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RESEARCH ARTICLE

# PREPARATION AND CHARACTERIZATION OF FAST DISNTEGRATING TABLETS OF HYDRALAZINE HYDROCHLORIDE USING DESIGN OF EXPERIMENT TECHNIQUE

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**ABSTRACT**

Since the dose accuracy and patient's compliance are important prerequisites for a long term treatment, there is a demand to develop a dosage form which can overcome difficulty in swallowing, inconvenience in administration while travelling, and increase patient's acceptability. The present work was undertaken to develop fast disintegrating tablet of Hydralazine hydrochloride which will offer desired characteristics and intended benefits in hypertension. A $3^2$ full-factorial experimental design was constructed to study the effect of type and concentration of superdisintegrant on disintegration time, wetting time and dispersion time. The tablets were prepared by direct compression technique. The ANOVA results confirmed that the studied response variables were strongly dependen on chosen factors ($p<0.05$). More than 90% of drug from optimized tablet was released within 5 minutes during in-vitro dissolution studies. The short term accelerated stability studies of selected formulation indicated that there was insignificant change in the drug content and percent drug released ($p<0.05$). It was concluded that FDT of hydralazine hydrochloride were formulated successfully.

**Key words:** Fast disintegrating tablets, optimization, superdisintigrants, dysphagia

## INTRODUCTION:

The common problem of all age groups is dysphagia, or difficulty in swallowing [1]. About 35% of the general population, as well as an additional 30–40% of elderly institutionalized patients and 18–22% of all persons in long-term care facilities suffer from dysphagia [2]. In one other study 50% of population is found to be suffering from this problem [3]. Geriatric, pediatric and traveling patients are most in need of easy swallowing dosage form as they have not ready access to water [4].

Chewable tablets which are intended to disintegrate in the mouth under the action of chewing suffer from disadvantage of perception of drug's taste and throat grittiness by patient. To overcome these problems, a new dosage form called as Fast disintegrating tablets (FDT) are developed. The FDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and/or quick disintegrating tablet. FDA classifies them as orally disintegrating tablets (ODT). According to FDA, ODT are the solid dosage forms containing medicinal substances which disintegrates rapidly, usually within a matter of sonds, when placed upon the tongue. The literature search points toward the increased interest in FDTs [5, 6, 7]. The advantages of FDTs are good stability, accurate dosing, easy manufacturing, small packaging size, and easy handling by patients [3, 8, 9, 10]. FDTs also have the advantages of liquid formulations, such as easy administration and no risk of suffocation. As the drug can be absorbed from buccal and pharyngeal regions, it reduces the first pass metabolism and enhances the bioavailability.

Hydralazine hydrochloride (Figure 1) is antihypertensive having phthalazinone hydrazone hydrochloride chemical group and has proved very important and effective drug for management of hypertension. It directly relaxes vascular smooth muscle to cause peripheral vasodilation therefore decreasing arterial blood pressure and peripheral vascular resistance. It has 30 to 40% bioavailability and $T_{max}$ is 1 to 2 hour. It has high protein binding. It is extensively metabolized



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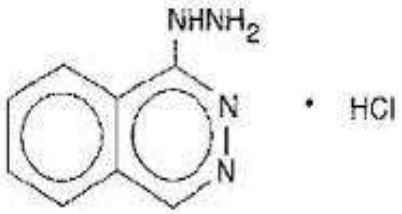


**Figure 1 structure of hydralazine hydrochloride**

in the liver and the metabolites are excreted in urine. Its elimination $t_{1/2}$ is 3 to 7 hour. Adverse effects associated with the use of hydralazine hydrochloride are facial flushing, palpitation, fluid retention, constipation and muscle cramps [11].

In the present study, an attempt was made to develop FDTs of hydralazine and to investigate the effects of physical and co-processed mixtures of disintegrants on the drug release profile.

## MATERIALS AND METHODS:

### MATERIALS:

Hydralazine hydrochloride was purchased from Magus Laboratories, Mohali. Microcrystalline cellulose (Avicel PH-102), mannitol (Pearlitol SD 200) was purchased from All Well Pharmaceutical Company, Chandigarh. Sodium starch glycolate and crosspovidone were purchased from Magus Laboratories, Mohali. All chemicals used were of chemical grade.

### PREPARATION OF CO PROCESSED SUPERDISINTEGRANTS GRANULES:

Crospovidone and sodium starch glycolate were mixed in different ratios. The mixture was added to isopropyl alcohol and was stirred on a magnetic stirrer at temperature 50- 60ºC. The stirring was continued till the most of isopropyl get evaporated. The wet coherent mass was passed through sieve (#40). The wet granules were dried in Tray dryer at temperature 60ºC for 20 minutes. The dried powder was again sifted through sieve (#60).

### PREPARATION OF TABLETS:

The tablets were prepared by direct compression method. A $3^2$ full-factorial experimental design was employed for selecting the optimum concentration of disintegrant. The concentration and the type of disintegrant were selected as independent variables. The composition of different formulation according to factorial design was given in Table 1. All the ingredients were weighed,

**Table 1: formulation according to factorial design level**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| **Hydralazine hydrochloride** | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| **Sodium starch glycolate** | **-1** | **-1** | **-1** | **0** | **0** | **0** | **+1** | **+1** | **+1** |
| **Crospovidone** | **-1** | **0** | **+1** | **-1** | **0** | **+1** | **-1** | **0** | **+1** |
| **Mannitol** | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| **Sodium Saccharine** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **MCC (Avicel PH 102)** | 99.5 | 98 | 95 | 95 | 96.5 | 95 | 96.5 | 95 | 93.5 |
| **Talc** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Lactose** | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |

co-grounded and mixed in a glass pestle motor. The resulting blend was evaluated for mass-volume relationship (bulk density, tapped density, Hausners ratio and compressibility index) and flow properties (angle of repose) [12, 13]. The mixture was compressed using a Lab press-I rotary tablet punching machine (Shakti rotary SLP-1) to produce convex shape tablets.

## EVALUATION OF TABLETS:

### Thickness:

The thickness of tablet was recorded using Vernier caliper. For each formulation, average of six tablets was calculated [14].

### Hardness:

For each batch, the hardness of 6 tablets was determined using Monsanto hardness tester [15].

### Uniformity of Content:

The average weight of ten randomly selected tablets was calculated and then, these tablets were powdered using glass mortar pestle. The powder equivalent to 25 mg of Hydralazine hydrochloride was weighed and dissolved in 100 ml of phosphate buffer (pH 7.2). The solution was filtered. An aliquot (1.0 ml) of solution was diluted appropriately with phosphate buffer (pH 7.2) and absorbance was measured at 272 nm [16].



 

**Uniformity of Weight:**

Twenty tablets were weighed individually and the percent deviation of each tablet from average weight was calculated using equation 1.

$$\text{Percent deviaion} = \frac{\text{Average weight of tablet} - \text{individual weight of tablet}}{\text{Average weight of tablet}} \times 100$$

**Friability:**

Friability of the tablets was determined using Roche Friability apparatus. The weighed amount of tablets was placed in the fibrilator which was then operated for 100rpm. The tablets were dusted and reweighed. The % friability is calculated using equation 2 [15].

$$\% F = \frac{(W_o - W) \times 100}{W_o}$$

where, $W_0$ is initial weight of the tablets before the test and W is the weight of the tablets after test.

**Disintegration Test:**

Disintegration of mouth dissolving tablet occurs in the mouth with the help of saliva. No tablet disintegration test was found in USP, BP and IP to simulate *in vivo* conditions. Therefore, a modified method was used to determine disintegration time. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed above the sieve (Figure 2). To determine disintegration time, 6ml of phosphate buffer (pH 7.2), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on sieve and the whole assembly was placed on the shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet [14].

**Figure 2: experimental set up for determination of disintegration time**

**Wetting Time:**

For determining the tablet wetting time, a piece of tissue paper (12 cm × 10.75 cm) folded twice was placed in a small petridish (ID = 6.5 cm) containing 6 ml of phosphate buffer (pH 7.2) (Figure 3). A tablet was put on the paper and the time for the complete wetting was measured [17].

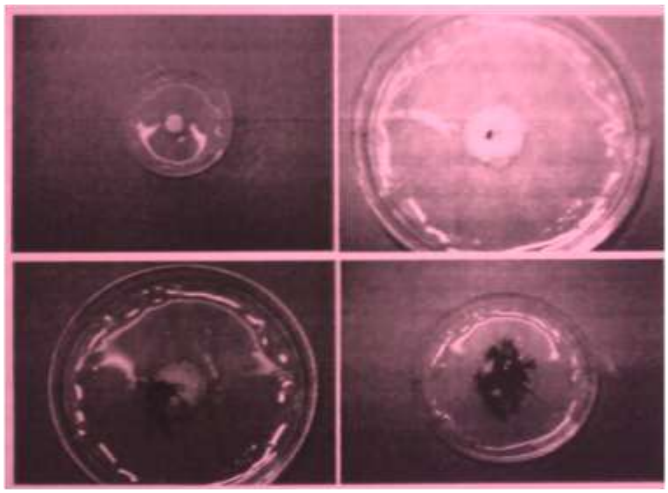

**Figure 3: schematic representation of wetting time determination**

**In-vitro Dispersion Time:**

In-vitro dispersion time was measured by dropping a tablet in a glass cylinder containing 6 ml of phosphate buffer (pH 7.2) [16].

**IN-VITRO DISSOLUTION STUDY:**

The drug release characteristics were studied using USP 2 dissolution apparatus. The phosphate buffer (pH 7.2, 900 ml) was used as dissolution media and the temperature was maintained at 37±0.5°C. The paddle was rotated at 50 rpm. After specified time intervals, the samples were withdrawn, filtered and measured spectrophotometrically at 272 nm. The data obtained was fitted in various mathematical models to know about release kinetics.

**ACCELERATED STABILITY STUDIES:**

In order to access the long term stability and storage condition, the optimized tablets of drug were packed in wide mouth air tight glass container and stored at (40± 2°C/75±5% RH) for a period of 3 months. The samples were withdrawn at predetermined time intervals (0, 30,



 

60 and 90 days) and characterized for parameters like physical appearance, drug content and dissolution profile.

**RESULT AND DISCUSSION:**

**PREPARATION OF FDT:**

The drug and excipients were mixed and evaluated for flow characterstics. Table 2 enlisted the result of evaluation of F1 to F2 formulation blends. The bulk density for all formulation blends varied between 0.31 ± 0.002 - 0.42 ± 0.002 g/cc. The tapped density was found in the range of 0.41 ± 0.003 - 0.43 ± 0.005 g/cc. The calculated Hausner's ratio for all blends was less than 1.25. So, the blends had good flow characteristics [12, 13]. Similarly, the values of compressibility index (less than 16%) and angle of repose (25º- 27º) revealed free flow behavior of mixture [18].

**Table 2: characterization of blends of different formulations**

| Parameter→ Formulation ↓ | Bulk Density (g/cc) (Mean ± SD) (n=6) | Tapped Density (g/cc) (Mean ± SD) (n=6) | Hausners Ratio (Mean ± SD) (n=6) | Compressibility Index (%)(Mean ± SD) (n=6) | Angle of Repose (θ) (Mean ± SD) (n=6) |
|---|---|---|---|---|---|
| **F1** | 0.391±0.001 | 0.420±0.002 | 1.07±0.002 | 6.601±0.001 | 23.27±0.114 |
| **F2** | 0.402±0.001 | 0.427±0.001 | 1.06±0.001 | 5.616±0.001 | 25.22±0.017 |
| **F3** | 0.393±0.002 | 0.413±0.002 | 1.05±0.001 | 4.551±0.002 | 27.27±0.052 |
| **F4** | 0.382±0.002 | 0.406±0.002 | 1.06±0.002 | 5.622±0.001 | 24.38±0.021 |
| **F5** | 0.396±0.001 | 0.427±0.001 | 1.07±0.001 | 6.793±0.001 | 25.94±0.021 |
| **F6** | 0.371±0.001 | 0.393±0.001 | 1.06±0.002 | 6.075±0.002 | 23.53±0.015 |
| **F7** | 0.403±0.002 | 0.433±0.001 | 1.07±0.001 | 6.423±0.002 | 26.53±0.018 |
| **F8** | 0.383±0.001 | 0.404±0.001 | 1.06±0.001 | 5.433±0.001 | 26.30±0.010 |
| **F9** | 0.385±0.001 | 0.417±0.001 | 1.08±0.001 | 7.602±0.001 | 25.20±0.016 |

**OPTIMIZATION OF TABLETS:**

The evaluation results of tablets, prepared according to $3^2$ Factorial design, was listed in Table 3. All the prepared tablets were found to be different in terms of disintegration, dispersion and wetting time (Table 4). A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The values of $r^2$ were quite high for all responses i.e. ranging from 0.917 to 0.962, so polynomial equations form excellent fit to the experimental data and are highly statistically valid. The analysis of variance (ANOVA) was performed to identify insignificant factors. The results clearly indicated that response variables are significantly dependent on chosen factors ($p<0.05$). So, the model reduction was not required. The analysis of

**Table 3 evaluation of tablets**

| Parameters→ Formulation ↓ | Thickness (mm) (Mean ± SD) (n=6) | Weight (mg) (Mean ± SD) (n=6) | Friability (%) (Mean ± SD) (n=6) | Hardness (kg/cm$^2$) (Mean ± SD) (n=6) |
|---|---|---|---|---|
| **F1** | 2.89±0.02 | 149.61±0.001 | 0.38±0.02 | 3.18±0.33 |
| **F2** | 2.93±0.02 | 152.03±0.002 | 0.44±0.02 | 3.25±0.10 |
| **F3** | 2.94±0.03 | 150.00±0.002 | 0.50±0.01 | 3.19±0.40 |
| **F4** | 2.92±0.02 | 148.96±0.002 | 0.67±0.81 | 3.25±0.11 |
| **F5** | 2.94±0.02 | 151.02±0.002 | 0.29±0.02 | 3.16±0.11 |
| **F6** | 2.90±0.01 | 150.47±0.001 | 0.63±0.02 | 3.19±0.11 |
| **F7** | 2.95±0.02 | 150.01±0.001 | 0.72±0.02 | 3.18±0.13 |
| **F8** | 2.92±0.01 | 149.91±0.001 | 0.27±0.01 | 3.24±0.14 |
| **F9** | 2.93±0.01 | 151.10±0.001 | 0.58±0.02 | 3.21±0.06 |

**Table 4 values of response variables of optimization studies**



 

| Parameters→ Formulation ↓ | Disintegration Time (s) (Mean ± SD) (n=6) | Wetting Time (s) (Mean ± SD) (n=6) | Dispersion Time (s) (Mean ± SD) (n=6) | Drug content (%) (Mean ± SD) (n=6) |
|---|---|---|---|---|
| **F1** | 42±0.68 | 34.10±0.06 | 56.42±0.23 | 96.02±0.21 |
| **F2** | 40±0.90 | 22.29±0.09 | 43.21±0.22 | 96.33±0.33 |
| **F3** | 39±0.81 | 31.32±0.04 | 55.43±0.27 | 96.04±0.33 |
| **F4** | 31±0.13 | 26.53±0.12 | 47.36±0.17 | 96.72±0.13 |
| **F5** | 39±0.11 | 16.13±0.07 | 39.94±0.86 | 96.05±0.56 |
| **F6** | 25±0.63 | 19.28±0.11 | 36.35±0.28 | 96.01±0.12 |
| **F7** | 26±0.45 | 14.22±0.07 | 31.31±0.12 | 96.81±0.19 |
| **F8** | 18±0.72 | 15.29±0.14 | 24.47±0.31 | 96.42±0.26 |
| **F9** | 39±0.73 | 33.51±0.05 | 67.36±0.33 | 96.17±0.26 |

contour and response surface plot revealed that concentration of sodium starch glycolate had pronounced effect on studied response variables *viz.* disintegration, wetting and dispersion time. The desirable optimal region was selected using overlay plotting technique. In the optimum formulation, the sodium glycolate and crosspovidone was present in ratio 2.18:1.38.

**IN-VITRO DRUG RELEASE:**

More than 90 % of drug is released in less than 5 minutes from the optimized tablet. The drug release profile was shown in Figure 4. From the values of coefficient of correlation (Table 5), the drug release was found to follow first order release model [18].

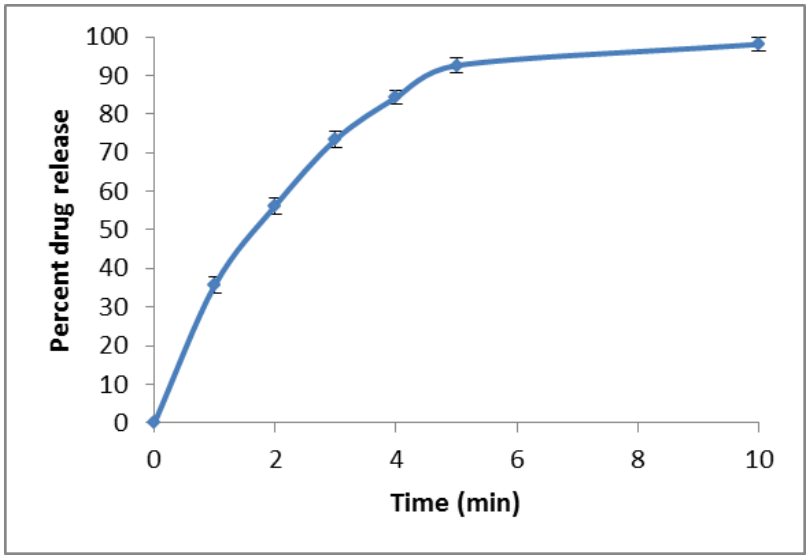


**Figure 4 drug release profile from optimized fast dissolving tablet**

**Table 5 coefficient of correlation and slope for different release model**

| Zero order | | First order | | Higuchi release | |
|---|---|---|---|---|---|
| $R^2$ | K | $R^2$ | K | $R^2$ | K |
| 0.784 | 7.981 | 0.9872 | 1.311 | 0.605 | 0.6519 |

**ACCELERATED STABILITY STUDIES:**

The results of accelerated stability studies were shown in Table 6. There was no significant change in physical appearance, percent friability and tablet weight. There was insignificant change in disintegration time and drug content ($p<0.05$). The dissolution studies had revealed that storage condition had little effect on the drug release. Therefore, the tablet can be stored at room temperature.



 

**Table 6: effect of storage condition on optimized formulation at accelerated storage condition (40+2ºC/75 ± 5% RH)**

| Time interval (Days) | Weight variation (mg) (Mean ± SD) (n=6) | Friability (%) (Mean ± SD) (n=6) | Hardness ($kg/cm^2$) (Mean ± SD) (n=6) | Disintegration Time (s) (Mean ± SD) (n=6) | Drug content (Mean ± SD) (n=6) | Drug Release (Mean ± SD) (n=6) |
|---|---|---|---|---|---|---|
| **0** | 150.35±0.01 | 0.50±0.01 | 3.21±0.12 | 30.66±0.49 | 96.28±0.23 | 98.10±0.35 |
| **15** | 152±0.93 | 0.52 ±0.26 | 0.591±0.01 | 35.5±0.59 | 96.40±0.11 | 98.11±0.20 |
| **30** | 152.04±0.92 | 0.51±0.10 | 0.596±0.02 | 35.5±0.54 | 96.41±0.57 | 98.15±0.33 |
| **45** | 152.1±0.86 | 0.53±0.21 | 0.601±0.02 | 35.3±0.59 | 96.18±0.01 | 98.19±0.63 |
| **60** | 151.98±0.75 | 0.56±0.20 | 0.602±0.02 | 35±0.21 | 96.15±0.06 | 98.12±0.18 |
| **75** | 152.03±1.03 | 0.58±0.10 | 0.602±0.02 | 35±0.23 | 96.12±0.13 | 98.10±0.58 |
| **90** | 152.01±1.05 | 0.51±0.20 | 0.602±0.01 | 35±0.89 | 96.10±0.08 | 98.13±0.36 |

## CONCLUSION:

The Hydralazine hydrochloride fast disintegrating tablets with commonly available excipients and techniques, was successfully developed.

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