FORMULATION EVALUATION AND OPTIMIZATION OF ORODISPERSIBLE TABLETS OF PANTOPRAZOLE SODIUM BY THE USING OF DIFFERENT SUPERDISINTEGRANTS

LOKENDRA SINGH CHUNDAWAT*, VISHAL SHARMA

Department of Pharmaceutics, Mandsaur University Mandsaur,Mandsaur, Madhya Pradesh, India. Email: chundawatlokendra@gmail.com

ABSTRACT

Objective: The objective of this study was to formulate and optimize an orodispersible formulation of pantoprazole sodium using a 3^2 factorial design for optimized the superdisintegrant concentration.

Methods: Various concentrations (2%, 4%, and 6%) of superdisintegrants (sodium starch glycollate [SSG] and crospovidone [CP]) were added in the formulation, all processing steps are carried out at a temperature below 250c and relative humidity <35%. Procedure to manufacture orodispersible tablets by direct compression was established.

Results: The results show that the presence of a superdisintegrants is desirable for orodispersion. The best-optimized batch found was the batch having amount of CP 4.37 mg and SSG 10.59 mg. All the formulations satisfied the limits of orodispersion with a dispersion time of <30 s best formulation showed a disintegration time (DT) of 30 s, % friability is 0.82%, drug content of 96– 99.4, and fast drug release rate of 80 % of drug release within 10 min.

Conclusion: The optimized batch was evaluated for thickness, weight variation, hardness, friability, DT dissolution, and accelerated stability study for a period of 3 months. The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The f^2 value was found more than 50 that indicate a good similarity between both the dissolution profiles. Hence, the results of stability studies reveal that the developed formulation has good stability.

Keywords: Pantoprazole sodium, Orodispersion, Crospovidone, Sodium starch glycollate, Factorial design, Tablet properties.

INTRODUCTION

Difficulty in swallowing is a common problem of all age groups, especially geriatric and pediatric patients, due to physiological changes associated with these groups. These problems can be solved by the development of a novel type of solid dosage form, namely, orodispersible tablet, which disintegrates and dissolves rapidly in saliva without the need of swallowing with drinking water since the tablet is placed in the mouth where it disperses rapidly before swallowing [1,2].

Pantoprazole is a potent and selective proton pump inhibitor. It is an effective agent in the treatment of peptic ulcers, gastroesophageal reflux disease, esophagitis, Zollinger-Ellison syndrome, and other gastrointestinal hypersecretory disorders. It provides rapid symptoms relief up to 85–90% of ulcer patients within 1 h of treatment. It has a mediocre bioavailability of 50% and poor aqueous solubility and thus makes its absorption and dissolution rate limited, delaying its onset of action to a certain extent. Pantoprazole is available as a conventional tablet in the market, and many patients find it difficult to swallow these, especially pediatric and geriatric subjects which result in high incidence of non-compliance and ineffective therapy. In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets, also called as OraSolv tablets, of pantoprazole using two different superdisintegrants, namely, crospovidone (CP) and sodium starch glycollate (SSG) by direct compression method. Evaluation of the tablets showed that all the tablets were found to be within official limits and the disintegration time (DT) for the formulations ranged from 15 s to 25 s. The formulated orally disintegrating tablets (ODT's) have potential advantages over conventional marketed tablets with their improved patient compliance, both in geriatrics and pediatrics, ease of administration, and bioavailability [3].

In this present study, an effort has been made to formulate fast disintegrating and rapid release tablets of pantoprazole using two different superdisintegrants, namely, CP and SSG [4] by direct compression method. The objective of this study was to enhance the safety and efficacy of the drug molecule, achieve better patient compliance, solve the problem of difficulty in swallowing, enhance onset of action and provide a stable dosage form [5].

EXPERIMENTAL

Materials
Pantoprazole sodium was a kind gift from Vasudha Pharma Ltd. (Andhra Pradesh, India), CP and SSG were purchased from Signet Chemical Corporation, Mumbai. Lactose and Mannitol were from Micro Labs (Hosur). Microcrystalline cellulose, aspartame was purchased from S.D. Fine Chemicals (Mumbai). Methanol and Water (HPLC Grade) were purchased from Merck (India). All other chemicals and reagents were of analytical grade.

Methods

Experimental design
Using 3^2 full factorial design [6], the optimization of independent factors (amount of superdisintegrant 1 - CP and amount of superdisintegrant 2 - SSG) was done. DT and friability factors were represented as dependent factors.

Code X1 is given for the amount of superdisintegrant 1 (CP), and Code X2 is given for the amount of superdisintegrant 2 (SSG) (Tables 1-3).

Formulation Orodispersible tablets
Pantoprazole orodispersible tablet was prepared by direct compression method [7].

The most common and simplest method available for tablet compression is direct compression in which the drug with other excipients is mixed thoroughly with the help of various mixers followed by the compression of the resulting powder. Using capsule shape punch in modified rotary compression machine (16 stations) by Cadmach CMD 3-16.

Evaluation of Orodispersible tablets

Hardness

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester.

Friability

The friability of the tablets was determined using Roche friabilator. It is expressed in percentage (%). 10 tablets were initially weighed and transferred into the friabilator. The friabilator was operated at 25 rpm for 4 min [8]. After 4 min the tablets were weighed again. The friability was then calculated using the formula:

$$\text{Friability } (\%) = \frac{\text{Initial weight-Final Weight}}{\text{Initial weight}} \times 100$$

Weight variation test

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets were calculated.

Table 1: 3^2 Full factorial design layout

Batch code	Factor 1 X1	Factor 2 X2
A_1	−1	−1
A_2	−1	0
A_3	−1	1
A_4	0	−1
A_5	0	0
A_6	0	1
A_7	1	−1
A_8	1	0
A_9	1	1

Assay

A total of 20 tablets from each batch were weighed and powdered.20 mg of pantoprazole sodium equivalent to pantoprazole was weighed and dissolved in ethanol; the solution was filtered and made the volume up to 50 ml with distilled water into the volumetric flask. [9]

Absorbance was measured at 289 nm using Shimadzu UV spectrophotometer and percent purity was determined.

In vitro drug release

Measure the absorbance of standard preparation and sample preparation in 1 cm cell on a suitable spectrophotometer at 289 nm, using dissolution medium as a blank. Calculate the quantity as a percentage of drug dissolved using following formula:

$$\text{Drug} \times (\text{mg/tab}) = AT/AS \times WS/100 \times 5/50 \times P/100 \times 100$$

Where,
AT=Absorbance of test solution
AS=Absorbance of standard solution
WS=Weight of working standard taken in mg
P=Percentage purity of working standard (on as is basis)

Stability study

The ICH Guidelines have established that long-term stability testing should be done at 25°C/60% RH; stress testing should be done at 40°C/75% RH for 6 months. If a significant change occurs at these stress condition, then the formulation should be tested at an intermediate condition, i.e., 30°C/65% RH (Table 4).

RESULTS AND DISCUSSION

The tablets were evaluated for different parameters and were within limits of weight variation, hardness, and drug content. Friability of the tablets was found to decrease with an increase in the concentration of both factors. MCC increases friability. CP is also known to produce mechanically strong tablets. Thus, both the factors had desired effects on DT and friability. These effects were further analyzed using statistical models.

According to the European Pharmacopoeia [10,11], the fast disintegrating/orodispersible tablets should disintegrate within 3 min without leaving any residue on the screen increase in the levels of CP

Table 2: Coded values for X1 and X2

Coded value	Amount of superdisintegrant 1 (CP) in mg X1	Amount of superdisintegrant 2 (SSG) in - 1 mg X2
−1	3.6	7.2
0	5.4	9
1	7.2	10.8

SSG: Sodium starch glycollate, CP: Crospovidone

Table 3: Formulation using 3^2 full factorial designs

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
Drug	23	23	23	23	23	23	23	23	23
Mgo	23	23	23	23	23	23	23	23	23
Ethyl cellulose	2	2	2	2	2	2	2	2	2
CP	3.6	5.4	7.2	3.6	5.4	7.2	3.6	5.4	7.2
SSG	7.2	7.2	7.2	9	9	9	10.8	10.8	10.8
MCC	27	27	27	27	27	27	27	27	27
Mannitol	32.5	32.5	32.5	32.5	32.5	32.5	32.5	32.5	32.5
Lactose	48.2	46.4	44.6	46.4	44.6	42.8	44.6	42.8	41
Aspartame	9	9	9	9	9	9	9	9	9
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mg starate	3	3	3	3	3	3	3	3	3
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight (mg)	180	180	180	180	180	180	180	180	180

SSG: Sodium starch glycollate, CP: Crospovidone

and SSG had a negative effect on DT, i.e., DT decreased with increase in the levels of both factors. CP is known for rapid disintegration activity due to fast water wicking action. The disintegrating time was found to be between 18 s and 94 s. Optimum effect is shown in following concentration range CP: 2–4% and SSG: 4–6%.

Dissolution studies

ODT should release not <80% of the stated amount of drug the dissolution profiles of all 9 trial batches showed more than 80% of drug release within 10 min. It was observed that there was not much

variation in dissolution profiles among the tablet formulation and the factors under study had no effect on the drug release (Tables 5 and 6, Figs. 1 and 2).

Optimization of tablets

Design layout for optimization (Table 7)

Tablets were optimized using a different combination of factor X1 and X2.Design layouts for optimization were given in Table 7

Statistical analysis of response

Statistical analysis is performed by multiple regression analysis using software Design Expert 8.0.7.1.

Nine batches were prepared, and polynomial equation [12] was derived for the desired response. Contour plots were prepared for the dependent variable. Derived equation is validated by preparing a checkpoint batch.

Factorial equation for response 1: Disintegration time

$R1 = +26.62 - 5.67 * A - 9.33 * B - 2.00 * A * B + 1.83 * A2 + 10.83 * B2$

Where, R1=Disintegration time

Result obtained from factorial design is explained below

Table 4: ICH guide lines for stability study

Study	Storage condition	Time period
Long-term*	25°C±2°C/60% RH±5% RH	12 months
	30°C±2°C/65% RH±5% RH	
Intermediate**	30°C±2°C/65% RH±5% RH	6 months
Accelerated	40°C±2°C/75% RH±5% RH	6 months

*Whether long-term stability studies are performed at 25 °C ± 2 °C/60% RH ± 5% RH or 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is determined by the climatic condition under which the API is intended to be stored (see Appendix 1). Testing at a more severe long-term condition can be an alternative to testing condition, i.e. 25 °C/60% RH or 30 °C/65% RH.
**If 30 °C ± 2 °C/65% RH ± 5% RH or 30 °C ± 2 °C/75% RH ± 5% RH is the long-term condition there is no intermediate condition.

Table 5: Optimization of prepared batches

Batch code	Thickness* (mm)	Avg weight* (mg)	Hardness* (kg/cm²)	Friability* (%)	Disintegration time* (s)	%Drug content*	%Drug release*
A1	2.11±0.12	179.6±0.70	4.09±0.13	0.71±o. 89	54±0.11	98.84±0.86	95.48±9.45
A2	1.96±0.12	180.8±1.17	3.86±0.12	0.76±0.74	42±0.69	99.76±0.34	97.29±3.72
A3	2.08±0.16	181.1±0.57	3.88±0.19	0.70±1.43	48±0.44	96.11±0.3	92.13±2.81
A4	1.99±0.02	179.6±2.18	3.64±0.17	0.77±1.51	32±0.12	98.67±0.21	91.61±3.72
A5	2.12±0.03	181.6±1.11	3.48±0.11	0.79±0.93	28±0.71	97.68±0.72	99.27±3.73
A6	2.02±0.12	180.4±0.91	3.52±0.10	0.86±1.07	18±0.92	98.38±0.29	97.80±3.72
A7	2.05±0.12	178.5±0.36	3.72±0.13	0.76±1.29	38±0.75	99.76±0.74	95.10±2.81
A8	2.08±0.16	180.5±2.59	3.64±0.16	0.82±0.81	26±0.14	96.41±0.11	97.51±9.45
A9	2.03±0.11	182.8±0.54	3.54±0.13	0.81±0.97	24±0.36	99.91±0.21	97.51±9.45

*The values represent mean±standard deviation, n=5

Table 6: Dissolution data of formulation A1 to A9% drug release in 900 ml 6.8 phosphate buffer 50 rpm, 37°C±0.1°C, USP Type II

Time	A1	A2	A3	A4	A5	A6	A7	A8	A9
0	0	0	0	0	0	0	0	0	0
1	18.12	28.34	23.12	30.85	35.26	46.19	18.9	26.3	39.23
2	31.67	40.8	36.67	43.92	52.75	59.57	42.25	48.59	54.49
4	50.31	53.49	56.31	56.34	69.08	73.92	62.31	65.82	69.96
6	68.36	68.36	74.36	70.05	82.23	84.71	74.35	75.56	78.56
8	79.95	82.95	88.95	83.27	91.15	93.94	83.26	84.95	86.54
10	91.48	93.29	92.13	94.61	99.27	97.8	95.1	97.51	95.51

Table 7: Response data for 3² Full factorial optimization design

Batch code	Factor 1 X1	Factor 2 X2	Response 1	Response 2
	Amount of CP (mg)	Amount of SSG (mg)	Disintegration time (s)	% Friability
A₁	5.4	9	28	0.79
A₂	7.2	10.8	24	0.81
A₃	5.4	10.8	26	0.82
A₄	7.2	9	18	0.86
A₅	7.2	7.2	48	0.70
A₆	3.6	9	32	0.77
A₇	3.6	7.2	54	0.71
A₈	3.6	10.8	38	0.76
A₉	5.4	7.2	42	0.76

SSG: Sodium starch glycollate, CP: Crospovidone

The model F value of 10.40 implies the model is significant. There is only a 0.39% chance that a "Model F value" this large could occur due to noise. Values of $p<0.0500$ indicate model terms are significant. Values >0.1000 indicate the model terms are not significant. p values for A, B, A2, and B2 were found to be 0.0019, 0.0288, 0.0392, and 0.0031 which is <0.05, thus the significant effect on dependent variable R1, p value for term AB was found to be 0.3428 which is >0.05, thus non-significant effect on R1. The R2 (0.9363) was high indicating the adequate fitting of quadratic model. The polynomial equation can also be used to draw the conclusion considering the magnitude of coefficient and the mathematical sign it carries, i.e., +ve or −ve. −ve sign of variable indicates that as the concentration of superdisintegrants increase DT decreases (Table 8).

Factorial equation for response 2: Friability

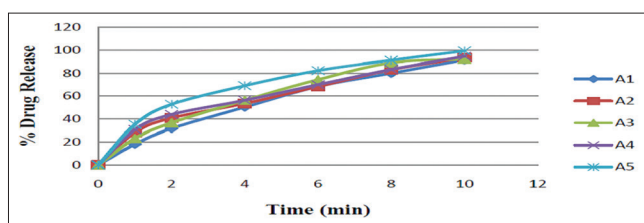$R_2 = +0.78 + 0.022 * A + 0.037 * B$

Where,

$R_2 = $ Friability

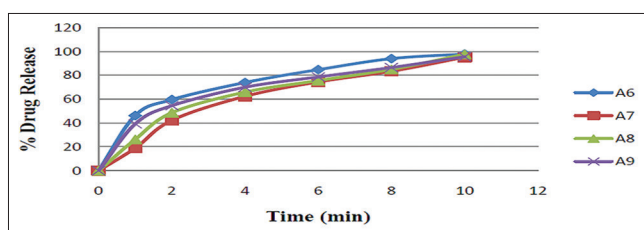**Fig. 1: Comparative dissolution profile of A_1 to A_5**

Fig. 2: Comparative dissolution profile of A_6 to A9

Result obtained from factorial design is explained below

The model F value of 5.08 implies the model is significant. There is only a 3.01% chance that a "model F value" this large could occur due to noise. $p<0.0500$ indicate model terms are significant. In this case, B is significant model terms. Values >0.1000 indicate the model terms are not significant. p values for B were found to be 0.0207, which is <0.05, thus significant effect on dependent variable R2. p value for term A was found to be 0.1360 which is >0.05, thus non-significant effect on R1. The R2 (0.9363) was high indicating the adequate fitting of quadratic model. The polynomial equation can also be used to draw the conclusion considering the magnitude of coefficient and the mathematical sign it carries, i.e., +ve or −ve. +ve sign of variable indicates that as the concentration of superdisintegrants increase friability also increases.

Construction of response surface plots (Figs. 3 and 4)

Overlay plot
The optimization of the formulation was carried out from overlay plot. Overlay plot gives the area of interest or area of the experiment. In Fig. 5, yellow region reflects the area of experiment (Fig. 5).

Check point batch
To confirm the equation generated by multiple regression analysis, checkpoint batch is prepared. The values of all possible combinations of two independent factors A and B were derived from contour plots, and data were filtered using excel software. A value for optimized formulation was obtained from overlay plot. It is called as checkpoint batch (Table 9).

Formulation of checkpoint batch C is given in table number 9

Validation of mathematical model
From the polynomial equation and contour plots, the best-optimized batch found was the batch having the amount of CP 4.37 mg and SSG 10.59 mg. Checkpoint batch was prepared for model validation.

The response DT and friability were evaluated and found within limits. The values of response predicted from the model analysis shown in Table 10. The close resemblance between the observed and the predicted response value assessed the robustness of prediction. These values indicate the validity of the generated model.
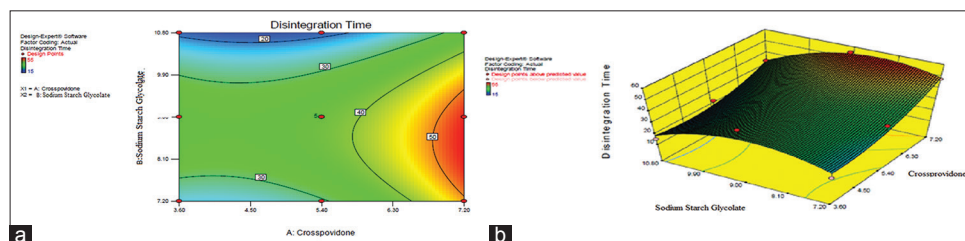

Fig. 3: Diagrammatic representation of (a) contour plot and (b) 3D view of effect of A and B on disintegration time
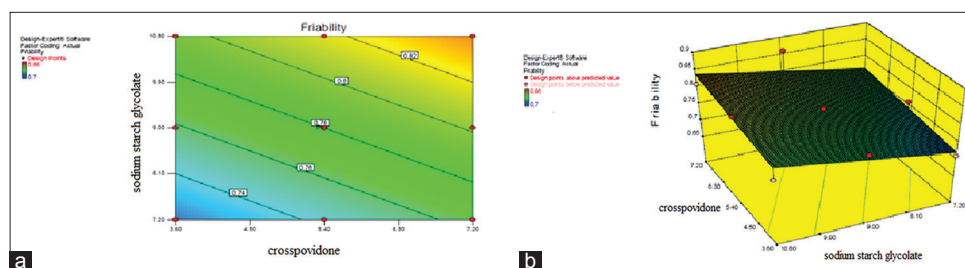

Fig. 4: Diagrammatic representation of (a) contour plot and (b) 3D view of effect of A and B on friability

The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The f^2 value was found more than 50 that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the DT after stability studies. Hence, the results of stability studies reveal that the developed formulation has good stability (Fig. 6 and Table 11).

CONCLUSION

The ODTs have potential advantages over conventional oral dosage forms as they improved patient compliance; Convenience, rapid onset of action and bioavailability .The present study developed Orodispersible tablet

Table 8: Regression output of R1 for 3^2 full factorial design

Parameter	Value	Parameter	Value
Sum of square	1255.75	Mean±SD	34.31±4.91
Degree of freedom	5	C.V %	10.39
Mean square	251.15	R^2	0.9363
Model F value	10.40	p value	0.0039

SD: Standard deviation

Parameter	Value	Parameter	Value
Sum of square	0.011	Mean±SD	0.78±0.033
Degree of freedom	2	C.V %	4.2
Mean square	5.442E-003	R^2	0.5039
Model F value	5.08	p value	0.0301

SD: Standard deviation

Table 9: Formulation of checkpoint batch – C

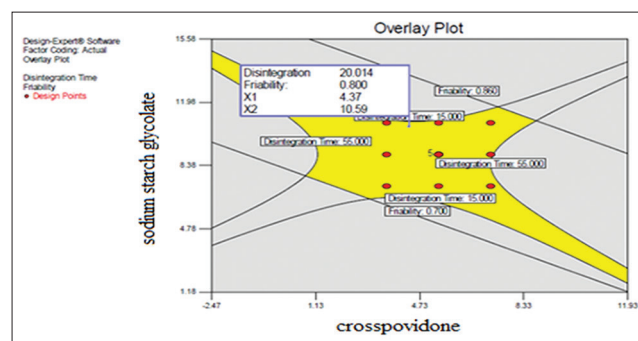| Ingredient	Quantity taken (mg)
Drug	23
MgO	23
Ethyl cellulose	2
CP	4.37
SSG	10.59
MCC	27
Mannitol	32.5
Lactose	44.04
Aspartame	9.0
Talc	1.5
Mg stearate	3.0
Flavor	q.s
Total weight (mg)	180

SSG: Sodium starch glycollate, CP: Crospovidone
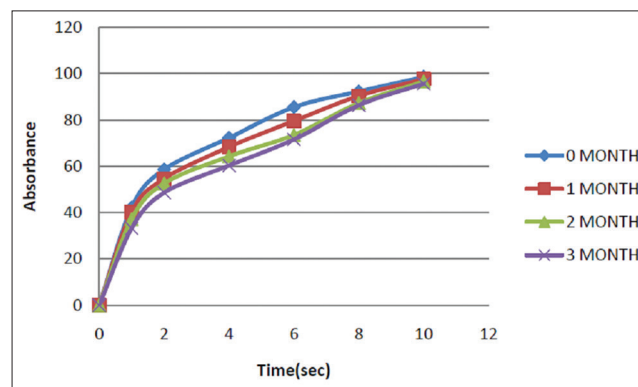
Table 10: Validation of mathematical model

Batch code	Dependent variable	Predicted value	Observed value	% error
C	Disintegration time (s)	20 s	21.25	6.25%
	% friability	0.8%	0.82%	2.5%

which is soluble in saliva are absorbed from the mouth, pharynx, and oesophagus as the saliva passes down into the stomach, thus enhance the bioavailability by avoiding first pass metabolism. Various concentrations (2%, 4%, and 6%) of superdisintegrants (SSG, CP) were added in the formulation, all processing steps are carried out at a temperature below 250c and relative humidity <35%. Procedure to manufacture orodispersible tablets by direct compression was established.

Developed ODT gave satisfactory results for various physicochemical evaluations such as hardness, friability, weight variation, drug content, and *in vitro* DT and *in vitro* dissolution profiles. DT and % friability of ODT depends on the concentration of superdisintegrants. The DT and % friability of all the formulation varied from 81±1.37 to 18±0.92 s and 0.87±1.95 to 0.70±1.43. Combination of superdisintegrants is used to derive the satisfactory result. The concentration of superdisintegrants was optimized using 3^2 full factorial design with the help of design expert 8.0.7.1 version software, in that two independent factors were a concentration of CP (2–4%) and concentration of SSG (4–6%). Three different levels were coded as (−1, 0, +1). From the polynomial equation and contour plots, the best-optimized batch found. Checkpoint batch was prepared for model validation. The close resemblance between the observed and the predicted response value assessed the robustness of prediction. These values indicate the validity of the generated model.

Fig. 5: Overlay plot

Fig. 6: Comparisons of release profile of stability batch at accelerated stability study

Table 11: Stability study evaluation data

Sr.no.	Evaluation Parameter	0 month	1 month	2 months	3 months
1	Appearance	White	White	White	White
2	Hardness	3.76±0.17	3.76±0.17	3.76±0.17	3.76±0.17
3	Disintegration time	22±0.19	22±0.54	24±0.92	26±0.38
4	% Friability	0.81±3.89	0.81±2.67	0.79±2.18	0.78±1.86
5	% Drug content	98.43±0.62	98.07±0.28	97.48±0.21	96.76±0.42
6	% Drug release	98.88±2.46	97.65±3.32	95±1.97	93.37±2.81
7	f^2 value	94.82	96.05	95.48	96.27

The optimized batch was evaluated for thickness, weight variation, hardness, friability, DT dissolution, and accelerated stability study for a period of 3 months. The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The f² value was found more than 50 that indicate a good similarity between both the dissolution profiles. Hence, the results of stability studies reveal that the developed formulation has good stability. This work needs to be proved more effective by its bioavailability, pre-clinical, and clinical studies further studies are needed to investigate these formulations for its performance *in vivo*. The result of the study indicates that orodispersible tablet of Pantoprazole sodium that can be successfully prepared. Undoubtedly, the availability of various technologies and the manifold advantages of ODT will surely enhance the patient compliance and its popularity in the near future.

CONFLICTS OF INTEREST

The author declares there is no conflict of interest.

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