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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF IMMEDIATE RELEASE TABLETS OF FLUNARIZINE DI-HYDROCHLORIDE

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ABSTRACT

Immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action, economical and lead to better patient compliance. The aim of the present study was to prepare an immediate release tablet of Flunarizine di-Hydrochloride for the effective treatment of migraine. Tablets were formulated using various concentrations of croscarmellose sodium as superdisintegrant. A total eight formulations were prepared. All formulation were satisfactory for physical appearance including size, shape, thickness and other evaluation factors like weight uniformity, disintegration time, friability, hardness, drug content and in-vitro drug release. The tablet disintegration time was found to be less than 1min for the optimum batch. In vitro drug release was found maximum in F8 formulation which is 97.75±0.43 %. The optimized formulation also showed satisfactory size, shape, thickness and other evaluation factors like weight uniformity (177.77 ± 0.59 mg), disintegration time (37 ± 0.42 sec) , friability (less than 1%), hardness (3.0 kg/$m^{2)}$, drug content (100.21±0.99%).

Key words: *Immediate Release, Superdisintegrant, Flunarizine dihydrochloride, croscarmellose sodium.*

INTRODUCTION:

An immediate release dosage form allows a manufacturer to extend market exclusively, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques. Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance. They are also a tool for expanding markets, extending product life cycles and generating opportunities. Three major factors that govern the rate and extent of drug absorption of immediate release (IR) solid oral dosage forms:

1. Dissolution rate.
2. Solubility.
3. Intestinal permeability.

For IR dosage forms containing active pharmaceutical ingredients (APIs) showing high solubility, high intestinal permeability and rapid dissolution, a waiver from performing bioequivalence studies (biowaiver) can be scientifically justified. Flunarizine dihydrochloride is a calcium channel blockers and inhibits the influx of extracellular calcium through myocardial and vascular membrane pores by physically plugging the channel. The decrease in intracellular calcium inhibits the contractile processes of smooth muscle cells, causing dilation of the coronary and systemic arteries, increased oxygen delivery to the myocardial tissue, decreased total peripheral resistance, decreased systemic blood pressure, and decreased after load.

MATERIALS AND METHOD:

Flunarizine dihydrochloride was obtained as a gift sample from Akum's pharmaceuticals and all other ingredients starch, microcrystalline cellulose, lactose, polyvinyl pyrrolidone, colloidal silicon dioxide, crosscarmellose sodium, magnesium stearate, talc were of analytical grade.

Methods:

Preparation of Immediate Release Tablets by wet granulation method:

All ingredients were weighed accurately and sieved. Flunarizine dihydrochloride, starch, microcrystalline cellulose and lactose were mixed together. Sunset yellow was also added in dry mix to produce color. Required

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quantity of purified water and polyvinyl pyrrolidone was taken to make a paste like preparation with continuous stirring. Binder was poured in the dry mixed material and rapid mixture granulator was run and passed through sieve #8. The wet mass was dried in rapid dryer at 55-60ºC for the appropriate period of time till loss on drying was 2%. Sifted granules were transferred to the blender. Lubricant was added to the blender and run for 10 minutes.

Evaluation of Immediate Released Tablets:

Tablet Hardness:

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in kg/cm^2. And was found to be in 3-4.2kg/cm^2 range

Friability:

Friability is the measure of tablet strength. Electrolab EF-2 friabilator (USP) was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min, the tablets were weighed and the percentage loss in tablet weight was determined. % loss = [(Initial wt. of tablets – Final wt. of tablets)/ Initial wt. of tablets] ×100

Uniformity of Weight:

Twenty tablets were selected at random and the average weight was calculated. Weight Variation was calculated and was compared with I. P. standards.

Drug content uniformity of tablets:

10 tablets were taken and weighed. Average weight was determined. Tablet powder equivalent to 10 mg of FLU was transferred in 100 ml volumetric flask, dissolved and diluted up to mark with methanol. The solution was sonicated for 15minutes. The solution was filtered through Whatman filter paper no. 42 and first few drops of filtrate were discarded. 1ml of the above solution was pipetted out in 10ml volumetric flask and diluted to mark with simple distilled water. Absorbance of the resulting solution was measured at 253.0 nm against simple distilled water.

In vitro disintegration time:

The disintegration time for all formulations was carried out using tablet disintegration test apparatus. Six tablets were placed individually in each tube of disintegration test apparatus and discs were placed. The water was maintained at a temperature of 37° ± 2°C and time taken for the entire tablet to disintegrate completely was noted.

In vitro dissolution studies:

Dissolution of finished product was carried out by using dissolution test USP Method II for Flunarizine dihydrochloride.

Simulated gastric fluid medium: - 1.2 pH Buffer; 900 ml.
Apparatus- USP II: - 50 rpm.
Time: - 5, 10, 15, 30, 45, 60 minute.
Temperature: - 37 ±0.5

900ml of simulated gastric fluid medium was transferred in vessel and the medium was allowed to equilibrate to temp-37±.5ºc. one tablet in was placed in each vessel and the apparatus was operated at 50 rpm for 5, 10, 15, 45, 60 min. 5 ml of the sample of dissolution medium was withdrawn by means of syringe fitted with a pre filter at known intervals of time. The sample was analyzed for drug release by measuring the absorbance at 253 nm using UV-visible spectrophotometer shimadzu -1800 after suitable dilutions. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium

Table 1: Composition of formulation for immediate release tablets (F1-F8) (All values are in mg)

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Flunarizine	12.6	12.6	12.6	12.6	12.6	12.6	12.6	12.6
Starch	59.97	59.57	59.33	59.2	58.82	58.32	58.09	57.49
Microcrystalline Cellulose	53.1	53.1	53.1	53.1	53.1	53.1	53.1	53.1
Lactose	35.4	35.4	35.4	35.4	35.4	35.4	35.4	35.4
Polyvinyl Pyrrolidone	3.18	3.18	3.18	3.18	3.18	3.18	3.18	3.18
Color Sunset Yellow	0.17	0.17	0.17	0.17	0.17	0.17	0.17	0.17
Cross Carmellose Sodium	0.35	0.75	0.99	1.12	1.50	2.00	2.23	2.83
Colloidal Silicon Dioxide	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Talcum	2.83	2.83	2.83	2.83	2.83	2.83	2.83	2.83
Magnesium Stearate	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7
Total	170	170	170	170	170	170	170	170

RESULTS AND DISCUSSIONS:

Table 2: Drug content of formulations F1 to F8

Formulation code	Percent drug content* ± SD	Disintegration time (sec)	Weight variation (mg)	Thickness (mm)
F1	99.82±1.15	42 ± 0.02	176.23 ± 0.02	4.58 ± 0.52
F2	98.81±0.80	56 ± 0.06	175.25 ± 0.05	4.61 ± 0.08
F3	98.68±0.90	50 ± 0.29	176.29 ± 0.08	4.55 ± 0.29
F4	99.43±1.10	64 ± 0.32	174.52 ± 0.52	4.52 ± 0.28
F5	98.18±1.41	37 ± 0.42	176.46 ± 0.25	4.58 ± 0.52
F6	98.43±1.29	11 ± 0.34	177.55 ± 0.29	4.61 ± 0.08
F7	97.70±0.62	52 ± 0.18	176.46 ± 0.25	4.58 ± 0.25
F8	100.21±0.99	75 ± 0.32	177.77 ± 0.59	4.51 ± 0.05

Table 3: *In-Vitro* Release Data of Formulations F1-F8:

Time (min)	Cumulative percent drug released* ±SD							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
5	8.77±0.19	7.25±0.63	9.68±0.54	6.40±0.52	7.30±0.64	6.47±0.43	5.70±0.49	6.35±0.70
10	18.35±0.24	16.12±0.65	14.52±0.74	11.21±0.72	15.41±0.66	16.18±0.14	13.85±0.69	14.30±0.36
15	28.72±0.21	30.63±0.28	32.28±0.35	30.43±0.56	25.95±0.21	28.32±0.22	27.71±0.81	20.66±0.53
20	33.51±0.96	41.10±0.73	38.74±0.65	39.25±0.47	35.69±0.75	34.79±0.46	35.86±0.30	42.91±0.39
25	40.69±0.86	45.94±1.10	49.23±0.26	45.65±0.35	49.48±0.11	44.50±0.37	55.43±0.54	54.04±0.71
30	44.68±0.30	51.58±0.50	58.91±1.09	55.27±0.76	56.78±0.12	55.83±0.56	73.36±0.72	64.37±0.86
35	50.26±0.7	60.45±0.32	68.60±0.22	63.28±0.02	65.70±0.55	63.11±0.74	75.81±0.37	71.53±0.11
40	56.65±0.27	66.90±0.53	73.44±0.13	70.49±0.13	73.82±0.02	72.82±0.63	80.70±0.51	78.68±0.36
45	63.03±0.21	73.35±0.21	76.67±0.01	78.50±0.51	77.87±0.73	81.72±0.25	83.15±0.29	85.04±0.91
50	69.41±0.32	78.18±0.70	83.94±0.25	84.10±0.31	82.74±0.21	84.96±0.23	88.04±0.82	91.40±0.73
55	78.99±0.13	84.63±1.14	88.78±0.31	88.11±0.65	88.42±0.31	89.81±0.52	91.30±0.71	94.58±0.28
60	88.56±0.69	90.27±0.33	91.20±0.17	92.11±0.23	93.29±0.09	94.67±0.89	95.38±0.28	97.75±0.43

***Figure 1: In-vitro* Drug Release Plots:**

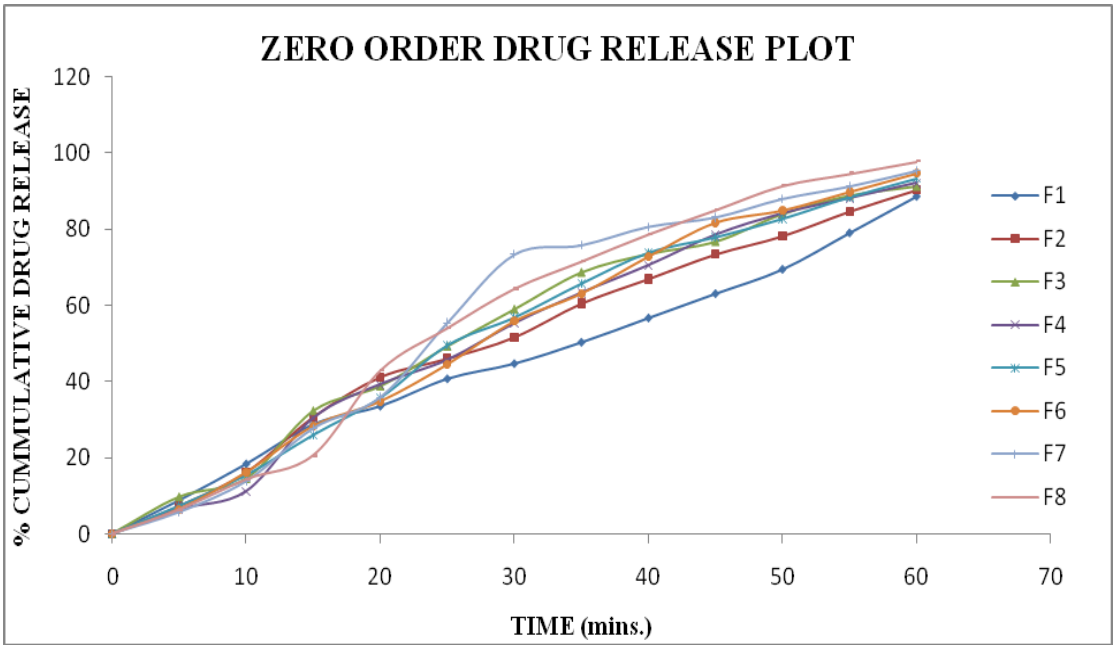
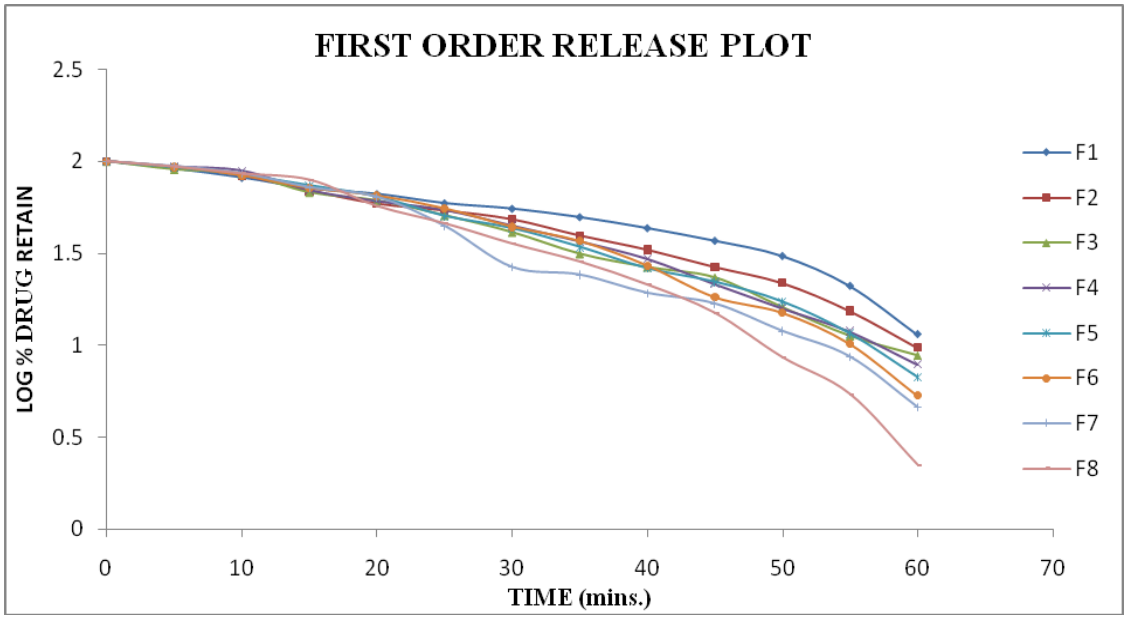


***Figure 2: In-vitro* Drug Release Plots:**



Kinetic Release Models

Table 4: Kinetics release model of immediate released tablets

	F1	F2	F3	F4	F5	F6	F7	F8
Zero order	0.991	0.983	0.971	0.980	0.980	0.964	0.937	0.987
First order	0.892	0.955	0.935	0.959	0.954	0.923	0.966	0.973

CONCLUSION:

All formulation were satisfactory for physical appearance including size, shape, thickness and other evaluation factors like weight uniformity, disintegration time, friability, hardness, drug content and in-vitro drug release. The tablet disintegration time was found to be less than 1min for the optimum batch. In vitro drug release was found maximum in F8 formulation which is 97.75±0.43 %. The optimize formulation also showed satisfactory size, shape, thickness and other evaluation factors like weight uniformity 177.77 ± 0.59 mg, disintegration time 37 ± 0.42 sec , friability less than 1%, hardness 3.0 kg/m^2, drug content 100.21±0.99%.

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