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# FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF FLUNARIZINE DIHYDROCHLORIDE BY USING SUPER DISINTEGRANTS

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## ABSTRACT

Mouth dissolving tablet is the fast growing and highly accepted drug delivery system, Convenience of self administration, compactness and easy manufacturing. This study was aimed at development of Flunarizine dihydrochloride mouth dissolving tablets which can disintegrate or dissolve rapidly once placed in the oral cavity. Flunarizine is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity. It is effective in the prophylaxis of migraine, occlusive peripheral vascular disease. The tablet was prepared with the three super disintegrants cross carmellose sodium, cross povidone and sodium starch glycolate at different concentrations. The blend was evaluated for angle of repose, bulkdensity, tapped density, compressibility index and hausner's ratio. The tablets were evaluated for thickness, hardness, friability, weight variation, content uniformity test, wetting time and water absorption ratio, in-vitro dispersion time, dissolution study and FTIR studies. Twelve formulations were for prepared and compare. The optimum formulation was chosen and their predicted results were found to be in close agreement with experimental finding.

**KEYWORDS**: Mouth dissolving tablets, Super disintegrants, Flunarizine dihydrochloride.

## INTRODUCTION

Mouth dissolving tablets are gaining importance as a potential drug delivery system. This dosage form dissolves and disintegrates in the oral cavity within minutes without need of water or chewing[1].Mouth dissolving tablets are also called as oral dispersable tablets, oral disintegrating, quick dissolving, fast melting, rapid disintegrating, freeze dried wafers, porous tablets and rapimelts[2].The benefits in terms of patient compliance such as rapid onset of action, increased bioavailability, rapid absorption through pre-gastric absorption of drugs from the mouth and good stability[3].

Flunarizine is a selective calcium entry blocker with calmodulin binding properties and histamine H1 blocking activity. It is effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central and peripheral origin and adjuvant in the therapy of epilepsy. Kuchekar et al and badhan studied on mouth dissolving tablets by direct compression method and using disintegrants like sodium starch glycolate,carboxy methyl cellulose sodium and agar[3]. Flunarizine dihydrochloride mouth dissolving tablets are prepared by direct compression method using three super disintegrants like sodium starch glycolate, cross carmellose sodium and cross povidone. Twelve formulations were prepared and compare with super disintegrants at different concentrations and effect on the in-vitro dispersion time, in-vitro drug release and FTIR studies was observed from these twelve formulations the optimum formulations were selected.

## MATERIALS AND METHODS

Flunarizine hydrochloride was obtained as a gift sample from madra's pharmaceuticals, Chennai, India. Sodium starch glycolate, cross carmellose sodium was obtained as gift sample from AET laboratories, Hyderabad, India. Cross povidone gift sample from LOBA chemic pvt.ltd, Mumbai, India. All other chemicals and reagents were of pharmacopoeial grade.

### Preparation of Flunarizine Dihydrochloride Tablets

Tablets are prepared by direct compression method. Accurately drug was weighed to this super disintegrants. Micro crystalline cellulose, mannitol, aspartame, aerosil, magnesium stearate are added, mixed properly and passed through sieve no.120. Tablets are punched by using 8mm flat punches by rotary tablet compression machine. Each formulation of F1 to F12 was composed of drug, various proportions of super disintegrants and excipients. As shown in table I.

### Characterization of mouth dissolving tablets

### Evaluation of blends

### Angle of repose:

Angle of repose was determined using funnel method [4].The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap(r) was measured and the angle of repose (q) was calculated using the formula.

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

### Bulk density:

Apparent bulk density ($p_b$) was determined by pouring the blend in to a graduated cylinder. The bulk volume ($V_b$) and weight of the powder (M) was calculated using the formula [4].

$$p_b = M / V_b$$

### Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume ($V_t$) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density ($\rho_t$)[4] was calculated using formula.

$$\rho_t = M / V_t$$

### Compressibility index:

The simplest way for measuring of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I)[4] which is calculated as follows .

$$I = V_0 - V_t / V_O \times 100$$

Where, Vo is the bulk volume and Vt is tapped volume. The value below 15% indicates a powder with usually give rise to good flow characteristics, where as above 25% indicates poor flowability.

### Hausner's ratio:

Hausner's ratio[5] is an indirect index of ease of powder flow. It is calculated by the following method

$$\text{Hausner ratio} = \rho_t / \rho_d$$

Where $\rho_t$ is tapped density and $\rho_d$ is bulkdensity lower hausner ratio (<1.25) indicates better flow properties than higher ones[6] (>1.25).

### Evaluation of Tablets

### Weight variation:

Twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and was compared with average weight[4].

### Friability:

Friability of the tablets was determining using Roche friabilator. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6inches in each revolution. Preweighed sample of tablets was placed in the

friabilator and were subjected to 100 revolutions. Tablets were deducted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$F = (1-W_0/W)\ 100$$

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

**Hardness:**

Hardness was measured using Monsanto tablet hardness tester[4].

**Thickness:**

10 tablets were taken from each formulation and their thickness was measured using digital Vernier calipers.

**Wetting time and water absorption ratio:**

The method reported by Yunixia et al [7] was followed to measure the tablet wetting time. A piece of tissue paper (12cm×10.75cm) folded twice was placed in a petridish containing 6ml of simulated saliva pH [8], a tablet was kept on the paper , and time required for complete wetting was measured. The wetted tablet was weighed. Water absorption ratio(R) was determined using following equation

$$R = 100 \times (W_a-W_b)/ W_b$$

Were $W_b$ is weight of tablet before water absorption and $W_a$ is weight of tablet after water absorbtion.

**In-vitro dispersion time:**

Tablets were placed in 10 ml beaker containing 6ml of 0.1 N HCL and time taken for complete dispersion of tablet was observed[9].

**Dissolution study of 0.1N HCL:**

Dissolution rate was studied by using USP type II apparatus at 50 rpm 0.1N HCL, 900ml was used as dissolution medium, Temperature $37^0$ + (-) $0.5^0$c. Absorption of filtered solution was checked by UV Spectroscopy at 254 nm and drug content was determined from standard calibration curve

**Fourier transforms infra red spectroscopy (FTIR):**

FTIR studies were performed on drug, excipient and the optimized formulation using (Shimadzu FTIR). The sample was analyzed between wave numbers 4000 and 400 $cm^{-1}$.

## RESULTS AND DISCUSSION

Twelve formulations of flunarizine dihydrochloride were prepared by direct compression method with varying concentration of three super disintegrants sodium starch glycolate, cross povidone, cross carmellose sodium. Taste masking was done by flavours and sweeteners and microcrystalline cellulose was used as diluents. The prepared tablets were evaluated for various parameters. The powder blend was evaluated the physical properties such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio Table 2. The angle of repose between $25^0$ to $32^0$ ,it show the possible flowability, the percentage compressibility index and hausner's ratio are within the limits of all the formulation were shown in the table 2.

The prepared tablets were evaluated for hardness, friability, thickness, weight variation, content uniformity were shown in table 3. Since the powder material was free flowing, tablets were obtained of uniform weight due to die fill, with acceptable weight variations as per specifications. The drug content was found in the range of 96% to 103% were acceptable limits and the hardness of the tablets between 2-2.6kg/$cm^2$ table 3. Friability of the tablet was found below 1%indicating a good mechanical resistance of tablets table 3.

The wetting time was determined for all the formulation from this F6 shows very less wetting time 34 seconds, this indicate quicker disintegration time of the tablets.

In-vitro dispersion test was done for all the formulation. The tablet disintegration was affected by the wicking and swelling of the disintegrants from the 12 formulations F6 shown less disintegration time 45 seconds when compared with others super disintegrants. Water absorption ratio for F6 is 84.1%, it show good water absorption capacity table III.

In-vitro drug release studies of prepared tablets F1 to F12 using different super disintegrating agents by different concentrations. The maximum drug release for the formulation F1, F2, F3 and F4 using different concentration of cross carmellose sodium. The drug release 95.4%, 95.4%, 96.4%, 90.1% at the end of the 15 minutes table 4. Fig.1 Respectively for the formulations F5, F6, F7 and F8 using cross povidone at different concentrations. The drug release was 96.2%, 95.4%, 95.6% and 95.9% at the end of 15 minutes. Shown in table 5, fig 2. Respectively for the formulation F9, F10, F11 and F12 using sodium starch glycolate at different concentrations. The drug release was found to be 61.9%, 65.35%, 86.1% and 89.2% at end of 15minutes table6, fig 3, from these three different super disintegrating agent cross povidone had shown good drug release.

The graph were plotted cubic root of 100-cubic root of drug remained vs time , the drug release for the optimized formulation F6 according to hixon and crowell equation.fig 4 it shows Hixons Crowell mechanisms.

FTIR spectra of the drug, excipients and optimized formulation were recorded in range of 4000-400$cm^{-1}$.in the optimized formulation F6 shows presence of all the characteristics peaks of the Flunarizine dihydrochloride indicates lack of any strong interaction between the drug and the excipients.

## CONCLUSION

In overall results suggest that a 6% super disintegrating agent cross povidone F6 formulation is suitable for the preparation of Flunarizine dihydrochloride. Mouth dissolving tablets show fast in-vitro dispersion wetting time is below one minute, and FTIR studies for optimized formulation there is lack of interaction between the drug and the excipients.

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**Table 1: Composition of different batches of Mouth dissolving tablets of Flunarizine dihydrochloride**

| **Ingredients** | **$F_1$ (mg)** | **$F_2$ (mg)** | **$F_3$ (mg)** | **$F_4$ (mg)** | **$F_5$ (mg)** | **$F_6$ (mg)** | **$F_7$ (mg)** | **$F_8$ (mg)** | **$F_9$ (mg)** | **$F_{10}$ (mg)** | **$F_{11}$ (mg)** | **$F_{12}$ (mg)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Cross carmellose sodium | 6 | 12 | 18 | 24 | _ | _ | _ | _ | _ | _ | _ | _ |
| Cross povidone | _ | _ | _ | _ | 6 | 12 | 18 | 24 | _ | _ | _ | _ |
| Sodium starch glycolate | _ | _ | _ | _ | _ | _ | _ | _ | 6 | 12 | 18 | 24 |
| Aspartame | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 | 16 |
| Magnesium stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Micro crystalline cellulose | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 | 55 |
| Aerosol | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Mannitol | 94 | 88 | 82 | 76 | 94 | 88 | 82 | 76 | 94 | 88 | 82 | 76 |
| Total weight | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Table 2: Tablet blend evaluation tests**

| Formulations | Angle of Repose | Bulk Density | Tapped Density | Percent Compressibility Index | Hausner Ratio |
|---|---|---|---|---|---|
| $F_1$ | 27.8±0.04 | 0.30 | 0.37 | 18.9 | 1.23 |
| $F_2$ | 25.6±0.09 | 0.21 | 0.25 | 16.0 | 1.19 |
| $F_3$ | 25.9±0.02 | 0.22 | 0.25 | 12.3 | 1.13 |
| $F_4$ | 26.5±0.14 | 0.21 | 0.30 | 16.0 | 1.19 |
| $F_5$ | 25.2±0.08 | 0.25 | 0.30 | 16.6 | 1.20 |
| $F_6$ | 25.5±0.04 | 0.25 | 0.30 | 16.6 | 1.19 |
| $F_7$ | 28.5±0.04 | 0.21 | 0.25 | 16.0 | 1.16 |
| $F_8$ | 28.2±0.08 | 0.25 | 0.31 | 19.3 | 1.24 |
| $F_9$ | 28.5±0.02 | 0.22 | 0.25 | 12.8 | 1.13 |
| $F_{10}$ | 31.2±0.12 | 0.37 | 0.45 | 17.7 | 1.21 |
| $F_{11}$ | 30.9±0.08 | 0.21 | 0.25 | 16.0 | 1.19 |
| $F_{12}$ | 32.6±0.02 | 0.20 | 0.25 | 20.0 | 1.25 |

**Table 3: Prepared tablets evaluation tests**

| Formulations | Weight in mg | Hardness $Kg/cm^2$ | Friability % | Thickness (mm) | Wetting time(Seconds) | In-vitro dispersion time | Water absorption ratio |
|---|---|---|---|---|---|---|---|
| $F_1$ | 198.35±1.01 | 2.1 | 0.69 | 4.61± 0.02 | 42 ±0.72 | 65 ± 1.08 | 69 ± 0.92 |
| $F_2$ | 200.0 ±1.85 | 2.2 | 0.59 | 4.60 ± 0.03 | 51 ± 1.35 | 57 ± 1.04 | 77.3 ± 0.85 |
| $F_3$ | 200.8 ± 0.10 | 2.18 | 0.74 | 4.63 ± 0.06 | 58 ± 0.98 | 58 ± 0.89 | 74.6 ± 0.95 |
| $F_4$ | 199.2± 1.01 | 2.2 | 0.59 | 4.57 ± 0.01 | 54 ± 1.15 | 73 ± 0.54 | 74.6 ± 0.58 |
| $F_5$ | 205.9 ± 0.14 | 2.2 | 0.78 | 4.61 ± 0.03 | 43 ± 0.88 | 53 ± 1.14 | 77.3 ± 0.54 |
| $F_6$ | 201.3 ± 0.48 | 2.1 | 0.59 | 4.59 ± 0.05 | 34 ± 0.78 | 45 ± 0.68 | 84.1 ± 0.45 |
| $F_7$ | 200.9 ± 1.41 | 2.2 | 0.73 | 4.69 ± 0.02 | 39 ± 0.76 | 60 ± 1.29 | 77.3 ± 0.32 |
| $F_8$ | 197.6 ± 1.13 | 2.3 | 0.59 | 4.63 ± 0.02 | 43 ± 0.89 | 63 ±1.06 | 72 ± 0.45 |
| $F_9$ | 201.5 ± 1.73 | 2.1 | 0.74 | 4.64 ± 0.04 | 58 ± 0.98 | 249 ± 0.74 | 59.6 ± 0.65 |
| $F_{10}$ | 201.05 ± 0.76 | 2.2 | 0.58 | 4.69 ± 0.01 | 62 ± 0.95 | 261 ± 0.96 | 62.6 ± 0.64 |
| $F_{11}$ | 203.18 ± 0.35 | 2.2 | 0.58 | 4.7± 0.02 | 67 ± 0.86 | 266 ± 0.98 | 53.8 ± 0.75 |
| $F_{12}$ | 201.65 ± 0.76 | 2.1 | 0.64 | 4.66± 0.01 | 70 ± 0.95 | 269 ± 0.78 | 49 ± 0.68 |

**Table 4: In-vitro Drug Release Studies of Cross carmellose sodium**

| Time (min) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 2 | 58.8± 0.84 | 56.7±0.79 | 52.8±0.23 | 56.8 ± 0.59 |
| 5 | 64.2± 0.21 | 63.8±0.62 | 61.3±0.68 | 69.7 ± 0.22 |
| 7 | 75.3±1.26 | 78.3±0.33 | 72.8±0.34 | 75.6 ± 0.15 |
| 10 | 87.3± 0.69 | 84.2±0.46 | 88.3±0.68 | 84.3 ± 0.59 |
| 15 | 95.4±1.91 | 95.4±0.22 | 96.4±0.52 | 90.1 ± 0.39 |
| 30 | 94.8±1.01 | 94.7±0.19 | 93.8±0.22 | 95.2 ± 0.65 |
| 45 | 93.6±0.62 | 93.3±0.32 | 93.4±0.19 | 93.1 ± 0.58 |

**Table 5: In-vitro Drug Release of Cross povidone**

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| Time (Min) | F5 | F6 | F7 | F8 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 2 | 51.8± 0.54 | 61.4± 0.19 | 48.5± 0.22 | 54.8± 0.35 |
| 5 | 62.3± 0.84 | 78.6± 0.19 | 63.8±0.15 | 62.4± 0.12 |
| 7 | 76.5± 0.45 | 85.9± 0.10 | 72.3± 0.38 | 71.4± 0.45 |
| 10 | 87.6± 0.84 | 96.2± 0.14 | 80.9± 0.14 | 82.7± 0.62 |
| 15 | 96.2± 0.64 | 95.4± 0.29 | 95.6± 0.27 | 95.9± 0.84 |
| 30 | 93.2± 0.13 | 93.2± 0.22 | 94.2± 0.46 | 94.6± 0.54 |
| 45 | 91.6±0.41 | 91.6±0.41 | 92.6±0.72 | 94.1±0.38 |

**Table 6: In-vitro drug release of Sodium starch glycolate**

| Time (Min) | F9 | F10 | F11 | F12 |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 2 | 33.8± 0.12 | 32.7± 0.33 | 49.5± 0.41 | 42.5±0.45 |
| 5 | 38.3± 0.25 | 35.5±0.26 | 52.3± 0.35 | 55.6±0.17 |
| 7 | 41.2± 0.61 | 46.4± 0.42 | 61.3±0.74 | 69.8±0.53 |
| 10 | 55.4± 0.33 | 59.5± 0.43 | 75.1± 0.84 | 71.3±0.22 |
| 15 | 61.9±0.21 | 65.3±0.12 | 86.1±0.61 | 89.2±0.18 |
| 30 | 72.6± 0.17 | 76.8± 0.24 | 94.2± 0.12 | 96.2±0.63 |
| 45 | 85.3±0.38 | 89.2±0.17 | 92.6±0.42 | 94.6±0.34 |

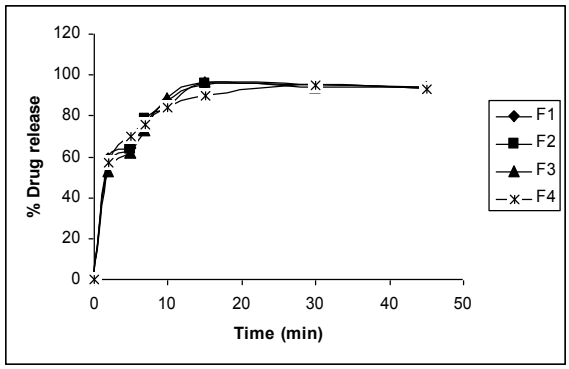


**Figure 1: In-Vitro Drug Release Studies of Prepared Tablets at Different Concentrations of cross carmellose sodium**

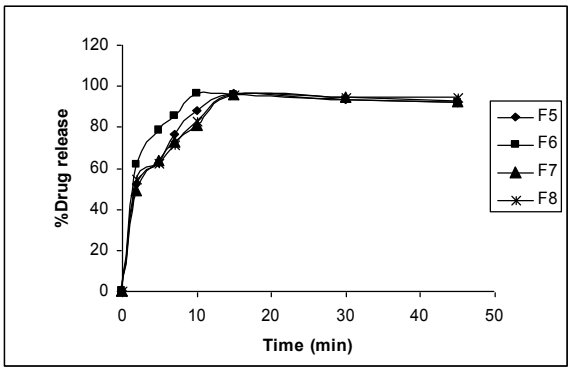


**Figure 2: In-vitro Drug Release at different concentrations of cross povidone**

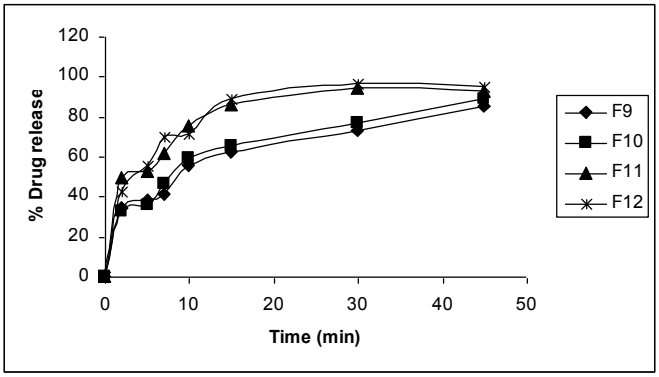


**Figure 3: In-vitro Drug Release at different concentrations of SSG**

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