetate phthalate or Drug coat L100) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for its weight variation, thickness, uniformity of drug content and *invitro* dissolution study.

iii. *Invitro* drug release studies

USP dissolution apparatus type II was employed to study the *in vitro* drug release from various formulations prepared. The dissolution medium used was 900 ml of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8 for 10 h. The tablet was kept in to the basket. The temperature was maintained at 37°C ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV- visible spectrophotometer at 283.5nm(pH1.2) and at288.5nm(pH6.8) against a blank. There lease studies were conducted in triplicate and

the mean values were plotted versus time.

iv.Selection of batches

The plan consists of manufacturing of 11 different batches. Among the different batches, the best one was identified and selected based on their physicochemical and release characteristics, for further studies.

v. Stability studies

A study was carried out to assess the stability of the pantoprazole sodium sesquihydrate cellulose acetate phthalate coated tablet formulation (ECF3). Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The tablets were packeding lass container and B listerpack. Stability studies were carried out for accelerated condition40±2°Cand75±5%RHoveraperiodof1monthSampleswere evaluated at 10^{th}, 20^{th} and 30^{th} days for different parameters such as physical appearance, hardness, weight variation, drug content and dissolution.

vi. Evaluation of anti ulcer activity Animals

Albino rats of Wister strain of either sex weighing between 150-200 g were used. They were housed in standard cages at room temp. (25 ± 2ºC) and provided with the food and water. The animals were deprived of food for 24 h before experimentation, but had free access to drinking water. The study was conducted after obtaininginstitutionalethicalcommitteeclearancebearingthenumberDSCP/Mpharmaceutics/IAEC/09/09-10.

vii. Evaluation of antiulcer activity

The antiulcer activity of the pantoprazole sodium sesquihydrate cellulose acetate phthalate coated tablet formulation (ECF3) was evaluated by using water immersion stress induced lcermodel.

i.Water immersion stress induced ulcer model Procedure

In the present study the animals were divided into two groups and kept six animals in each groups. Each group have received, group I-Control (distilled water), group II–Pantoprazole sodium sesquihydrate coated tablet formulation ECF3 at the dose of 10 mg/kg body weight. Animals in all the groups were fasted for 24 h after the respective assigned treatment. After the drug treatment the animals were allow to swim in water for 3 h.

Thus, the animals were anaesthetized with anesthetic chloroform and the stomach of each animal was removed and the extent of gastric damage assessed as described bellow.

0=Normal colored stomach
0.5 = Red coloration
1=Spot ulcers
1.5 = Hemorrhagic streaks
1.6 2 = Ulcer >3mm but
1.7 <5mm
1.8 3=Ulcer>5 mm

Meanulcer score for eachanimal was expressed asulcer index. The ulcer index was determined using the following formula

Ulcer index=10/x

Where x is the total mucosal are adivided by total ulcerated area.

4. Results and Discussion

4.1 Pre-formulation Study:

4.1.1 Calibration Curve of Pantoprazole:

The calibration curve of Pantoprazole drug was constructed by plotting Concentration range Vs absorbance of its respective concentration. The drug solution was prepared by using 0.1N hydrochloric acid as diluent. The Concentration range was ranging from 0-25 µg/ml. The results of calibration curve are given in table 2. The linearity equation was found to be y=0.0351x+0.0098 and the regression coefficient was found to be 0.9992. The Calibration curve is depicted in Figure 2

Table 2: Results of Calibration curve of Pantoprazole in 0.1N HCl

Conc (µg/ml)	Absorbance
0	0
5	0.189
10	0.365
15	0.545
20	0.721
25	0.875

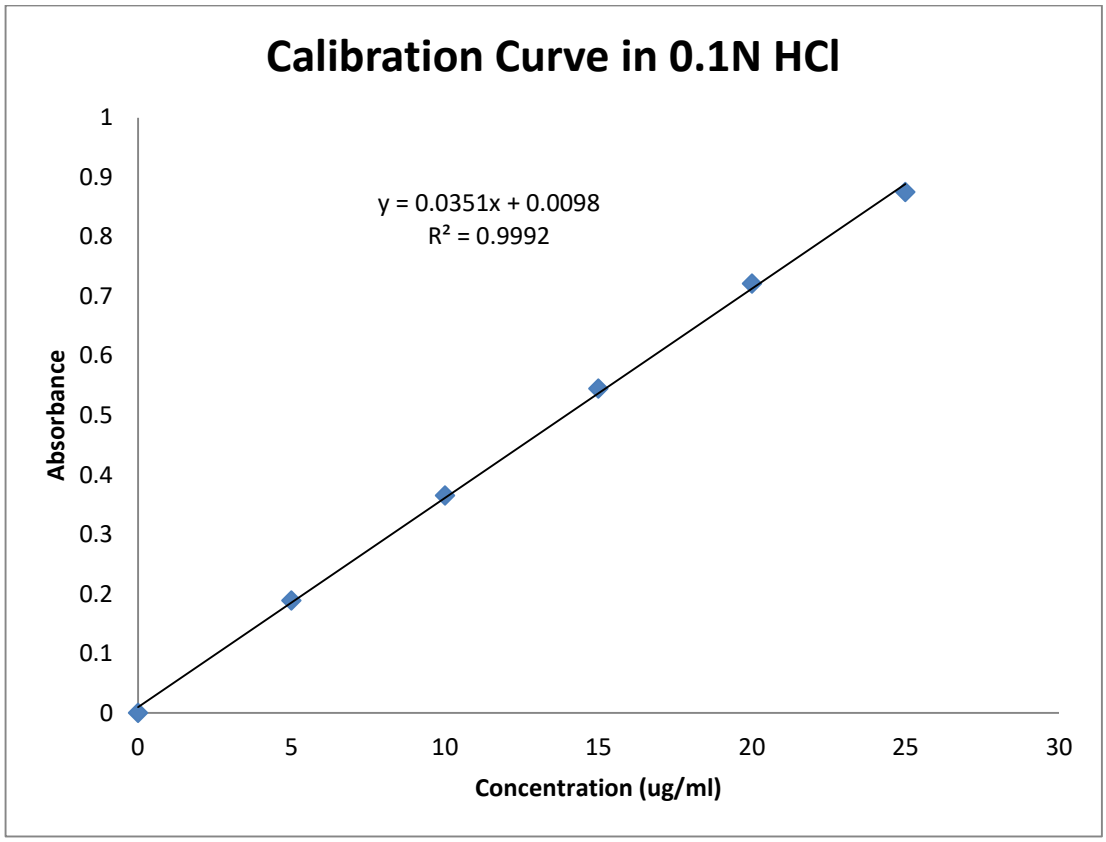

Figure 2: Calibration curve of Pantoprazole in 0.1N HCl

Also, The calibration curve of Pantoprazole drug was constructed by plotting Concentration range Vs absorbance of its respective concentration by using Phosphate Buffer pH 6.8 as diluent. The Concentration range was ranging from 0-25 µg/ml. The results of calibration curve are given in table 3 The linearity equation was found to be y=0.037x+0.003 and the regression coefficient was found to be 0.9989. The Calibration curve is depicted in Figure 3

Table 3: Results of Calibration curve of Pantoprazole in Phosphate Buffer pH 6.8

Conc (ug/ml)	Absorbance
0	0
5	0.196
10	0.372
15	0.542
20	0.760
25	0.922

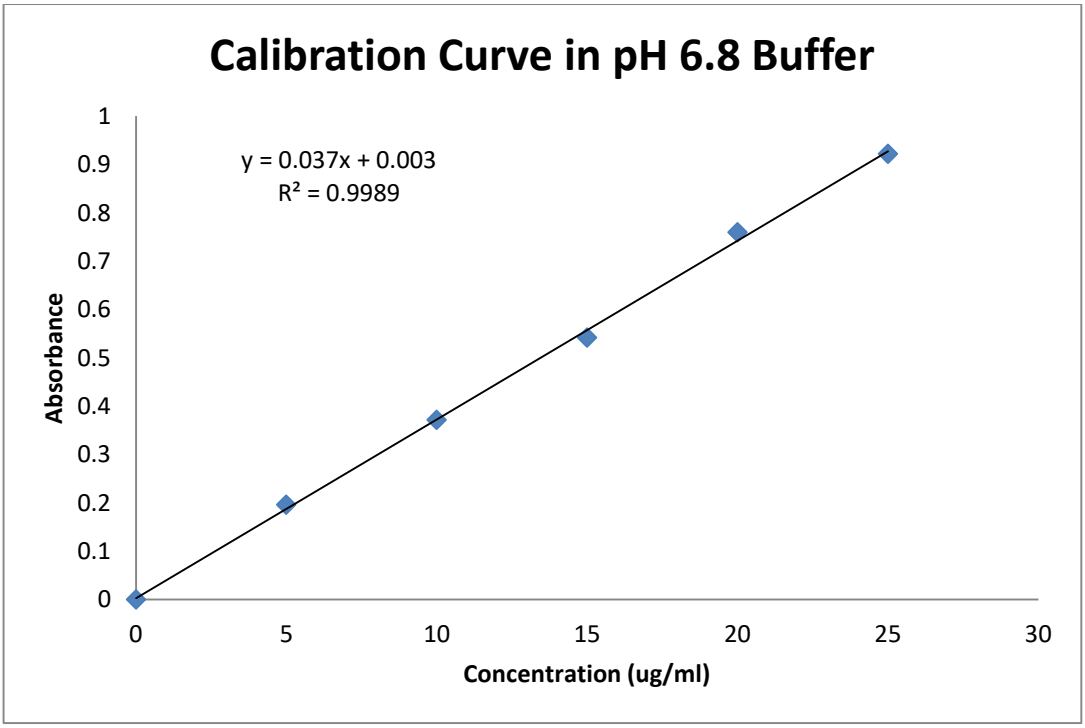

Figure 3: Calibration curve of Pantoprazole in Phosphate Buffer pH 6.8

4.2 Optimization by Risk assessment and Quality by Design:

Based on the preliminary risk assessment of formulation variables (Table 4), justification for categorization of risk for each formulation variable was mentioned in (Table 5**Error! Reference source not found.**), it was identified that formulation variables Binder level, disintegrant level, seal coating level, and enteric coating level were found to have impact on drug product CQA's like DT, Acid resistance, Dissolution in pH 6.8 buffer, and granules flow properties.

Hence 2 $^{(4-1)}$ fractional factorial design (Table 6) was selected for the composition optimization of Pantoprazole 40 mg Delayed release formulation.

A total of 11 experimental runs were obtained based on the model chosen and all the factors as mentioned in Table 7 were selected based on the risk assessment. Ranges for each factor were fixed based on the domain knowledge and previous experimental results. Responses were Table 8 selected as per the intermediate and finished product CQA's as mentioned in below table.

Table 4: Formulation Risk Assessment

Name	Flow properties	Disintegration Time	Assay	Dissolution 0.1 N HCl	Dissolution in pH 6.8 Buffer	Related substances
HPC (Klucel EF)	High	High	Low	High	High	Low
Crospovidone (Polyplasdone XL 10)	Low	High	Low	High	High	Low
Seal Coating (Instacoat IC-S-329)	NA	NA	Low	High	High	Low
Enteric Coating (Sheffcoat ENT 5Y)	NA	NA	Low	High	High	Low

Table 5: Justification for Formulation Risk Assessment

Name	CQA's	Justification
Hydroxy Propyl cellulose (Klucel EF)	Flow Properties	Effect of binder concentration on flow properties is high as the granules bulk density, and PSD is governed by the binder level.
	Disintegration Time	Effect of binder concentration on DT is high as the granules porosity and strength is governed by the binder level
	Assay	Effect of binder concentration on Assay is low as it doesn't have any impact on the same

	Dissolution in 0.1 N HCl	Effect of binder concentration on DT is high as the granules porosity, strength and tablet DT/dissolution is governed by the binder level
	Dissolution in pH 6.8 Phosphate buffer	Effect of binder concentration on DT is high as the granules porosity, strength and tablet DT/dissolution is governed by the binder level
	Related substances	Effect of binder concentration on RS is low as it doesn't have any impact on the same
Polypladone XL 10	Flow Properties	Effect of disintegrant concentration on flow properties is low as it doesn't have any impact on the same
	Disintegration Time	Effect of disintegrant concentration on DT is high as the concentration of the same would directly impact the DT of tablets
	Assay	Effect of disintegrant concentration on assay is low as it doesn't have any impact on the same
	Dissolution in 0.1 N HCl	Effect of disintegrant concentration on Dissolution is high as the concentration of the same would directly impact the DT and disintegration of tablets
	Dissolution in pH 6.8 Phosphate buffer	Effect of disintegrant concentration on Dissolution is high as the concentration of the same would directly impact the DT and dissolution of tablets
	Related substances	Effect of disintegrant concentration on RS is low as it doesn't have any impact on the same
Coating	Flow Properties	Effect of coating is unrelated to the flow properties hence risk is low
	Disintegration Time	Effect of coating is unrelated to the DT of core tablets hence risk is low
	Assay	Effect of coating is unrelated to the assay of core tablets hence risk is low
	Dissolution in 0.1 N HCl	Effect of coating on Dissolution is high as the concentration of the same would directly impact the dissolution of tablets
	Dissolution in pH 6.8 Phosphate buffer	Effect of coating on Dissolution is high as the concentration of the same would directly impact the dissolution of tablets
	Related substances	Effect of coating on RS is low as it doesn't have any impact on the same

Table 6: Design Selection

Study Type	Factorial
Initial Design	2 Level Factorial
Center Points	3
Design Model	Reduced 2FI
Runs	11

Table 7: Factors and levels

Factor	Name	Low (-1)	High (+1)	Centre point (0)
A	Klucel EF (mg/tab)	1.5	4.5	3
B	Polyplasdone XL 10 (mg/tab)	5	15	10
C	Instacoat IC-S-329 (mg/tab)	4	8	6
D	Sheffcoat ENT 5Y (mg/tab)	14	18	16

Table 8: Responses

Response	Name	Units	Analysis	Minimum	Maximum	Mean	Std. Dev.
Y1	DT	Seconds	Factorial	78	389	215.5	113.9
Y2	0.1 N HCl Release	% Release	Factorial	0.1	2.1	1.0	0.8
Y3	pH 6.8 Release	% Release	Factorial	65	94.29	83.6	9.1
Y4	BD	g/mL	Factorial	0.43	0.57	0.5	0.0
Y5	# 60 retains	% Cumulative	Factorial	40	68	53.5	9.7

4.3 Evaluation of Pantoprazole Granules

The Table 9 shows, Pantoprazole granules evaluation like Percentage yield (%) and Mean Granule Size (% Cumulative). All the Batches showed good percentage yield i.e. of above 85%. The Batches F1, F4, F6, F8, F9, F10 and F11 showed percentage yield of above 90%. Hence, it can be said that the granulation process was successfully carried out. The mean Granula size was also measured and the average % cumulative 53.45 and the least % cumulative was 40 and the highest % cumulative was 68.

Table 9: Results of Evaluation of Pantoprazole Granules

Batches	Percentage yield	Mean Granule Size
Unit	**%**	**% Cumulative**
F1	90.19	65
F2	89.87	68
F3	89.34	45
F4	91.89	42
F5	88.64	52
F6	93.28	55
F7	89.67	65
F8	91.25	42
F9	90.57	54
F10	90.85	40
F11	91.13	60

The Table 10 shows, Micromeritics evalualtion of Pantoprazole granules, in which the average Bulk density was 0.50 gm/ml, and the least Bulk density was 0.43 in batch F4 and the higher Bulk density was 0.57 in batch F1. The average Tapped density was 0.55 gm/ml, and the least Tapped density was 0.46 in batch F4 and the higher Tapped density was 0.61 in batch F2 and F11. The Flow character is excellent when the compressibility index is lss than or equal to 10 and the batches with excellent flow are F1, F2, F3, F4, F8 and F9. The Flow character is excellent when the Hausner's ratio is less than or between 1- 1.11 and the batches with excellent flow are F1, F2, F3, F4, F8, F9 and F10. The flow property is excellent when the Angle of Repose lies between 25-30 and the batches which shows Excellent Angle of Repose are F3, F4, F5, F8 and F11.

Table 10: Results of Micromeritics evaluation of Pantoprazole Granules

Batches	Bulk Density	Tapped Density	Compressibility Index	Hausner's Ratio	Angle of Repose
Unit	**gm/ml**	**gm/ml**	**%**	**-**	**Ɵ**
F1	0.57	0.59	3.39	1.04	35.97
F2	0.55	0.61	9.84	1.11	31.78
F3	0.46	0.49	6.12	1.07	28.64
F4	0.43	0.46	6.52	1.07	27.38
F5	0.50	0.56	10.71	1.12	29.25
F6	0.51	0.59	13.56	1.16	34.33
F7	0.56	0.63	11.11	1.13	31.58
F8	0.45	0.47	4.26	1.04	26.18
F9	0.50	0.55	9.09	1.10	36.19
F10	0.44	0.49	10.20	1.11	32.19
F11	0.52	0.61	14.75	1.17	25.67

4.4 Post-Compression evaluation of Pantoprazole uncoated tablet:

Post compression evaluation of Pantoprazole uncoated tablets were shown in Table 11. The average hardness od all the Batches was 2.59 kg/cm^2, in which Batch F3 showed least hardness of 1.92 kg/cm^2 and batch F10 showed highest hardness of 3.77 kg/cm^2.The average thickness was 1.96 mm, in which least thickness was 1.7 mm in batch F6 and the highest thickness was 2.2 mm in batch F1 and F5. The average Friability was 0.69%, and the least Friable batch was F4 and F11 with friability of 0.51% and the high friable batch was F6 and F10 with friability of 0.88%. The average Weight variation was 203.73 mg, the least weight variation was 201 mg in batch F1 and F5 and the highest weight variation was 208 mg in batch F11. The average Drug content uniformity was 99.65%, Batch F2 showed least drug content uniformity of 97.9% and batch F11 showed highest drug content uniformity of 100.9%. The average disintegration time was 215.55 seconds, the least

disintegration time was 78 seconds in batch F1 and the highest disintegration time was 389 seconds in batch F10.

Table 11: Results of Post-compression evaluation of Pantoprazole uncoated tablet

Batches	Hardness	Thickness	Friability	Weight Variation	Drug Content Uniformity	Disintegration Time
Unit	kg/cm2	mm	%	mg	%	seconds
F1	1.97	2.2	0.59	201	100.4	78
F2	3.42	2.1	0.63	203	97.9	350
F3	1.92	1.8	0.72	204	99.9	85
F4	2.03	1.9	0.51	205	100.1	95
F5	2.16	2.2	0.78	201	98.5	212
F6	2.22	1.7	0.88	203	100.9	200
F7	3.03	1.9	0.78	202	99.1	325
F8	3.25	1.8	0.59	203	100.8	346
F9	2.77	2.0	0.71	204	100.2	195
F10	3.77	2.1	0.88	207	98.6	389
F11	1.96	1.9	0.51	208	99.8	96

The in-vitro drug release of Pantoprazole uncoated tablet was performed in 0.1N HCl for 2 hours for all the batches as the tablets were uncoated it was expected to release the entire drug within 2 hours. As expected, all the batches showed drug release in this media. The maximum drug release obtained with 2 hours was 98.51% for F8 batch and showed least drug release of 78.25% for F5 batch. The results of drug release are given in Table 12 and is depicted in figure 4

Table 12: Results of In vitro drug release of Pantoprazole uncoated tablet

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	28.96	32.85	28.47	15.95	25.32	36.45	32.41	24.25	36.74	23.25	12.63
1.00	54.21	57.25	58.74	45.85	41.21	61.25	58.25	48.25	59.25	56.23	41.25
1.50	91.32	92.45	87.25	67.25	59.21	87.25	78.46	75.61	69.25	87.25	59.25
2.00	95.21	96.32	92.56	92.45	78.25	93.54	91.45	98.51	89.36	95.11	79.25

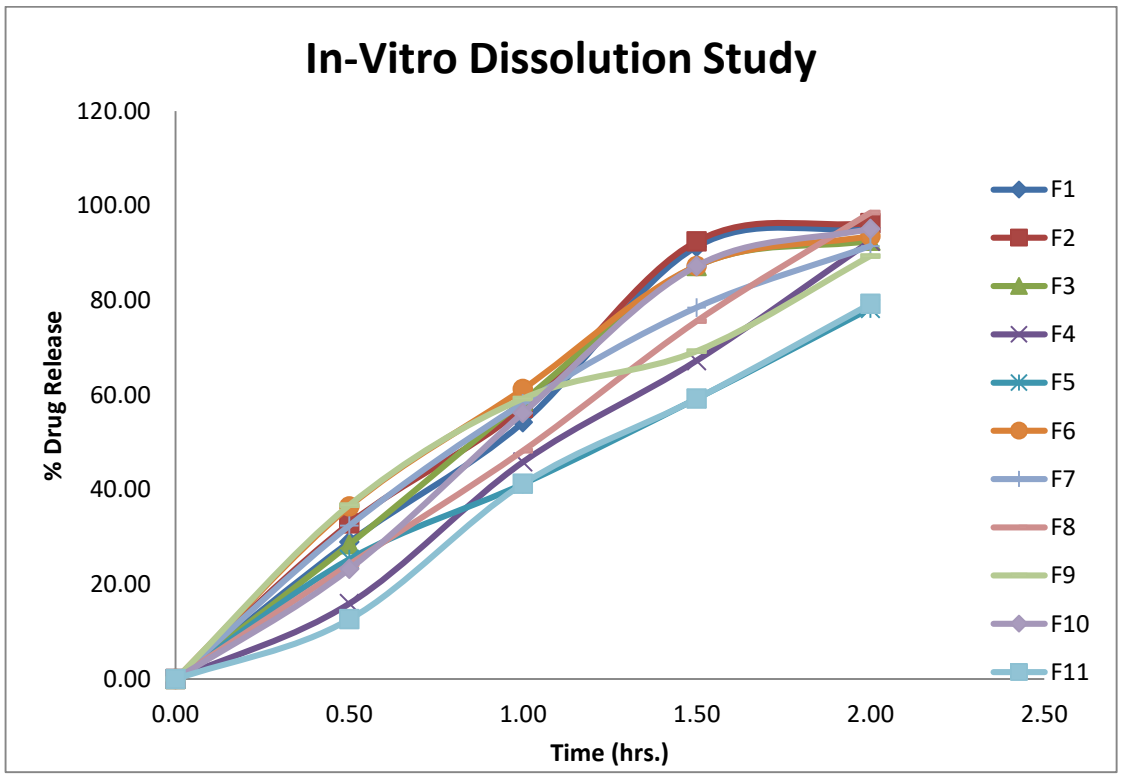

Figure 4: In vitro drug release of Pantoprazole uncoated tablet

4.5 Formulation composition of DoE runs:

Table 13: Formulation of Pantoprazole Coated Tablet

Rand Run order	API	Mannitol (Pearlitol SD 200)	Na2CO3	A:Klucel EF	Mannitol (Pearlitol SD 200)	B: Polyplasdone XL 10	Ca. Stearate	C: Instacoat IC-S-329	D: Sheffcoat ENT 5Y	Core	Coated
	mg/ tab	mg/ tab	mg/ tab	mg/ tab	mg/ tab	mg/ tab	mg/ tab	mg/ tab	mg/ tab	Weight	Tab weight
3	47.36	97.64	5	1.5	20	15	2.5	8	14	189	211
8	47.36	107.64	5	1.5	20	5	2.5	4	14	189	207
1	47.36	94.64	5	4.5	20	15	2.5	4	14	189	207
2	47.36	104.64	5	4.5	20	5	2.5	8	14	189	211
5	47.36	101.14	5	3	20	10	2.5	6	16	189	211
6	47.36	101.14	5	3	20	10	2.5	6	16	189	211
9	47.36	101.14	5	3	20	10	2.5	6	16	189	211
4	47.36	97.64	5	1.5	20	15	2.5	4	18	189	211
10	47.36	107.64	5	1.5	20	5	2.5	8	18	189	215
7	47.36	104.64	5	4.5	20	5	2.5	4	18	189	211
11	47.36	94.64	5	4.5	20	15	2.5	8	18	189	215
Finalized composition	47.36		5	3	20	10	2.5	6	16	189	211

4.6 Post-Compression evaluation of Pantoprazole enteric coated tablet:

Post compression evaluation of Pantoprazole enteric coated tablets were shown in Table 14. The average hardness od all the Batches was 2.97 kg/cm^2, in which Batch F3 showed least hardness of 2.12 kg/cm^2 and batch F9 showed highest hardness of 3.72 kg/cm^2.The average thickness was 2.27 mm, in which least thickness was 2.1 mm in batch F3 and F6 and the highest thickness was 2.5 mm in batch F5. The average Friability was 0.52%, and the least Friable batch was F4 with friability of 0.39% and the high friable batch was F10 with friability of 0.72%. The average Weight variation was 212.45 mg, the least weight variation was 201 mg in batch F3and the highest weight variation was 216 mg in batch F7. The average Drug content uniformity was 99.66%, Batch F2 showed least drug content uniformity of 97.3% and batch F8 showed highest drug content uniformity of 101.2%. The Hardness, Thickness and Friability improved due to enteric coating of the tablet.

Table 14: Results of Post-compression evaluation of Pantoprazole enteric coated tablet

Batches	Hardness	Thickness	Friability	Weight Variation	Drug Content Uniformity
Unit	kg/cm2	mm	%	mg	%
F1	2.25	2.4	0.43	211	100.8
F2	3.37	2.3	0.41	213	97.3
F3	2.12	2.1	0.49	207	99.4
F4	3.49	2.2	0.39	215	100.3
F5	2.78	2.5	0.59	211	98.8
F6	2.83	2.1	0.66	214	100.4
F7	2.19	2.2	0.49	216	99.9
F8	3.52	2.2	0.46	213	101.2
F9	3.72	2.3	0.57	212	100.4
F10	3.42	2.4	0.72	211	98.3
F11	2.95	2.3	0.47	214	99.6

The results of in-vitro drug release study of Pantoprazole enteric coated tablet are given in Table 15. All the batches showed less than 2.5% drug release within initial 2 hours in 0.1N HCl hence, it can be estimated that the enteric coating process was effective and the maximum drug release was found to be of F1 batch with 94.29% drug release within a period of over 12 hours and least was found for F10 batch with 65% drug release. All the batches showed effective increase in drug concentration within 8 hours and after 8 hours there was stagnant growth observed up to further 12 hours. The in vitro release of pantoprazole enteric coated tablet is depicted in Figure 5.

Table 15: Results of In vitro drug release of Pantoprazole enteric coated tablet

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.50	0.29	0.42	0.38	0.00	0.16	0.09	0.00	0.45	0.08	0.00	0.02
1.00	0.77	0.98	1.02	0.03	0.44	0.24	0.02	0.96	0.16	0.01	0.04
1.50	1.20	1.18	1.54	0.06	0.74	0.52	0.11	1.62	0.57	0.05	0.07
2.00	1.90	1.83	2.00	0.10	1.00	0.90	0.20	2.10	0.80	0.10	0.10
3.00	14.96	13.36	14.36	3.65	10.36	9.36	2.84	11.75	8.54	12.35	11.00
4.00	32.98	29.65	25.33	13.22	22.36	16.33	10.69	29.56	20.39	28.32	25.74
5.00	54.65	39.33	45.63	29.63	41.32	29.44	19.56	52.91	52.36	39.12	38.54

6.00	84.36	62.36	59.33	37.36	59.33	49.32	35.69	85.66	68.25	48.29	57.25
7.00	89.45	79.36	86.36	69.33	72.21	67.25	47.33	87.37	79.35	59.32	68.14
8.00	90.89	86.36	89.74	70.33	80.33	78.52	69.36	89.81	84.32	61.33	71.32
10.00	92.64	90.55	92.33	74.99	84.69	83.33	74.36	90.35	86.32	64.21	73.16
12.00	94.29	92.33	93.47	76.58	85.12	85.42	76.36	92.45	88.34	65.00	74.45

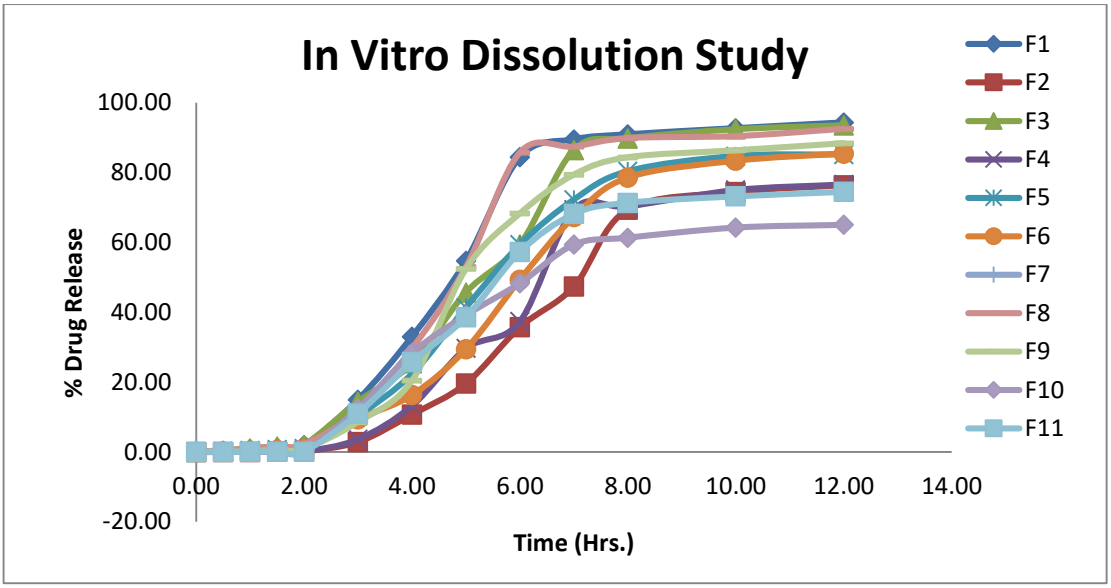

Figure 5: In vitro drug release of Pantoprazole enteric coated tablet

7.6 Stability study:

The Stability study performed at 40±2°C and 75±5% RH for 1 month and at each interval i.e. after each 10 days the sample was evaluated for Hardness, weight variation, drug content uniformity and in vitro dissolution study. Batch F3 was selected as final optimized batch based on the physicochemical evaluations. For Hardness, the standard deviation at all-time intervals was found to be 0.0082. For weight variation, the standard deviation of all the time intervals was found to be 1.2910. For content of drug, the standard deviation was found to be 0.82. The standard deviations of the parameters were within the acceptance criteria and hence it was found to be stable. The results are depicted in table 16.

Table 16: Results of Stability study of F8 Batch

Stability Study of F8 batch			
Time point	**Hardness**	**Weight Variation**	**Drug Content Uniformity**
Unit	**kg/cm2**	**mg**	**%**
0 day	3.52	213	101.2
10th day	3.53	210	100.8
20th day	3.52	211	99.3
30th day	3.51	212	100.4

The in vitro drug release study of Batch F8 was studied at each time interval and showed similar pattern for drug release at every time interval. The results of in vitro dissolution study are given in table 17 and depicted in figure 6.

Table 17: Results of In vitro study of Stability Batch F8

Time (hrs)	**0 Day**	**10th day**	**20th Day**	**30th day**
0.00	0.00	0.00	0.00	0.00
0.50	0.45	0.43	0.38	0.35
1.00	0.96	0.95	0.89	0.85
1.50	1.62	1.60	1.54	1.49
2.00	2.10	2.08	1.96	1.84
3.00	11.75	11.73	10.59	9.25
4.00	29.56	29.52	28.23	26.32
5.00	52.91	52.89	51.25	49.52

6.00	85.66	85.62	84.25	80.36
7.00	87.37	87.31	85.21	82.20
8.00	89.81	89.72	87.25	85.96
10.00	90.35	90.12	89.98	87.64
12.00	92.45	92.03	91.23	90.21

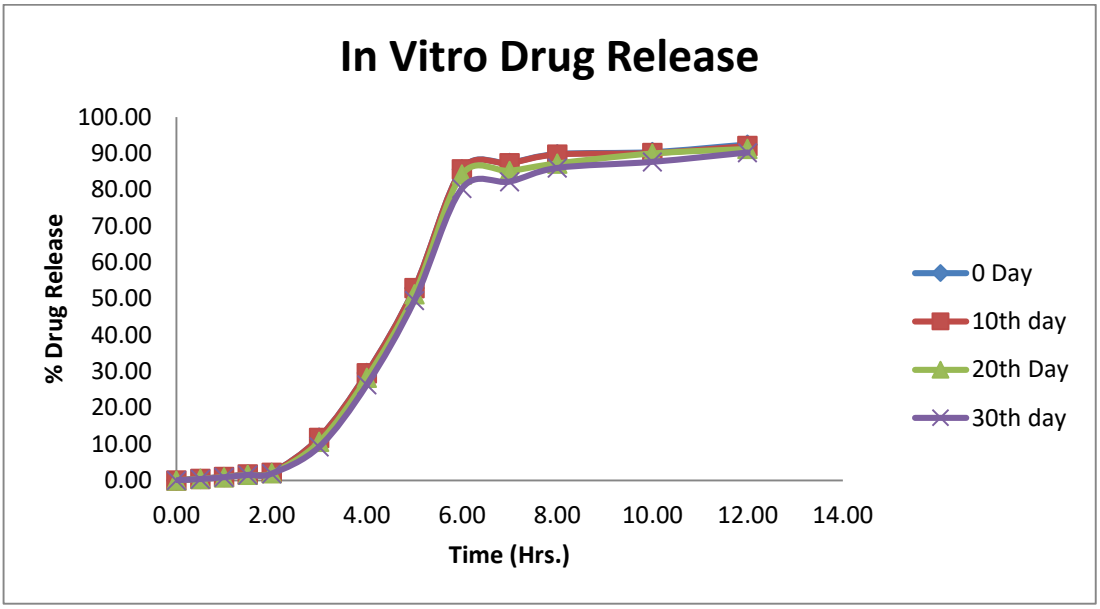

Figure 6: In vitro study of Stability Batch

4.7 Design of Experiment

Based on the DoE, below constraints were given for the solutions from DoE.

Name	Goal	Lower Limit	Upper Limit
Klucel EF	is in range	1.5	4.5
Polyplasdone XL 10	is in range	5	15
Instacoat IC-S-329	is in range	4	8
Sheffcoat ENT 5Y	is in range	14	18
Disintegration Time	is target = 200	78	389
Drug release in 0.1 N HCl	is target = 0.8	0.1	1.8
Drug release in pH 6.8 Release	is target = 85	65	94
Bulk Density	is target = 0.5	0.43	0.57
# 60 retains	is target = 55	40	68

Based on the targets mentioned in the table, below solutions were obtained with the desirability of 0.9

Solutions										
No.	**Klucel EF**	**Polyplasdone XL 10**	**Instacoat IC-S-329***	**Sheffcoat ENT 5Y**	**DT**	**0.1 N HCl Release**	**pH 6.8 Release**	**BD**	**# 60 retains**	**Desirability**
1	**3.14**	**10.78**	**4.61**	**16.52**	**200.00**	**0.80**	**80.15**	**0.50**	**54.38**	**0.92**
2	3.13	10.78	**5.59**	16.52	200.00	0.80	80.15	0.50	54.37	0.92
3	3.14	10.78	**7.88**	16.52	200.00	0.80	80.15	0.50	54.39	0.92
4	3.14	10.78	**4.3**	16.52	200.00	0.80	80.15	0.50	54.41	0.92
5	3.14	10.78	**6.99**	16.52	200.00	0.80	80.15	0.50	54.39	0.92
6	3.13	10.78	**7.8**	16.52	200.00	0.80	80.15	0.50	54.36	0.92
7	3.13	10.78	**4.05**	16.52	200.00	0.80	80.15	0.50	54.38	0.92
8	3.13	10.78	**4.01**	16.52	200.00	0.80	80.15	0.50	54.33	0.92
9	3.14	10.78	**5.84**	16.52	200.00	0.80	80.15	0.50	54.41	0.92
10	3.13	10.78	**7.02**	16.52	200.00	0.80	80.15	0.50	54.34	0.92

Below desirability plot was obtained for the solution 1 with predicted response of above solutions, hence these values are rounded as Klucel EF as 3 mg/tab, Polyplasdone 10 mg/tab, Instacoat 6 mg/tab, and Shefcoat as 16 mg/tab

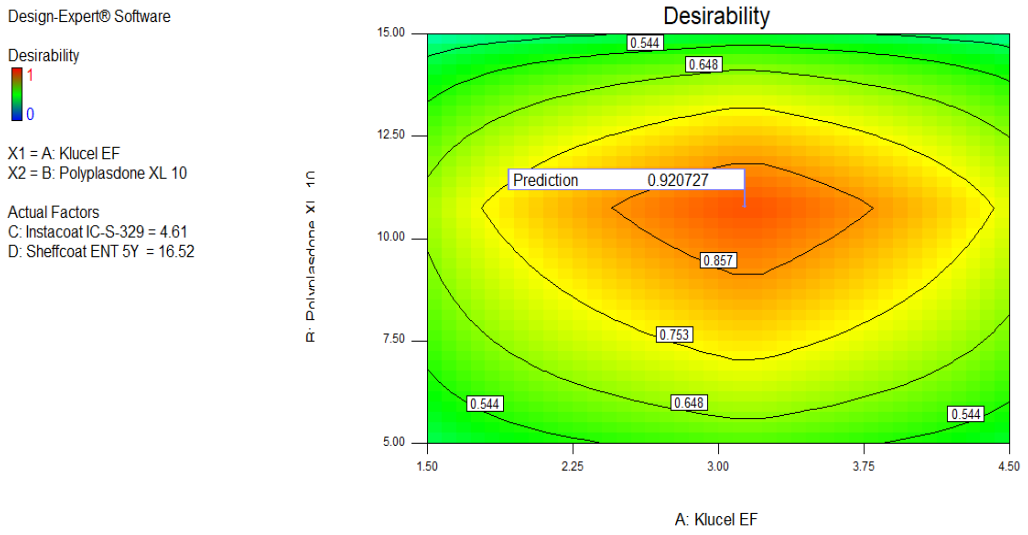

Figure 7: Desirability plot

4.8 Animal study for Evaluation of antiulcer activity:

For individual Animal Study data refer to Supplementary data. Summary for 12 subjects in-vivo analysis is shown below in table 18.

Table 18: Summary of In-Vivo studies

T1	C-max (ng/ml)	T-max (hr)	AUC (0-inf)(ng.hr/ml) Limit (80-125)
Subject 1	100.92	3	104.24
Subject 2	102.44	3	97.82
Subject 3	109.97	3	113.59
Subject 4	119.27	3	123.19
Subject 5	87.16	3	90.03
Subject 6	92.8	3	88.62
Subject 8	88.47	3	84.48
Subject 9	117.74	3	121.61
Subject 10	110.53	3	114.17
Subject 11	132.63	3	137
Subject 12	111.16	3	114.81

Subject 7 lead to false data and therefore was eliminated from the review. Based on the summary it can be noted that all the subjects except subject 11, fell under the AUC curve fitting and therefore implying the release of our formulation in comparison to reference formulation.

5. Conclusion:

An attempt was to formulate Pantoprazole delayed release tablet to overcome various drawbacks as mentioned in the summary. The prepared delayed release tablets of Pantoprazole were physicochemical parameters like Hardness, Thickness, Friability, Weight Variation, Drug content uniformity and in-vitro dissolution testing. All the batch tends to pass the above tests and batch F8 was found to be optimized batch. Further upon performing anti-ulcer activity it was concluded that delayed release tablet can be the potential candidate for delivery of Pantoprazole for treatment of ulcer.

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