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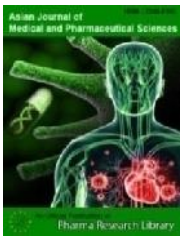

Research Article **Open Access**

Formulation Evaluation of Flunarizine Oro dispersible tablets

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A B S T R A C T

The present dissertation work is an attempt to select the best possible diluent- disintegrant combination to formulate rapidly disintegrating tablets of Flunarizine, which disintegrates in matter of seconds in the oral cavity, thereby reducing the first-pass metabolism and the time of onset of pharmacological action. Crospovidone, Croscarmellose sodium and Sodium starch glycolate were used as super-disintegrants. Avicel was used as diluent. Aspartame was used as a sweetening agent. Magnesium stearate and Aerosil were used as lubricant and glidant respectively. Aqueous Wet-granulation method was employed to formulate the tablets, because direct compression showed tablet defects like capping and poor flow of powder blend. The precompression parameters like bulk density, tapped density, Carr's index and angle of repose were determined. All the 9 formulations showed acceptable flow properties. The postcompression parameters of the tablet like the hardness, thickness, friability and weight variation, disintegration time, wetting time, and *Invitro* release were carried out and the values were found to be within IP limits. The percentage drug content of all the tablets was found to be between 92.55 % and 99.34 % of Flunarizine, which was within the acceptable limits. From the data obtained, it is observed that amongst the various combinations of diluents and disintegrants used in the study, tablets that were formulated (wet granulation) using Crospovidone (3.33%), Croscarmellose sodium and sodium starch glycolate (each 0.83%) exhibited quicker disintegration of tablets than compared to those other combination of disintegrants in different concentration. The effectiveness of super-disintegrants was in order of CP>CCS>SSG.

Keywords: Flunarizine, Croscarmellose sodium, sodium starch glycolate, Carr's index

A R T I C L E I N F O

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1. Introduction

The Center for Drug Evaluation and Research defines ODT as "a solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed under the tongue [1]. According to the US Food and Drug Administration Center for Drug Evaluation and Research (CDER) defines an orally disintegrating tablet as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.

The European Pharmacopoeia however defines a similar term, *oro disperse*, as a tablet that can be place in the mouth where it disperses rapidly before swallowing. Oral routes of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly the patient compliance. The most popular solid dosage forms are being tablets and capsules; one important drawback of this dosage forms for some patients, is the difficulty to swallow. Drinking water plays an important role in the swallowing of oral dosage form [2, 3]. Fast dissolving tablets are those when put on tongue disintegrate instantaneously releasing the drug which dissolve or disperses in the saliva. The faster the drug into solution, quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablets dosage form.

The target of these new oral dissolving/disintegrating dosage forms have generally been pediatric, geriatric, bedridden and developmentally disabled patients and also patients with persistent nausea, who are in traveling, or who have little or no access to water are also good candidates for ODTs. The major advantage of the ODT formulation is that it combines the advantages of both liquid and conventional tablet formulations, and also offering advantages over both traditional dosage forms. It provides the convenience of a tablet formulation, and also allowing the ease of swallowing provided by the liquid formulation. ODTs allow the luxury of much more accurate dosing than primary alternate, oral liquid [4]. In the present study Flunarizine which is a calcium channel antagonist is used as a model for the development of oral disintegrating tablets. Flunarizine is effective in prophylaxis of migraine and as an adjuvant in the therapy of epilepsy.

2. Experimental

Flunarizine(Natco Laboratories, Hyderabad), Crospovidone (ISP pharmaceuticals ISP pharmaceuticals), CCS (S D Fine chemicals limited, Mumbai), SSG (DFE Pharma, Germany), MCC (Nihar traders Pvt Ltd), Magnesium Stearate (Himedia Laboratories), Talc (SD fine chemicals Mumbai), Potassium dihydrogen Orthophosphate purified (S D Fine chemicals limited, Mumbai), Sodium hydroxide Pellets (Finar chemicals limited, Ahmedabad).

Preparation of Flunarizine orodispersible tablets by direct compression method: Different formulations of Flunarizine orodispersible tablets were designed to be prepared by direct compression technique using three super disintegrants. Super disintegrants were varied with 2 different concentrations (i.e.,3,5, respectively) keeping all other ingredients constant [5]. Composition is shown in Table 1.

Preparation of Flunarizine orodispersible tablets by wet granulation method

- Drug, super disintegrants, Microcrystalline cellulose were accurately weighed and mixed in a glass mortar for 15 minutes.
- The powder was mixed with binder and wet mass was screened through a 40-mesh screen to get uniform size particles.
- The obtained granules were lubricated with Talc and aerosil was added and mixing was continued for further 5 minutes.

The resultant mixture was compressed into tablets by using 6mm round flat faced punch of rotary tabletting machine. Compression force was kept.

2.3. Pre compression studies of Flunarizine Oro dispersible tablets [7]

The powder blend was subjected for the following studies

- Angle of repose
- Bulk density
- Tapped density
- Carr's index
- Hausner's ratio

2.3.1. Angle of repose

The angle of repose of powders was determined by the funnel method. Accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powders. The powders were allowed to pass through the funnel freely onto the surface. The diameter and height of the powder cone was measured and angle of repose was calculated by using the given formula. The results were shown in Table 3.

$$\tan\theta = \frac{h}{r}$$

Where, **h** = height of the powder cone
r = radius of the powder cone

2.3.2. Bulk density and tapped density

A quantity of 4gms of powder from each formula was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was tapped continuously until no further change in volume was observed. Then bulk density (BD) and tapped density (TD) were calculated by using the given formula. The results were shown in Table 3.

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

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

2.3.3. Carr's index

The Compressibility of the powder blend was determined by Carr's compressibility index. It is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple test to evaluate the bulk density and tapped density of a powder and the rate at which it is packed. The formula for carr's Index is given below. The results were shown in Table 3.

$$\text{Carr's index}\,(\%) = \frac{\text{TD} - \text{BD}}{\text{TD}} \times 100$$

2.3.4. Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. It is calculated by using the given formula. The results were shown in Table 3.

$$\text{Hausner's ratio} = \frac{\text{TD}}{\text{BD}}$$

2.4. Post compression studies of Flunarizine Oro dispersible tablets [8]

2.4.1. Thickness

Tablet thickness can be measured using digital vernier calipers. 3 tablets were taken and their thickness was measured and the average thickness for each tablet was calculated. The results were shown in Table 4.

2.4.2. Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of mouth dissolve tablets because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using monsanto hardness tester. The results were shown in Table 4.

2.4.3. Friability test

Friability of the tablets was determined using Roche friability. This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre-weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. Conventional tablets that lose less than 1% of their weight are acceptable. The results were shown in Table 4.

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

2.4.4. Weight variation

The weight variation test is done by weighing 10 tablets individually, calculating average weight and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit. The results were shown in Table 4.

$$\%\ \text{Weight variation} = \frac{\text{Average weight} - \text{Initial weight}}{\text{Average weight}} \times 100$$

2.5. Evaluation of Flunarizine Oro dispersible tablets

2.5.1. Drug Content estimation:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Four tablets were weighed and crushed in the mortar. The powder equivalent to 1.25 mg of the drug were weighed and dissolved in 100ml phosphate buffer pH 6.8 to give a concentration of 12.5 µg/ml. 2ml of this solution was taken and diluted to 10ml to give a concentration of 2.5µg/ml. The absorbance of the prepared solution was measured at 308nm using UV Visible spectrophotometer [9].The results were shown in Table 4.

2.5.2. Disintegration test

It is time taken by the tablet to breakup into smaller particles. The disintegration test is carried out in an apparatus containing a basket rack assembly with six glass tubes with the bottom containing a 10 mesh sieve. The basket is set a frequency of 28-32 cycles per minute in a medium of 900 ml which is maintained at 37 ± 2^{o} C. The tablets were placed in the tubes and the time required per complete passage of tablet particles through 10 mesh sieve was considered as disintegration time of tablet [10].The results were shown in Table 4.

2.5.3. Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of simulated salivary fluid of p^{H} 6.8 containing a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. Three tablets from each formulation were selected randomly and the average wetting time was determined [11]. The results were shown in Table 8.

2.5.3. *In-Vitro* Dissolution Studies

Method:

Dissolution test was carried out by using USP type II apparatus. The paddle was rotated at 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900ml) and was maintained at 35 ± 1^{0}C. Samples of 5ml were withdrawn at predetermined intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the drug at 308 nm by using ultra violet double beam spectrophotometer. Each dissolution study was performed for three times and mean values were taken [12].The results were shown in Table 8 and Figure 1-3.

3. Results and Discussion

In present investigation attempt was made to prepare dispersible tablet formulation of Flunarizine using superdisintegrants by direct compression. In preliminary study, different batches were prepared as per the composition given in Table 1. All the batches were evaluated as per the standard evaluation parameter. The powder flow property in batch T-1 is very poor and tablet is show the defect of capping. In batch T-2 flow is slightly improved but it's still poor and capping problem is still continue. In batch T-3 still flow property is not improved.

Then was made to prepare dispersible tablet formulation of Flunarizine using superdisintegrant by wet granulation to improve flow property and remove capping. In preliminary study, different batches were prepared as per the composition given in Table 2.

The values for angle of repose were found in the range of 26.78°-29.34°. Bulk densities and tapped densities of various formulations were found to be in the range of 0.41±0.006 to 0.60±0.007 (gm/cc) and 0.60±0.030 to 0.68±0.003 (gm/cc) respectively. Carr's index of the prepared blends fall in the range of 13.06% to 18.18%.The Hausner's ratio fall in range of 1.16 to 1.22. From the result it was concluded that the powder blends had good flow properties and these can be used for tablet manufacture.

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet and was shown in the Table 4. The average weight of the tablet is approximately in range of 101 to 106 mg, so the permissible limit is ±10 %. The results of the test showed that, the tablet weights were within the pharmacopoeia limit. Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the datawas shown in Table 4.

The results showed that the hardness of the tablets is in range of 2.71 to 2.81 kg/cm^2,which was within IP limits. Thickness of three tablets of each batch was checked by using Vernier Caliper and data shown in Table 4. The result showed that thickness of the tablet is raging from 2.72 to 3.11.Tablets of each batch were evaluated for percentage friability and the data's were shown in the Table 4. The average friability of all the formulations lies in the range of 0.341 to 0.613 % which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content was performed for the prepared formulations. From the assay studies it was concluded that all the formulations were showing the %drug content values within 92.55 -99.34%.The average wetting time of all the formulations was obtained in the range of 98-100 seconds as shown in the Table 5. The formulation F3showed maximum wetting time of 103 seconds and the formulation F9 had showed minimum wetting time of 90 seconds. On comparing superdisintegrants, the formulation containing SSG take more wetting time than CCS and Crospovidone. Wetting is related to the inner structure of the tablets and hydrophobicity of the components. This may be due to the fact that SSG is disintegrated by swelling mechanism leading to longer wetting time.

Crospovidone and CCS perform their disintegration by wicking through capillary action and fibrous structure respectively with minimum gelling. Tablets of each batch were evaluated for in vitro disintegration time. The results showed that the disintegration time of prepared tablets were in the range of 3.6 to 6 seconds. These trials indicated that amongst the disintegrants used, Crospovidone and CCS were better disintegrants to formulate fast dissolving tablets of Flunarizine than Sodium starch glycolate. Tablets were evaluated for *in vitro* dissolution studies in acid buffer (pH-1.2) and the results were shown in the Table 6 and Fig.1-3.Among the various formulations tablets of batch F8 prepared CCS and crospovidone showed 98.17release of drug within 30 min.

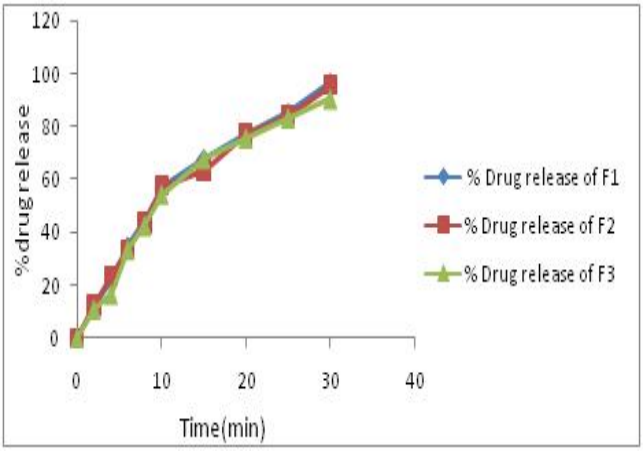

Figure 1: *In-vitro* dissolution profile of formulation F1-F3

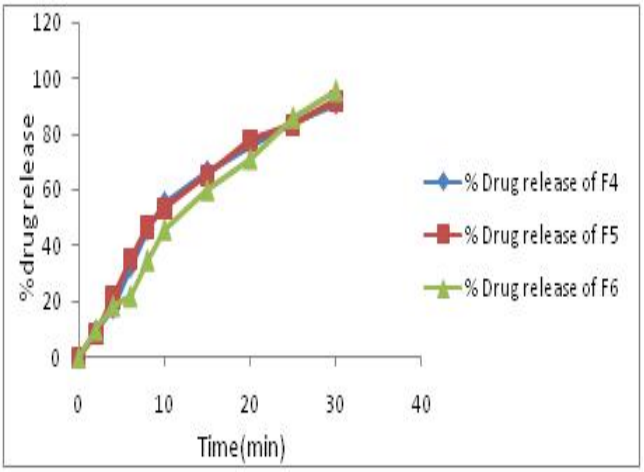

Figure 2: *In-vitro* dissolution profile of formulation F4-F6

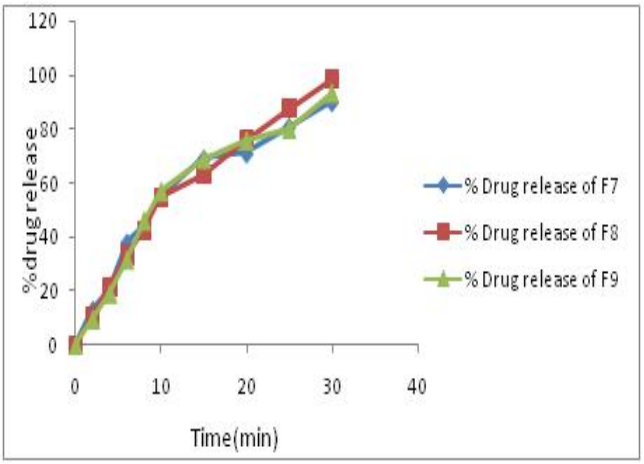

Figure 3: *In-vitro* dissolution profile of formulation F7-F9

Table 1: Composition of Flunarizine orodispersible tablets by direct compression method

Super disintegrant used	Concentration (%)	Formulation code
Primellose (CCS)	3	T1
Primogel (SSG)	3	T2
PolyplasdoneXL-10 (Crospovidone)	3	T3

Table 2: Composition of Flunarizine orodispersible tablets by wet granulation method

Materials (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flunarizine	5	5	5	5	5	5	5	5	5
Primellose (CCS)	7.5	12.5	-	-	-	-	7.5	7.5	-
Polyplasdone XL-10 (Crospovidone)	-	-	-	-	7.5	12.5	-	12.5	7.5
Primogel (SSG)	-	-	7.5	12.5	-	-	12.5	-	12.5
Aerosil	5	5	5	5	5	5	5	5	5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aspartame	5	5	5	5	5	5	5	5	5
Starch	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Avicel pH 102	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
Total weight of tablet	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

Table 3: Pre-compressional parameters of powder blend

Formulation Code	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner's ratio	Angle of Repose(Θ)
F1	0.46±0.006	0.66±0.002	18.18	1.22	27.91±0.890
F2	0.47±0.006	0.66±0.010	14.64	1.17	28.23±0.680
F3	0.60±0.007	0.68±0.003	13.79	1.16	29.34±0.680
F4	0.46±0.003	0.66±0.006	16.36	1.19	26.71±0.260
F6	0.60±0.007	0.68±0.003	13.79	1.16	29.34±0.680
F6	0.47±0.006	0.66±0.010	14.64	1.17	28.23±0.680
F7	0.60±0.007	0.68±0.003	13.79	1.16	29.34±0.680
F8	0.41±0.006	0.60±0.030	18	1.21	26.78±0.410
F9	0.41±0.006	0.60±0.030	18	1.21	26.78±0.410

Table 4: Post-compressional parameters of tablets

Formulation Code	Weight variation(mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	103±1	2.76±0.01	6.12±0.01	0.420
F2	104±2	2.74±0.04	6.14±0.02	0.341
F3	101±1	2.71±0.01	6.01±0.01	0.363
F4	104±2	2.80±0.06	6.03±0.03	0.661
F6	106±3	2.81±0.04	6.04±0.04	0.482
F6	104±1	2.74±0.06	6.09±0.06	0.613
F7	99±1	2.76±0.03	6.11±0.03	0.412
F8	100±2	2.71±0.04	6.09±0.06	0.432
F9	100±3	2.73±0.03	6.03±0.02	0.612

Table 5: Evaluation of tablets

Formulation Code	Disintegration Time (sec)	Drug content (%)	Wetting time (sec)
F1	4.6±0.7	97.23	99±0.12
F2	4.2±0.6	92.55	99±0.3
F3	3.6±0.6	98.16	103±0.1
F4	4.8±0.6	93.34	100±0.3
F6	3.8±0.4	98.16	99±0.6

F6	4.4±0.6	98.55	99±0.4
F7	6.0 ± 0.1	98.16	98±0.9
F8	3.6±0.2	99.34	99±0.1
F9	4.0±0.3	94.25	90±0.1

Table 6: *In-vitro* dissolution data of Flunarizine tablets

Time (min)	F1	F2	F3	F4	F6	F6	F7	F8	F9
2	11.09	12.66	10.87	9.78	8.76	9.90	12.89	10.21	9.64
4	21.89	23.66	16.64	17.66	21.64	18.64	19.83	21.30	19.01
6	34.67	33.64	33.46	32.46	36.46	21.90	37.89	33.34	31.67
8	43.98	43.66	42.66	46.78	46.76	34.89	43.87	42.32	46.93
10	66.76	67.64	64.46	66.67	63.46	46.86	64.70	64.66	66.86
16	67.87	63.34	67.89	66.76	66.46	69.90	69.03	62.89	68.96
20	76.86	77.12	76.76	76.23	77.87	71.09	71.02	76.76	76.67
26	86.12	84.43	83.34	84.66	83.21	86.87	80.91	87.64	80.09
30	96.67	96.67	90.66	90.87	91.89	96.47	90.07	98.17	93.40

4. Conclusion

In the present work, an attempt has been made to develop oro-disintegrating tablets of Flunarizine. The result of physical parameter of preliminary trials by direct compression showed poor flow property and capping also observed after compression. So aqueous wet-granulation method was utilized. The effectiveness of super-disintegrants was in order of CP >CCS > SSG. Formulation F8 was the optimized formulation having least disintegration time as well as other parameters was in acceptable range. The stability studies revealed that there was no significant change in tablet properties with aging at different storage conditions.

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