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

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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 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:

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

**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 | Factor 2 |
|------------|----------|----------|
| A₁         | -1       | -1       |
| A₂         | -1       | 0        |
| A₃         | 0        | 1        |
| A₄         | 0        | 1        |
| A₅         | 1        | -1       |
| A₆         | 1        | 0        |
| A₇         | 1        | 1        |

**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                                        | 1.08                                          |

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      |
| Mgp          | 23      | 23      | 23      | 23      | 23      | 23      | 23      | 23      | 23      |
| Ethyl cellulose | 2      | 2       | 2       | 2       | 2       | 2       | 2       | 2       | 2       |
| CP           | 3.6     | 3.6     | 3.6     | 3.6     | 3.6     | 3.6     | 3.6     | 3.6     | 3.6     |
| SSG          | 7.2     | 7.2     | 7.2     | 7.2     | 7.2     | 7.2     | 7.2     | 7.2     | 7.2     |
| 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    | 46.4    | 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 table 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**

\[ R_1 = +26.62 - 5.67 \times A - 9.33 \times B - 2.00 \times A \times B + 1.83 \times A^2 + 10.83 \times B^2 \]

Where, \( R_1 \) = 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   |
| 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         | 2.1±0.12        | 179.6±0.70       | 4.0±0.13           | 0.71±0.89      | 54±0.11                 | 98.84±0.86    | 95.48±9.45    |
| A2         | 1.9±0.12        | 180.8±1.17       | 3.8±0.12           | 0.76±0.74      | 42±0.69                 | 99.76±0.34    | 97.29±3.72    |
| A3         | 2.0±0.16        | 181.1±0.57       | 3.8±0.19           | 0.70±1.43      | 48±0.44                 | 96.11±0.93    | 92.13±2.81    |
| A4         | 1.9±0.02        | 179.6±2.18       | 3.6±0.17           | 0.77±1.51      | 32±0.12                 | 98.67±0.21    | 91.61±3.72    |
| A5         | 2.1±0.03        | 181.6±1.11       | 3.4±0.11           | 0.79±0.93      | 28±0.71                 | 97.68±0.72    | 99.27±3.73    |
| A6         | 2.0±0.12        | 180.4±0.91       | 3.5±0.10           | 0.86±1.07      | 18±0.92                 | 98.38±0.29    | 97.80±3.72    |
| A7         | 2.0±0.12        | 178.5±0.36       | 3.7±0.13           | 0.76±1.29      | 30±0.75                 | 99.76±0.74    | 95.10±2.81    |
| A8         | 2.0±0.16        | 180.5±2.59       | 3.6±0.16           | 0.82±0.81      | 26±0.14                 | 96.41±0.11    | 97.51±9.45    |
| A9         | 2.0±0.11        | 182.8±0.54       | 3.5±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 | 89.85 | 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 | Amount of CP (mg) | Amount of SSG (mg) | Disintegration time (s) | %Friability |
|------------|-------------------|--------------------|-------------------------|-------------|
| A1         | 5.4               | 2                 | 10.0                    | 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               | 9                 | 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

\[ R^2 = +0.78 + 0.022 \times A + 0.037 \times B \]

Where,

\[ R^2 = \text{Friability} \]

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.
The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The F 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 tablets 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 25°C 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 3² 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.

Table 8: Regression output of R1 for 3² full factorial design

| Parameter     | Value   | Parameter | Value   |
|---------------|---------|-----------|---------|
| Sum of square | 1255.75 | Mean±SD   | 34.31±4.91 |
| Degree of freedom | 5 | CV %       | 10.39  |
| Mean square   | 251.15  | R²        | 0.9363  |
| Model F value | 10.40   | p value   | 0.0039  |

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%    |

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      | % Drug content       | 0.81±3.89     | 0.79±2.18      | 0.78±1.86     | 0.78±1.86     |
| 5      | % Drug release       | 98.43±0.62    | 98.07±0.28     | 97.48±0.21    | 96.76±0.42    |
| 6      | F² value             | 98.88±2.46    | 97.65±3.32     | 95.1±9.7      | 93.7±2.81     |
| 7      |                      | 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 $F$ 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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