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FORMULATION OPTIMIZATION AND EVALUATION OF FAST DISINTEGRATING EFFERVESCENT TABLET OF PANTOPRAZOLE SODIUM

***Punam Shankar Patil, (M Pharm) and Dr. S. D. Barhate, (M Pharm, PhD)**

Department of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner. Tal-Jamner, Dist. Jalgaon, Maharashtra, 424206.

***Corresponding Author: Punam Shankar Patil (M Pharm)**
Department of Pharmaceutics, Shree Sureshdada Jain Institute of Pharmaceutical Education and Research, Jamner. Tal-Jamner, Dist. Jalgaon, Maharashtra, 424206.

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ABSTRACT

The objective of this study was to formulate, optimize and evaluate fast disintegrating effervescent tablet of pantoprazole sodium by using the central composite design (CCD) to optimize the superdisintegrant concentration. The dosage forms were designed with incorporation of superdisintegrants i.e. crosscarmellose sodium and two effervescent agents i.e. citric acid, sodium bicarbonate to develop a dosage form which can accelerate drug disintegration and dissolution to enhance patient compliance. The dosage form was prepared by using direct compression method. The prepared fast disintegrating effervescent tablets were evaluated for pre-compression and post-compression parameters. FTIR studies indicated drug and excipients were compatible with each other. The optimized batch PS5 were passes all the pre-compression and post-compression parameters and it was given as best by the CCD. The disintegration time and % drug released was found to be 21 seconds and 98.57 % within 30 min respectively. It was concluded that fast disintegrating effervescent tablets of pantoprazole sodium were successfully prepared by direct compression method using crosscarmellose sodium and effervescent agents by using central composite design shows better results.

KEYWORDS: Pantoprazole sodium, Crosscarmellose sodium, Citric acid, Sodium bicarbonate, Fast disintegrating effervescent tablets, Central composite design.

INTRODUCTION[1,2,4,8,12,13]

Oral administration is the most popular route about 50-60 % of total dosage form are administered due to ease of ingestion, pain avoidance, versality (to accommodates various types of drug candidates) and most importantly patient compliance. Solid oral drug delivery systems do not require sterile conditions and are therefore less expensive to manufacture. One important drawback of solid dosage form is the difficulty in swallowing (dysphasia) or chewing in some patients particularly pediatric and geriatrics. The problem of swallowing is common phenomenon in geriatric patients due to fear of choking, hand tremors, dysphasia and in children due to underdeveloped muscular and nervous systems and in schizophrenic patients resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Difficulties in swallowing of tablet and capsule also occur when water is not available, in diarrhea, cough during the common cold, allergic condition and bronchial infection. Oral fast disintegrating drug delivery system is one such novel approach to increase consumer acceptance by virtue of rapid disintegration and self- administration without water or chewing. Fast disintegrating tablets are solid unit dosage forms like conventional tablets, which help them to disintegrate the tablet rapidly in saliva. Moreover drug candidates that undergo pre-gastric absorption when formulated as FDTs may show increased oral bioavailability. It provides good stability, accurate dosing and easy manufacturing.

- United States Food and Drug Administration (USFDA) defined FDT as “a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue”.
- As per CDER (Centre for Drug Evaluation and Research) a solid dosage form containing medical substances which disintegrate rapidly within a 30 sec when place upon the tongue.

Fast disintegrating tablet also called as mouth dissolving tablets, fast dissolving tablets, oral disintegrating tablets, orodispersible tablets, rapid melt tablets, quick dissolving tablets.

Pantoprazole sodium (Molecular Formula- $C_{16}H_{14}F_2N_3NaO_4S$) is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H^+, K^+) –

ATPase enzyme system at the secretory surface of the gastric parietal cells. This effect is dose related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+, K^+) – ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

MATERIALS AND METHODS

Pantoprazole sodium was received from Farmson Pharmaceutical Pvt. Ltd. Vadodara. Crosscarmellose sodium, sodium starch glycolate were received from Loba Chemie Pvt. Ltd. Mumbai. Citric acid, sodium bicarbonate, magnesium stearate and talc were received from Jinendra Scientific, Jalgaon. Sodium saccharin and mannitol were received from S. D. Fine Chemicals Ltd. Mumbai**.** Orange flavor were received from Medley Pharma Ltd, Andheri, Mumbai.

COMPATIBILITY STUDY

Fourier Transform Infrared Spectroscopy[3,5]

It is an analytical technique used to identify organic, polymeric and in some cases inorganic materials. The FTIR analysis method uses infrared light to scan test samples and observe chemical properties. The mixture of drug and excipients were subjected to FTIR studies to check whether there was any drug and excipients interaction.

Design of Experiment[6,18]

Central composite design (CCD) is the most efficient mathematical design commonly applied for the optimization of pharmaceutical formulations. CCD is the most applicable design with response surface methodology (RSM) principally comprises of factorial, axial and centre points. It is generated by polynomial equations and mapping the responses over formulation variables to determine the optimum formulation.

Two factor three level central composite designs were employed to evaluate by the effects of formulation variables. The independent variables studied were taken as the concentration of crosscarmellose sodium (X_1), concentration of MCC (pH 102) (X_2). The dependent variables or responses were the disintegration time (Y_1), % drug released (Y_2), wetting time (Y_3). All the analysis was performed using the Design Expert* 7.1.5 Software.

Preparation of fast disintegrating effervescent tablet by direct compression method[2,4,8,12,13]

- The fast disintegrating effervescent tablets of pantoprazole sodium were prepared by direct compression method. Initiallly citric acid and sodium bicarbonate were dried for 30 min at 60° C for to remove the any impurities present in it.
- Then accurate amount of all ingredients except magnesium stearate and talc were passed over mesh 40 and mixed homogeneously using geometric dilution.
- At last, magnesium stearate and talc were added to lubricate and mixed in 15 min.
- The blended material was weighed in 250mg of each tablet and directly compressed by a tablet punching machine with concave faced 9mm punch and dye set.
- The compression force and mass of all tablets were kept stable and each tablet containing pantoprazole sodium equivalent to 40mg pantoprazole.

Formulation Development[17,18]

Pantoprazole Sodium is Equivalent to Pantoprazole

Pantoprazole Sodium = Pantoprazole

$C_{16}H_{14}F_2N_3NaO_4S = C_{16}H_{15}F_2N_3O_4S$

$12\times16+1\times14+18\times2+14\times3+22+16\times4+32 = 12\times16+1\times15+18\times2+14\times3+16\times4+32$

$192+14+36+42+22+64+32 = 192+15+36+42+64+32$

$402 = 381$

Factor = 402/381

= 1.04

$40\times1.04 = 41.6$

*Take 41.6 mg of pantoprazole sodium to make it 40 mg of pantoprazole

Table 1: Composition of Batches by Central Composite Design

Ingredients	Batches								
	PS1	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**	**PS8**	**PS9**
Pantoprazole Sodium	41.6	41.6	41.6	41.6	**41.6**	41.6	41.6	41.6	41.6
Crosscarmellose Sodium	15	12.92	20	27.07	**20**	27	15	27	20
MCC (pH102)	110.4	115.4	107.92	115.4	**115.4**	120	120	110.4	122.07
Mannitol	49	46.08	46.48	31.23	**39**	37.4	39.4	37	32.33
Citric Acid	10	10	10	10	**10**	10	10	10	10
Sodium Bicarbonate	15	15	15	15	**15**	15	15	15	15
Sodium Saccharin	2	2	2	2	**2**	2	2	2	2
Orange Flavor	3	3	3	3	**3**	3	3	3	3
Magnesium Stearate	2	2	2	2	**2**	2	2	2	2
Talc	2	2	2	2	**2**	2	2	2	2
Average wt. (mg)	250	250	250	250	**250**	250	250	250	250

Evaluation of Pre-Compression Parameters of Granules[2,4, 8, 9]

Bulk Density

A bulk density was determined a quantity of 10gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into 10ml measuring cylinder and measured the volume and weight. Bulk density can be calculated by using the formula-

$$BD = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}}$$

Tapped Density

A tapped density was determined a quantity of 10gm of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into 10ml measuring cylinder. The cylinder is allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping is continued until no further change in volume is noted. Tapped density can be calculated by using formula-

$$TD = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}}$$

Hausner's Ratio

Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to bulk density. Hausner's ratio is calculated as:

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Compressibility Index

The simplest way for measurement of flow of the powder is its compressibility, an indication of the ease with which a material can be induced to flow. It is expressed as compressibility index (CI) which can be calculated as follows-

$$\%\ CI = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Angle of Repose

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method.

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

Where,

h- Height of powder pile

r- Radius of powder pile

Θ- Angle of repose

Evaluation of Post Compression of FDET[2,4,8,9,10,12,13,14,15,16]

Weight Variation Test

The weight variation test is carried out to ensure uniformity in the weight of tablets in a batch. First, the total weight of 20 tablets from each formulation was determined and then average weight is calculated. The individual weight of each tablet is also determined to find out the weight variation. The percentage weight variation is calculated by using the following formula.

$$\text{Weight variation} = \frac{\text{Individual wt.} - \text{Average wt.}}{\text{Average wt.}} \times 100$$

Thickness

Tablet thickness and diameter can be measured using a Vernier caliper. The thickness and diameter can be determined by placing the tablet between the two arms of Vernier caliper. The test passed if none of the individual diameter and thickness value deviated by ±5 % of average.

Hardness

The hardness of tablet is an indication of its strength. It is the required to break a tablet by compression in the radical direction. Monsanto hardness tester was used to check the hardness of the tablet. The tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load was increased and at collapse the applied pressure from the spring was measured in kg/cm^2. The hardness for FDTs should be preferably 2-3 kg/cm^2.

Friability

The friability of sample of 20 tablets was measured using a friability rate test apparatus. 20 pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fine's using 60 mesh screens and the percentage of weight loss was calculated. In friability test % weight loss usually should not exceed 0.5-1 %.

$$\%\ F = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

Drug Content

Three tablets were selected randomly and their average weight was determined. Tablets were triturated using mortar and pestle and powder equivalent to 40 mg of pantoprazole was taken and dissolved in 100 ml of 0.1 N HCl which gives 100 µg/ml. From this 1 ml was taken and dissolved in 10 ml to obtain 10µg/ml. This solution was measured using UV- visible spectrophotometer at 288.70 nm against respective reagent blank.

$$\text{Drug Content} = \frac{\text{Absorbance of Test Sample}}{\text{Absorbance of Standard}} \times 100$$

Disintegration Time

The test was carried out on 6 tablets using the disintegration test apparatus. Distilled water at 37˚C ± 2˚C was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. As per USFDA disintegration time limit of FDT is within a 60 sec and as per CDER disintegration time limit of FDT is within a 30 sec.

Uniformity of Dispersion

Keep two tablets in 100 ml water and stir gently for 2 minutes. Then this dispersion was passed through 22 #. The tablets will be considered as passable if there is no residue remained on the screen.

Wetting Time

A double folded tissue paper was placed in a petridish (internal diameter of petri dish 6.5cm). 10 ml of water containing a water-soluble dye (methylene blue) was added to the petridish. A tablet (pre-weighed) was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablet was noted as the wetting time.

Invitro Dissolution Study

Dissolution test of pantoprazole sodium was performed using 900 ml of 0.1N HCl using dissolution type II apparatus (Paddle Type) at 50 rpm and 37±0.5˚ C temperature. Test sample (5 ml) was withdrawn at particular time interval and replaced with fresh dissolution medium maintained sink condition at 37±0.5˚ C. The test sample was filtered and sonicated for few minutes, analyzed under UV spectrophotometer at 288.70 nm using a UV-Visible Spectrophotometer (Shimadzu 1800). % drug released was calculated by using std. dilution of pantoprazole sodium.

Stability Studies

Stability testing is an integral part of formulation development. Stability testing ensures that a drug substance will be safe and effective throughout the shelf-life of the product. The stability study of the formulated batches of pantoprazole sodium tablets were conducted as per ICH guidelines. The accelerated stability study was conducted at temperature of 40±2˚ C. The tablets were stored at the temperature 40±2˚ C for 30 days at RH 75±5 %. The tablets were withdrawn on the 15th and 30th days and evaluated for their physical appearance, hardness, thickness, friability, drug content, disintegration time, and drug release studies at specified time interval.

RESULT AND DISCUSSION

FTIR Studies

The drug subjected to fourier transform infrared studies to confirm the drug using FTIR, also the drug polymer compatibility studies confirm. The IR spectra of pantoprazole sodium, crosscarmellose sodium, sodium starch glycolate and overlay spectra are shown in Fig.

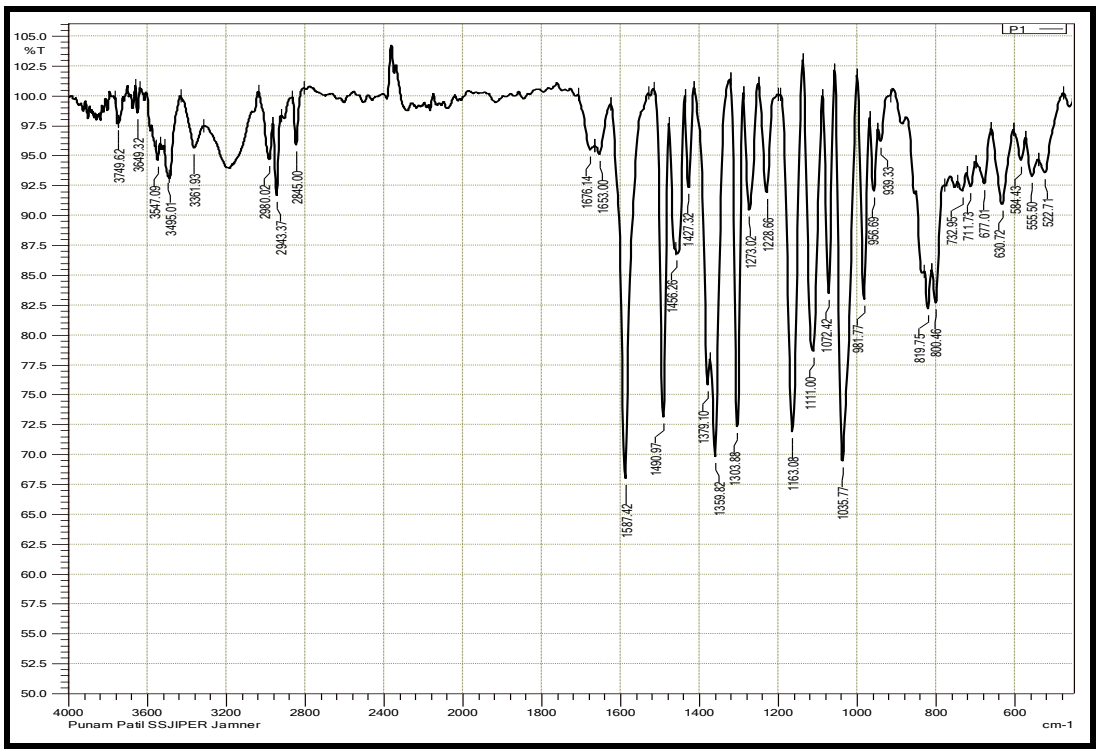

Fig: FTIR Spectra of Pantoprazole Sodium

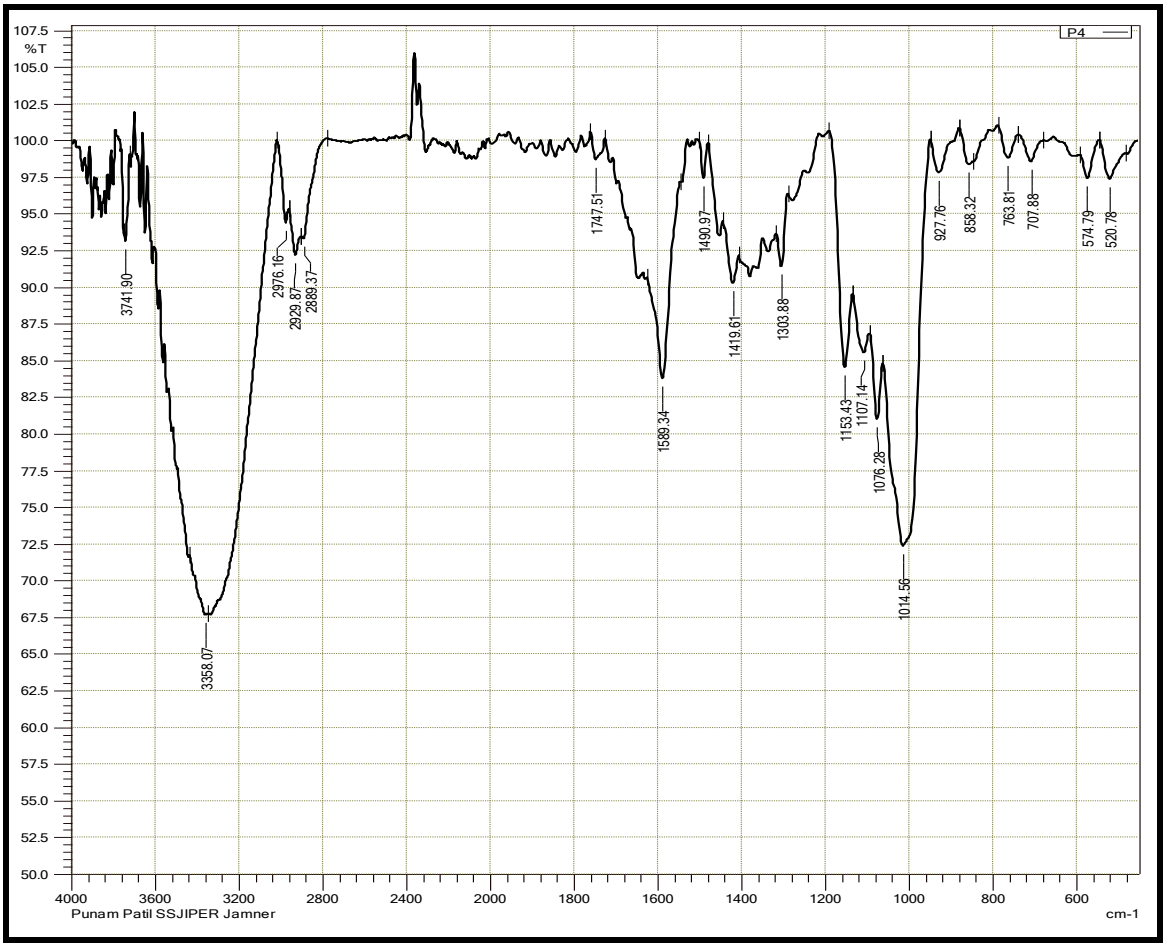

Fig: Overlay Spectrum of Drug, CCS and SSG

Determination of Wavelength

100 mg of pantoprazole sodium was accurately weighed and added into 100 ml volumetric flask and the volume was made up with the 0.1 N HCl to get the concentration of 1000µg/ml. From this 1 ml was withdrawn and diluted to 100 ml 0.1 N HCl to get concentration 100µg/ml. The solutions in concentration range of 5-25 µg/ml were prepared by appropriate dilution of stock solution. The absorbance of these solutions was measured spectrophotometrically at λmax 288.70 nm. The calibration curve of pantoprazole sodium in 0.1 N HCl was shown in fig.

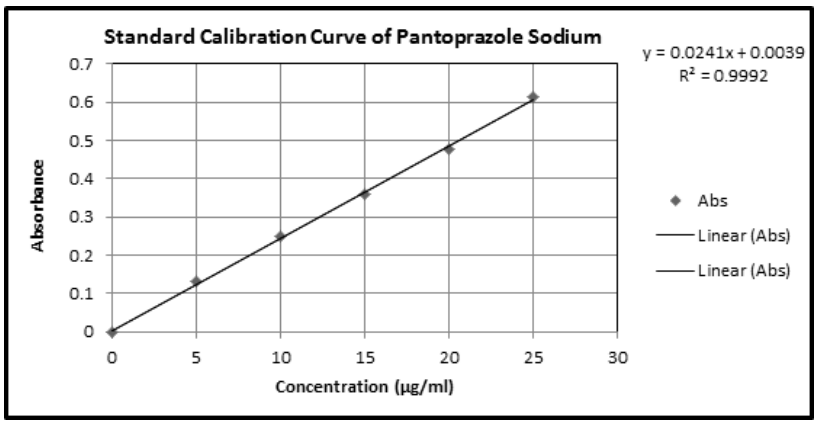

Fig. Standard Calibration Curve of Pantoprazole Sodium in 0.1 N HCl

The prepared blend for all batches granules shows very good free-flowing properties. Compressibility index and Hausner's ratio was found to be in the range of 10.6% to 15% and range of 1.11 to 1.18 respectively. The results show in table 2.

All the compressed fast disintegrating effervescent tablets were evaluated for weight variation, thickness, hardness and friability which were found in official limit as per USP. The formulated tablets were disintegrated within an 18 to 33 seconds. The wetting time for tablets

was observed within a 28 to 45 seconds. The percentage drug released for optimized formulation PS5 was found to be 98.57%. All the results were shown in table 3.

Pre-Compression Parameters

Table 2: Pre-Compression Parameters of CCD Batches

Pre-compression Parameters	Batches								
	PS1	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**	**PS8**	**PS9**
Bulk Density (gm/ml)	0.46 ± 0.01	0.45 ± 0.01	0.43 ± 0.01	0.44 ± 0.01	**0.42 ± 0.01**	0.47 ± 0.01	0.43 ± 0.01	0.48 ± 0.01	0.42 ± 0.01
Tapped Density (gm/ml)	0.54 ± 0.02	0.53 ± 0.02	0.50 ± 0.02	0.51 ± 0.02	**0.47 ± 0.02**	0.53 ± 0.02	0.49 ± 0.02	0.54 ± 0.02	0.48 ± 0.02
Compressibility Index (%)	14.8 ± 0.20	15.0 ± 0.21	14.0 ± 0.25	13.7 ± 0.10	**10.6 ± 0.36**	11.3 ± 0.32	12.2 ± 0..18	11.1 ± 0.38	12.5 ± 0.01
Hausner's Ratio	1.17 ± 0.19	1.17 ± 0.25	1.16 ± 0.21	1.18 ± 0.09	**1.11 ± 0.11**	1.12 ± 0.08	1.13 ± 0.14	1.12 ± 0.13	1.14 ± 0.19
Angle of Repose (°C)	25.13 ± 0.22	26.22 ± 0.16	25.51 ± 0.12	22.50 ± 0.30	**21.15 ± 0.10**	23.12 ± 0.20	25.87 ± 0.10	22.45 ± 0.19	26.71 ± 0.04

*All the values were in mean ±SD, n=3

Post-Compression Parameters

Table 3: Post-Compression Parameters of CCD Batches

Post Compression Parameters	Batches								
	PS1	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**	**PS8**	**PS9**
Weight Variation (mg)	249 ± 1.09	248 ± 1.8	247 ± 1.0	249 ± 1.5	**250 ± 1.2**	248 ± 0.23	249 ± 0.71	248 ± 1.5	247 ± 1.4
Thickness (mm)	4.78 ± 0.01	4.80 ± 0.02	4.77 ± 0.01	4.82 ± 0.01	**4.85 ± 0.02**	4.83± 0.01	4.73 ± 0.01	4.82 ± 0.02	4.78 ± 0.01
Hardness (Kg/cm^2)	1.0 ± 0.5	1.1 ± 0.8	1.0 ± 0.1	1.2 ± 0.2	**1.3 ± 0.6**	1.2 ± 0.4	1.1 ± 0.7	1.2 ± 0.1	1.1 ± 0.3
Friability (%)	0.75 ± 0.01	0.77 ± 0.01	0.74 ± 0.01	0.79 ± 0.01	**0.86 ± 0.01**	0.80 ± 0.01	0.73 ± 0.01	0.69 ± 0.01	0.71 ± 0.01
Wetting Time (Sec)	44	47	45	29	**29**	28	31	30	31
Drug Content (%)	97.39	98.56	99.22	99.12	**100.07**	99.78	98.43	98.81	97.16
Disintegration Time (Sec)	30	32	33	19	**21**	18	24	20	24
% drug released	88.08	87.54	98.56	99.16	**98.57**	100.02	98.33	98.12	98.21

*All the values were in mean ±SD, n=3

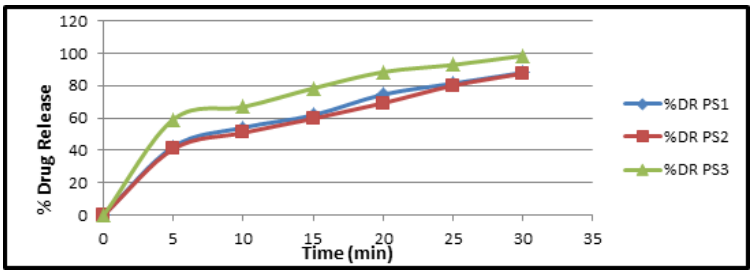

Fig: In-Vitro Drug Released Study of Optimized Batches of Pantoprazole Sodium FDETs Generated by CCD (PS1-PS3)

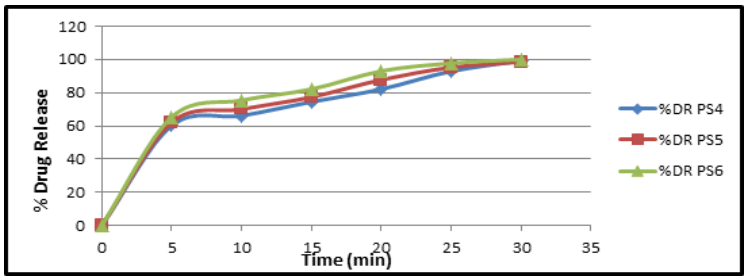

Fig.: In-Vitro Drug Released Study of Optimized Batches of Pantoprazole Sodium FDETs Generated by CCD (PS4-PS6)

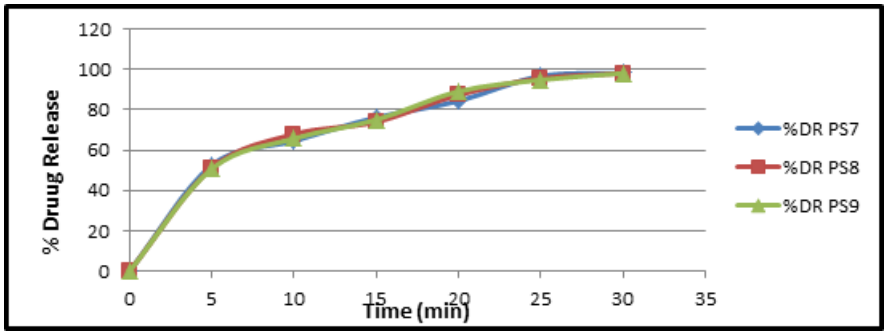

Fig.: In-Vitro Drug Released Study of Optimized Batches of Pantoprazole Sodium FDETs Generated by CCD (PS7-PS9)

Uniformity of Dispersion

All the tablets from preliminary and optimized batches were tested for uniformity of dispersion. The tablets were considered as passable as there was no residue remained on the screen.

Stability Studies

Table 4: - Stability Data for PS5 Optimized Batch of Pantoprazole Sodium Fast Disintegrating Effervescent

Parameters		Condition 40 ± 2°C / 75 ± 5% RH		
		Initial	15 Days	1 Month
Physical	Average Weight (mg)	249	249	248
	Thickness (mm)	4.75	4.75	4.72
	Hardness (Kg/cm^2)	1.2	1.2	1.3
	Friability (%)	0.77	0.77	0.74
	Disintegration Time (Sec)	22	22	24
Chemical	Drug Released (%)	98.17	98.04	97.89
	Drug Content (%)	99.93	99.43	99.02

Statistical Analysis and Optimization

The general central composite design was applied to optimize the fast disintegrating effervescent tablet of pantoprazole sodium. The response surface methodology was used to illustrate the qualitative effect of variable on responses. Statistically analyzed data clearly indicate that the DT, % DR and WT values were mainly depending upon the selected independent variables. The regression equations for the responses fitted in quadratic model were generated. ANOVA was used to identify the significant effect. Obtained value of F is larger than critical F-value, the result was found to be significant at that level of probability ($p<0.05$). Only statistically significant ($p<0.05$) coefficient were included in regression equation.

Regression Equations of Quadratic Model

• Disintegration Time

Final equation in terms of coded form-

$$DT = 21.40 - 4.30X_1 - 2.59X2 + 1.00X_1X_2 + 1.05X_1^2 + 2.55X_2^2$$

Concerning disintegration time, the results of multiple linear regression analysis showed that the coefficients X1 bears negative sign and X2 also bear a negative sign. It revealed that the disintegration time decreased with increase in crosscarmellose sodium and also disintegration time decreased with increase in MCC (pH102). Crosscarmellose sodium 8% and MCC (pH102) 46% were selected as optimum concentration that showed the minimum disintegration time of 21 seconds. It was observed that further increase in the concentration of superdisintegrants led to the fall in disintegration time. ANOVA was used to identify the significant effect.

• % drug released

Final equation in terms of coded form-

$$\%\ DR = 98.58 + 3.52X_1 + 1.46X_2 - 2.09X_1X_2 - 2.55X_1^2 - 0.028X_2^2$$

Concerning % drug released, the results of multiple linear regression analysis showed that the coefficients X1 bears positive sign and X2 also bear a positive sign. It revealed that the increase in the concentration of crosscarmellose sodium and MCC (pH102) increases the % drug released due to faster disintegration of tablet. Crosscarmellose sodium 8% and MCC (pH102) 46% were selected as optimum concentration that showed the 98.57% drug released in 30 min. ANOVA was used to identify the significant effect.

- **Wetting Time**

Final equation in terms of coded form

$$WT = 29.20 - 5.31X_1 - 4.35X_2 + 2.75X_1X_2 + 3.21X_1^2 + 3.21X_2^2$$

Concerning wetting time, the results of multiple linear regression analysis showed that the coefficients X1 bears negative sign and X2 also bear a negative sign. That's

via the increasing the concentration of crosscarmellose sodium and MCC (pH102) decreased the wetting time. Crosscarmellose sodium 8% and MCC (pH102) 46% were selected as optimum concentration that showed the minimum wetting time 29 seconds. ANOVA was used to identify the significant effect.

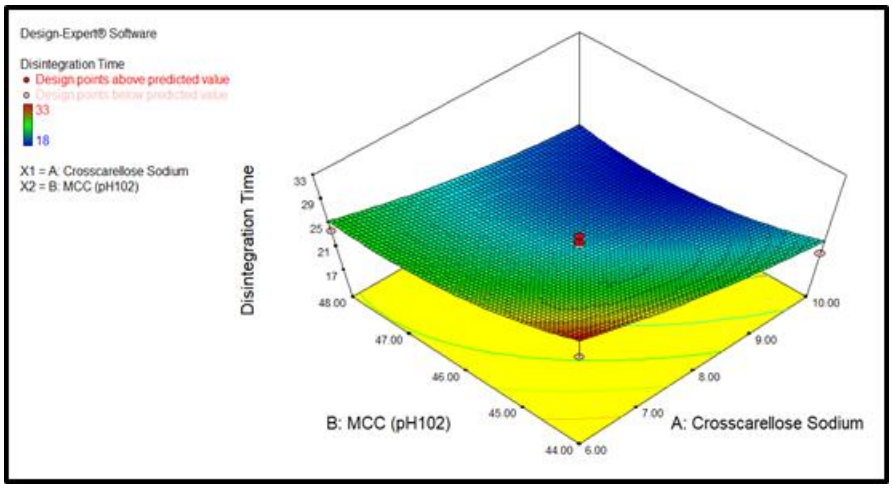

Fig. D Response Surface Graph Showing the Influence of CCS (X1) and MCC (pH102) (X2) on the Disintegration Time (Y1)

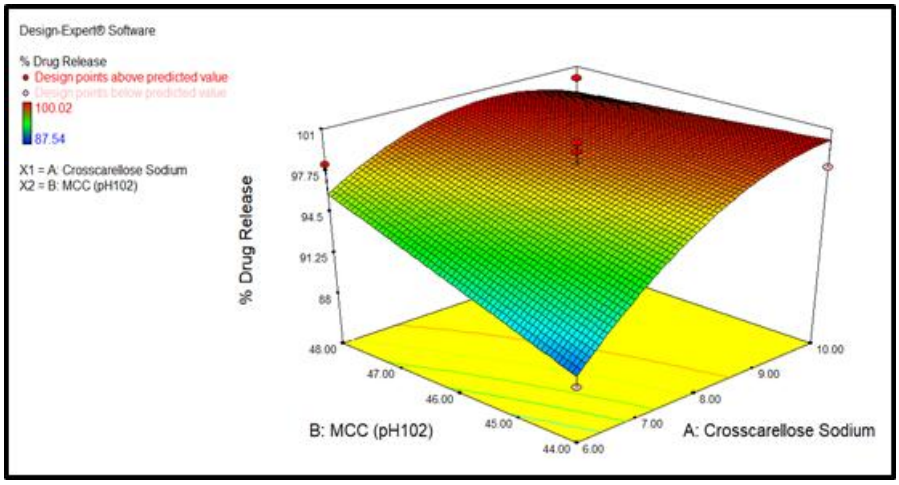

Fig. D Response Surface Graph Showing the Influence of CCS (X1) and MCC (pH102) (X2) on the % drug released (Y2)

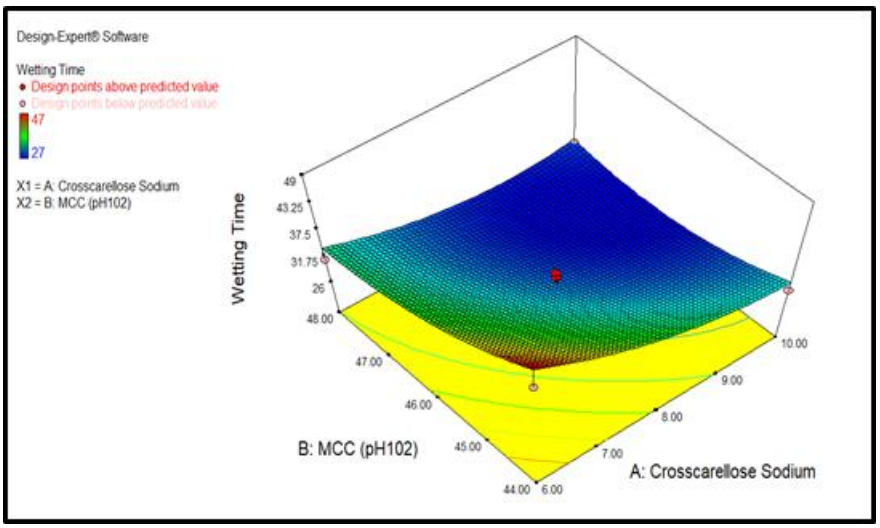

Fig. D Response Surface Graph Showing the Influence of CCS (X1) and MCC (pH102) (X2) on the Wetting Time (Y3)

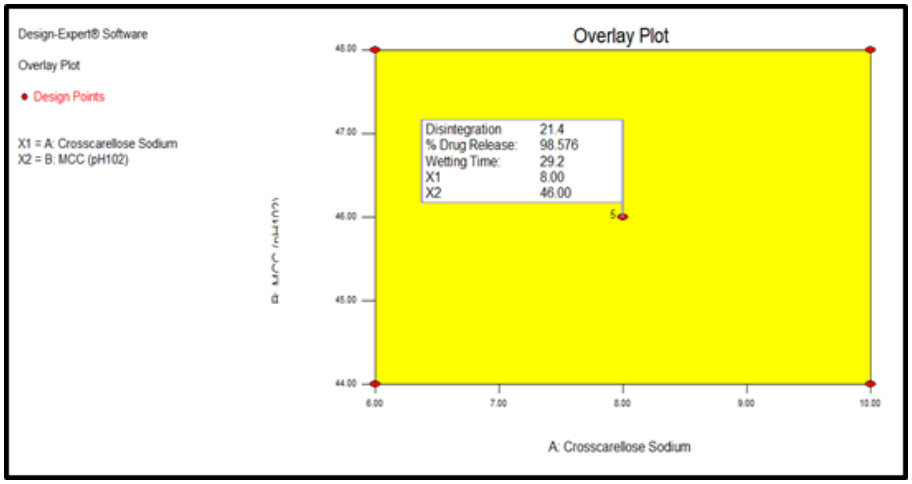

Fig. Overlay Plot Showing Combinations for Optimized Batch

Table 5: Results of Analysis of Variance

ANOVA for Y_1 (Disintegration Time)					
Source	***DF**	**Sum of Square**	**Mean Square**	***F value**	**P value, Prob > F**
Model	5	254.37	50.87	8.75	0.0064 – Significant
Residual	7	40.71	5.82	-	-
Total	12	295.08	-	-	-
ANOVA for Y_2 (% drug released)					
Source	***DF**	**Sum of Square**	**Mean Square**	***F value**	**P value, Prob > F**
Model	5	179.29	35.86	9.27	0.0054 – Significant
Residual	7	27.15	3.88	-	-
Total	12	206.44	-	-	-
ANOVA for Y_3 (Wetting Time)					
Source	***DF**	**Sum of Square**	**Mean Square**	***F value**	**P value, Prob > F**
Model	5	533.95	106.79	11.04	0.0032 – Significant
Residual	7	67.74	9.68	-	-
Total	12	601.69	-	-	-

*DF indicates Degree of freedom; F indicates Fischer's ratio

CONCLUSION

It was concluded that formulation, optimization and evaluation of fast disintegrating effervescent tablet of pantoprazole sodium were successfully prepared by direct compression method using crosscarmellose sodium as superdisintegrants and citric acid, sodium bicarbonate as effervescent agent using central composite design. As per CDER guideline it shows disintegration time within 5-30 seconds. The data observed showed that experimental design was successfully applied to optimize the concentration of superdisintegrant to formulate FDETs with desirable properties of less disintegration time (21 Sec.), wetting time (29 Sec.) and % drug released (98.57%). Central composite design could be successfully applied for the development of pantoprazole sodium fast disintegrating effervescent tablets a dosage form which can accelerate drug disintegration and dissolution to enhance patient compliance.

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