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FORMULATION & EVALUATION OF BUFFERED PANTOPRAZOLE SODIUM TABLET

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ABSTRACT: The aim of this study was to prepare buffered tablets of acid labile drug, Pantoprazole sodium for oral administration using buffering agents to protect a drug from gastric fluid. Its mechanism of action was inhibition of H+/K+-adenosine triphosphate, an enzyme present in the gastric parietal cells. The tablets were prepared by wet granulation method. The formulations contain sodium carbonate, sodium bicarbonate as buffering agents and crospovidone as superdisintegrant. The formulation were prepared, optimized and evaluated by 3^2 factorial design. In this design independent variables were sodium carbonate, sodium bicarbonate, cross povidone and dependent variables were pH and disintegration time. The tablets were evaluated for friability, hardness, disintegration, dissolution and drug content. The formulation F6 was selected by factorial design it was selected due to results as this formulation maintain neutral pH of stomach and drug release simultaneously within 50 seconds after administration.

INTRODUCTION: Peptic ulcer disease comprises a group of chronic ulcerative conditions that primarily affect the gastric mucosa and proximal duodenum.

The drug like H_2 blockers cimetidine, ranitidine and famotidine reduce the amount of acid produced by stomach. But Proton Pump Inhibitors (PPIs) are a group of drugs whose main action is pronounced and long-lasting reduction of gastric acid production.

The key action mechanism of the PPIs is inhibition of H+/K+-adenosine triphosphate, an enzyme present in the gastric parietal cells.

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These drugs are metabolized in the parietal cells to active sulfonamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion [1, 2].

Pantoprazole is a lipophilic weak base with poor aqueous solubility at low pH. It is unstable in low pH solutions and undergoes rapid acid-catalyzed degradation, though it is relatively stable at neutral or high pH. Due to the pH sensitivity of Pantoprazole Sodium, effective drug delivery is problematic.

Most of the PPIs are formulated in an enteric-coated solid dosage form (either a delayed-release capsule or tablet) or as an intravenous solution. There are some problems associated with enteric-coated preparations as dissolution of the enteric coating is pH-dependent and gastric empting time. pH profile of the gastrointestinal tract in an individual is variable at different times and is dependent on numerous physiological factors (e.g.,

the fed or fasted state), variable dissolution times for the enteric coat and variable pharmacokinetic profiles of individuals may affects [3, 4, 5].

The acid-labile drugs for oral administration may also be protected from gastric acidity by neutralizing the pH of the gastric fluid. So the current frontier in PPI therapy is immediate-release tablet combined with buffering agents which prevent degradation of drug by neutralizing the pH of stomach before absorption and protect the drug from low pH. Such dosage forms are known as buffered tablet and such tablet is advantageously devoid of any enteric coating or delayed or sustained-release delivery [6, 7].

MATERIAL AND METHOD:

Materials: Pantoprazole sodium, mannitol, colloidal silicon dioxide, calcium stearate, sodium bicarbonate, sodium carbonate, crospovidone received from Genpharma International Pvt. Ltd Pune.

Method:

Drug Excipients Compatibility Study: Sample of pure drug, coating, physical mixture of coating material and drug in 1:1 ratio was placed at accelerated stability condition 40±2°C and 75±5% relative humidity for a period of 3 month. At the end of 3 month samples were evaluated for drug–excipients compatibility using Fourier transformed infrared spectroscopy (FT-IR) (Shimadzu Corporation, Japan, 8400s).

Preparation of buffered tablet of pantoprazole sodium: Buffered tablets were prepared by wet granulation technique using varying proportion of Ingredients. The detail process is as follows:-

- **Sifting**: The Drug, Mannitol, Sodium carbonate, sodium bicarbonate, Crosspovidone, Polyvinyl pyrrolidone K-30 (PVPK-30) were sifted through sieve # 40.
- **Mixing**: The sifted ingredients were mixed thoroughly in a polybag for 15min.
- **Preparation of Granules**: The Isopropyl alcohol was added in well mixed powder till the desired wet mass was formed. This wet mass was sifted through sieve #10.
- **Drying**: The prepared granules were dried in an oven at 45^0C for 1 hr and sifted through sieve #20. Loss on drying was done.
- **Lubrication**: Calcium stearate were sifted through sieve #40 and mixed with the prepared granules in a polybag for 5min.

The compositions of the tablet formulations were listed in **table 1**.

TABLE 1: TABLET FORMULATIONS

	Pantoprazole Sodium	Sodium Bicarbonate	Sodium Carbonate	PVPK -30	Calcium stearate	Colloidal silicon dioxide	Cross-povidone	Mannitol	Total
F1	20	80	450	10	5	25	160	150	900
F2	20	100	450	10	5	25	140	150	900
F3	20	120	530	10	5	25	135	55	900
F4	20	80	530	10	5	25	120	110	900
F5	20	120	450	10	5	25	115	95	900
F6	20	100	530	10	5	25	110	160	900
F7	20	80	610	10	5	25	90	60	900
F8	20	100	610	10	5	25	95	35	900
F9	20	120	610	10	5	25	70	40	900

Selection of buffering agent and there combinations in 500 ml SGF: Different buffering agents and alkaline agents are used for neutralizing pH of SGF and there combination also tried for same shown in **table 2**.

TABLE 2: COMBINATION OF BUFFER

Name of Buffering agent	Buffering agent conc.	Conc. of sodium bicarbonate	pH Achieve
Meglumin	350	350	1.61
	200	500	1.68
	500	200	1.37
Calcium carbonate	350	350	5.51
	200	500	5.73
	300	200	6.04
Di sodium hydrogen phosphate	350	350	1.68`
	200	300	1.83
	300	200	1.62
Sodium carbonate	350	350	6.75
	200	300	6.51
	300	200	7.02

Evaluation of Tablets [8, 9, 10]:

Bulk density: LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by 44 gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 5 cm at 2 second intervals. The reading of tapping was continued until no further change in volume was noted using the following equation.

LBD and TBD were calculated:

LBD = Weight of the powder / volume of the packing.

TBD = Weight of the powder / Tapping volume of the packing.

Compressibility index: The compressibility index of the granules was determined by Carr's compressibility index:

Carr's index (%) = {(TBD – LBD) X 100}/TBD

Angle of Repose: The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation;

Angle of Repose $\theta = \tan^{-1} h/r$

Where, h = height of the powder cone, r = radius of the powder cone

Thickness measurement: It is carried out on 20 tablets by measuring thickness using Vernier's calipers. Mean and standard deviation were determined.

Hardness determination: 20 tablets were taken randomly and hardness was measured using Hardness tester (Electrolab India Ltd). The mean hardness of 20 tablets of each formulation was determined.

Friability test: Friability was determined on 20 tablets. Tablet samples were weighed accurately and placed in friabilator (Electrolab India Ltd). After 100 rotations (4 min at 25 rpm) loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand the wear. The percentage friability was determined by using following formula:

$$\% \, Friability = \frac{Initial\ wt - Final\ wt}{Initial\ wt} \times 100$$

Disintegration test: Disintegration time was determined to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. The tablets were examined using the USP- XXIV disintegration apparatus (Electrolab India). Six tablets were tested for each batch.

***In vitro* dissolution studies:** *In vitro* dissolution studies were carried out using USP 30 dissolution apparatus type II at 25 rpm in an Electrolab TDT-08L dissolution tester,

The dissolution was conducted for a total period of 30 mint using 500ml simulated gastric fluid pH 1.2 at 37.0 ± 0.5ºC. Samples were withdrawn from each vessels at 5,10,15,20,25,30 from starting the amount of drug present was determined according to the USP monograph for Pantoprazole sodium tablets using UV at 294nm.

Full Factorial Design: A 3^2 randomized full factorial design was used in this study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed at all 9 possible combinations.

The ratio of Intra granulation Crosspovidone (X_1) and Amount of intra granulation Crosspovidone (X_2) in tablet were selected as independent variables. The time required to Disintegration of tablet (Y) was selected as dependent variables. The experimental design with corresponding formulation outline in **Table 3**.

TABLET 3: COMPOSITION OF TABLET

Levels	X_1 Amount of Sodium Carbonate	X_2 Amount of Sodium Bi Carbonate
-1	450	80
0	530	100
1	610	120

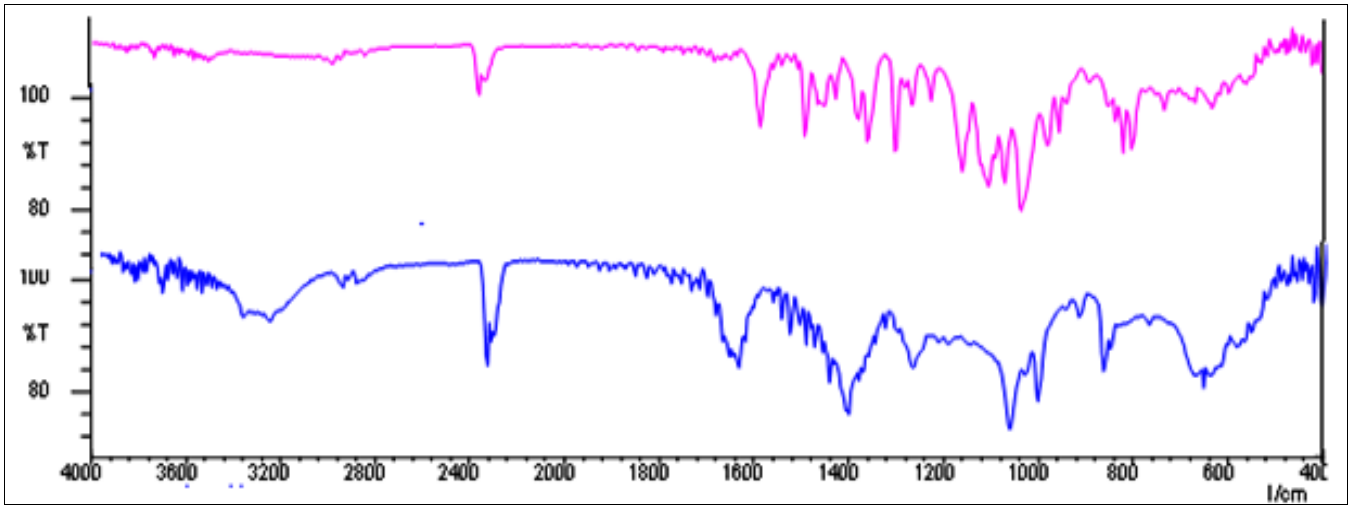
Stability Studies: One selected formulation was packaged into ALU-ALU strip and kept for stability study at both room condition (30±2ºC / 65±5%RH) and accelerated condition (40±2ºC / 75±5 %RH) according to ICH Guideline [ICH Q1A (R2)].13 Samples were withdrawn at 0, 1st, 3rd and month for evaluation of physical condition, drug content and *in vitro* release and accelerated condition.

Batch code	X_1	X_2
F1	-1	1
F2	-1	-1
F3	-1	0
F4	0	1
F5	0	-1
F6	0	0
F7	1	1
F8	1	-1
F9	1	0

RESULT AND DISCUSSION

Compatibility study:

Drug-Excipient Interactions: The IR spectra of Formulation were compared with the standard spectrum of Pantoprazole sodium (**Fig. 1**). IR spectrum of Pantoprazole sodium was characterized by the absorption of -S=O group at 1037 cm^{-1} & - C-F group at 1105. In spectra of Formulation, band was same absorption pattern as that of pure drug. Mentioned evidences thus lead to the conclusion that changes were not seen as there was no physical interaction between the drug and polymers.



FIUGRE NO.1 IR SPECTRUM OF DRUG AND FORMULATION

Preparation of Tablets: Tablets were prepared by using 2 independent variables as different concentrations of polymers by using 3^2 factorial design. In the preparation of tablet, Sodium bicarbonate, sodium carbonate, Crosspovidone, mannitol cab-o-sil, PVPK -30 were used. In this formulation, Mannitol was used as a filler and PVPK-30 as a binder. Sodium bicarbonate, sodium carbonate were generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. But here they were used to produce or maintain an alkaline pH in a preparation. Crosspovidone is used in a variety of pharmaceutical formulations; it is primarily used in solid-dosage forms. In tableting, Crosspovidone solutions are used superdisintegrating agent in wet-granulation processes.

Pre-compression characteristics for powder blend: The drug content was found to be optimum in all the cases. The blend of the optimized formulation containing Pantoprazole sodium and tablet were evaluated for parameters like angle of repose was found to be 39.58 Bulk density was found to be 0.780 g/cm^3 and tapped density 1.0789 g/cm^3. Hausner's ratio was found to be 1.38 as shown in **table 4**.

TABLE 4: PRE-COMPRESSION PARAMETERS FOR POWDER BLEND

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk Density (g/cm^3)	0.789	0.784	0.699	0.776	0.784	0.780	0.784	0.774	0.789
Tapped Density (g/cm^3)	1.067	1.078	1.666	1.079	1.0768	1.0789	1.078	1.076	1.076
Angle of Repose (θ)	39.13	36.24	33.87	32.11	34.45	39.58	36.19	33.74	33.87
Carrs index (%)	26.89	26.60	26.45	26.75	26.87	26.77	26.87	26.67	26.67
Hausners ratio (HR)	1.34	1.32	1.35	1.31	1.33	1.38	1.31	1.38	1.36

Post-compression characteristics of tablets: In the present study, Pantoprazole sodium Buffered tablets were prepared using buffering agent such as sodium bicarbonate and sodium carbonate. The hardness of the tablets was found to be between 16 to 18 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance as shown in **Table 5**.

TABLE 5: POST-COMPRESSION PARAMETERS FOR TABLETS

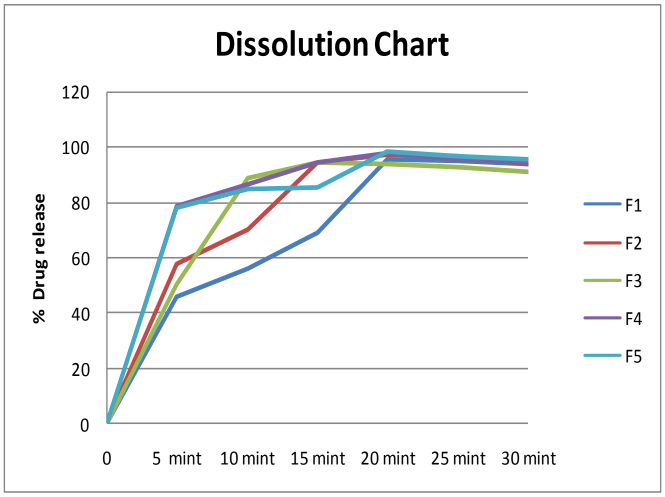
Test Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight Variation (mg) n=20	900±0.70	900±2.1	901±1.41	900±0.70	900±2.82	902±2.12	901±2.3	903±0.04	901±1.4
Average Thickness, n=3	6.14±0.028	6.11±0.035	6.1±0.007	6.09±0.007	6.1±0.012	6.16±0.014	6.15±0.067	6.25±0.08	6.30±0.027
Hardness (Kg/cm^2) n=3	16±0.614	8±0.707	4±2.12	17±1	18±0.664	18±0.746	17±0.67	16±1.87	18±0.098
Friability %, n=10	0.07	0.08	0.03	0.05	0.02	0.034	0.04	0.03	0.05
Disintegration time (sec) n=3	100	50	30	110	70	40	90	120	160

***In vitro* dissolution studies:** In the present study, pH of F 6 batch was found to be optimum and disintegration time is 40 sec. In-vitro drug release studies were done for the selected formulations from each batch. The drug release was found to show maximum drug release in case of F6 with 99.99% in 30 minutes as shown in **table 6 and figure 2, 3**.

Stability study: The stability of this optimized formulation was known by performing stability studies for three months at accelerated conditions of 30±2ºC /75%RH and 40°C±75 % RH on optimized formulation. The formulation was found to be stable, with insignificant change in the hardness, disintegration time as shown in **Table 7**.

TABLE 6: *IN VITRO* DISSOLUTION STUDIES FOR FORMULATIONS F1-F9

Formulations	Average % of drug release of tablets								
Time	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5 mint	45.78	57.88	50.3	78.82	78.08	78.86	75.98	74.98	78.4
10 mint	55.8	70.34	88.53	86.7	84.59	97.91	94.65	95.65	94.87
15 mint	68.88	94.58	94.28	94.49	85.49	99.99	99.8	98.4	98.76
20 mint	95.34	97.34	93.56	97.76	98.25	99.67	92.23	94.36	95.34
25 mint	94.74	96.67	92.76	95.78	96.45	97.34	90.7	90.8	90.32
30 mint	93.78	93.76	90.7	94.6	95.67	96.1	85.67	88.54	87.76



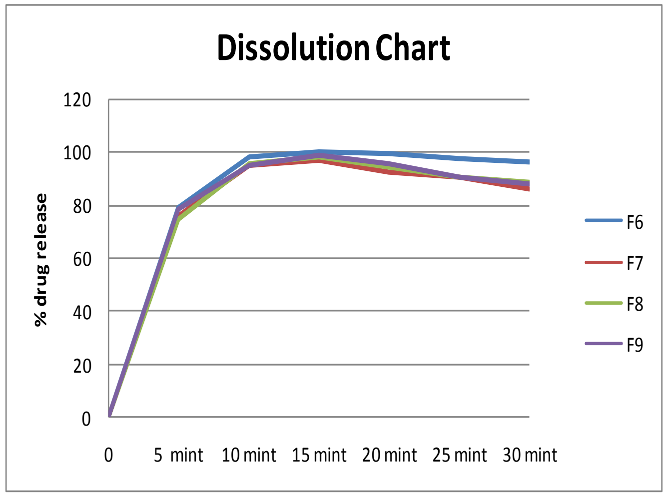


FIGURE 2, 3: DISSOLUTION CHART FOR F1 TO F9

TABLE 7: STABILITY STUDY OF OPTIMIZED FORMULATION

Condition	30±2ºC /75%RH		40±2ºC / 75±5 %RH	
Period	1 Month	3 Month	1 Month	3 Month
Appearance	Pal Yellow	Pal Yellow	Pal Yellow	Pal Yellow
Disintegration time (sec)	40	40	40	40
Hardness (Kg/cm^2)	18	17	18	17
Assay %	99.79%	95.67%	97.75%	96.87%
Dissolution study at 30 mint	95.10	93.54	94.34	92.65

Factorial Design: Full factorial design was constructed to study the effect of the amount of Intra-granular Crosspovidone (X_1) and the amount of Extra-granular Crosspovidone (X_2) on the Disintegration of tablet. The dependent variables chosen were times required to disintegration of tablet within 40 seconds. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_0 is the estimated coefficient for the factor X_1 The main effects (X_1) and (X_2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X_1, X_2) show how the response changes when 2 factors are changed simultaneously. The polynomial terms (X_{12}) and (X_{22}) are included to investigate nonlinearity. The statistical analysis of the factorial design batches was performed by multiple linear regression analysis using Microsoft Excel. The time of disintegration of tablets of each batch (F1 to F9) showed a wide variation the result is shown in **figure 3**. The fitted equations relating the response Disintegration time, shown in Equation1, and Equation 2, respectively;

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X^2{}_2, \ldots \ldots (1)$$

$$Y=35.56-8.33X_131X_2+20.00X_1X_2+31.67A^2+41.67B^2 \ldots .. (2)$$

The values of the correlation coefficient indicate a good fit. The polynomial equation can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries, (i.e., positive or negative).

Figure 3 shows the plot of the amount of Intra-granular povidone (X_1) and amount of extra granular povidone (X_2) versus Disintegration time. The plot was drawn using Sigma Design Expert 8. The data demonstrate that both X1 and X2 affect the Disintegration time. It may also be concluded that the low level of X1 and the higher level of X2 favor the preparation to disintegration of tablets. The results in table indicate that batches F2, F3, F6, fulfill the above criteria. But batch F6 showed the best among all the batches.

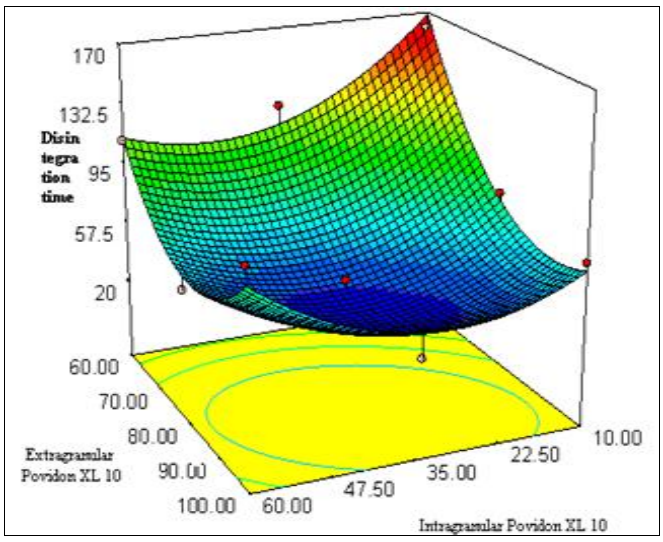


FIGURE 3: RESPONSE SURFACE PLOT FOR DISINTEGRATION TIME

CONCLUSION: In the present work, an attempt was made to develop Buffered tablet of Pantoprazole sodium by wet granulation method using sodium carbonate, sodium bicarbonate as a buffering agent, Crosspovidone as Super-disintegrants and mannitol as a diluents. Nine formulations (F1-F9) were prepared, the optimum concentration were identified based on the disintegration time and *in vitro* drug release results. Based on the observation, it was concluded that formulation F6 had obtain the pH 7 and disintegrated within 40 second, optimized combination due to its fast *in vitro* disintegration time. The results demonstrated the effective use of buffered tablet Pantoprazole tablets and as an ideal drug release formulation for treatment of peptic ulcers and different acidic conditions .

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