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Research Article

FORMULATION AND EVALUATION OF ORALLY DISINTEGRATING TABLETS OF ANTIHYPERTENSIVE DRUG NAFTOPIDIL

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ABSTRACT

In the present work, orally disintegrating tablets of naftopidil were designed with a view to enhance patient compliance. A combination of superdisintegrants i.e sodium starch glycolate and crospovidone XL were used along with directly compressible mannitol to enhance mouth feel. The prepared batches of tablets were evaluated for hardness, weight variation test, friability, wetting time, disintegration time and In-vitro drug release studies. The prepared tablets were characterized by DSC studies. Different formulations showed disintegration time in the range of 20 to 37 sec. Among all the formulation, F7 showed 97.98% drug release within 60 minutes and considered best among the other formulations. No chemical interaction between the drug and excipients was confirmed by DSC studies. The stability study was conducted as per ICH guidelines and the formulation (F7) was found to be stable, with insignificant change in disintegration time, wetting time and in-vitro drug release pattern. The results revealed that orally disintegrating tablets of the poorly soluble drug naftopidil showed enhanced dissolution and, hence, better patient compliance.

Key Words: *Orally disintegrating tablets, Naftopidil, Superdisintegrants*

INTRODUCTION

Recent developments in the technology have prompted scientists to develop orally disintegrating tablets with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without chewing and water. Orally disintegrating tablet break in mouth within a seconds and rapidly come to the contact with its dissolution medium which rapidly dissolve and shows faster action. With the proper guideline it should disintegrate on the tongue within 45 second without presence of any solid residue on the tongue.

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Orally disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules. Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action. It provides good stability, accurate dosing, easy manufacturing, small packaging size and easy to handle by patients. It is easy to administer for pediatric, geriatric and institutionalized patients (especially for mentally retarded and psychiatric patients) [1, 2].

Many technologies have come up for fast dissolving tablets like Zydis, OraSolv, DuraSolv, FlashTab and WowTab.Technologies like Zydis, FlashTab have resulted in tablets with a very low

disintegration time, but poor mechanical strength. On the other hand, techniques like OraSolv, DuraSolv have resulted in products with sufficient mechanical strength but a comparatively longer disintegration time [3, 4].

Naftopidil is used for the treatment of lower urinary tract symptoms compatible with benign prostatic hyperplasia. Benign prostatic hyperplasia (BPH) is a common condition in aging men causing lower urinary tract symptoms (LUTS). Treatment aims are to relieve symptoms and prevent disease progression. Of the different alpha-1 adrenergic receptors (ARs) in the prostate, alpha- 1a receptors are known to be central to prostatic smooth muscle contraction. Naftopidil is chemically described as 1-[4-(2-methoxyphenyl) piperazin-1-yl]-3-(1-naphthyloxy) propan-2-ol [5, 6].

In the present research work, orally disintegrating tablets of Naftopidil was formulated and evaluated using different superdisintegrants to achieve better compliance, and solve the problem of difficulty in swallowing.

Preparation of orally disintegrating tablets

Table 1: Tablet composition (%w/w) of different formulations of naftopidil orally Disintegrating tablets

S. No.	Ingredients mg/ tab.	F1	F2	F3	F4	F5	F6	F7
Intragranular								
1.	Naftopidil (micronized)	75	75	75	75	75	75	75
2.	Perlitol SD-200	181.5	171	172.5	180	165	80	78
3.	Aerosil 200	3			6		79	15
4	Magnesium Stearate			4.5				
5	Syloid 44-FP		6					
6	Crospovidone XL				9	9	15	3
7	PVP K-30						9	
8	HPC LH-11	30	36	36	15	18	18	78
9	Purified water	qs	qs	qs	qs	qs	qs	qs
Extragranular								
10	L-Menthol	1.5				12		3
11	Sodium Stearyl Fumarate (SSF)	3	3	3	4.5	3	3	6
12	Magnesium Stearate	6	6	4.5	4.5	3	6	6
13	Syloid 44-FP		3	1.5				
14	Aerosil 200			3	6	3	3	6
15	Crospovidone XL					3	12	15
16	Sodium Starch Glycolate (SSG)					9		15
	Total	**300**	**300**	**300**	**300**	**300**	**300**	**300**

MATERIALS AND METHODS

The drug Naftopidil was procured as gift sample from Asahi Kasai Corporation, Japan; Superdisintegrants (Sodium Starch Glycolate, HPC LH-11, and crospovidone XL) were procured from Ranbaxy Lab., Gurgaon. MCC PH-200, PVP K-30 and Mannitol were procured from S. D. Fine Chemicals, Mumbai. All other chemicals were procured locally and were of analytical grade.

Procedure:

- Sift all intragranular ingredients through the 40#. Aerosil was mixed with HPC LH-11 and then passed through 40# and Magnesium Stearate, SSF, L-Menthol was passed through the 60#.
- Mixed all intragranular ingredients in rapid mixer granulator for 10 minute with the help of impeller at 150 rpm.
- Granulation was carried out with aqueous solvent like water in rapid mixer granulator for 1 minute with the help of impeller at 150 rpm. Kneading was given by chopper to proper granulation of materials at 1500 rpm. Granules were dried in rapid dryer for 20 to 30 minute at 60 to 65°c. Granules were sifted through 30# and mixed for 10 minutes in conta blender at 18 rpm. L-Menthol, SSF was also added.
- Magnesium Stearate was added to above blend and mixed for 5 minute in conta blender at 18 rpm. The tablets were compressed using 5.5 mm round FFBE (flat faced beveled edges) punch on 16- station rotary tablet compression machine (Cadmach, Ahmedabad).

Evaluation of Tablets:

Evaluation of physical properties:

The prepared orally disintegrating tablets were evaluated for uniformity of weight, hardness, friability, disintegration time and wetting time. Uniformity of weight was performed according to official method [7]. Hardness of the tablets was tested using a Monsanto hardness tester and the friability of the tablets was determined in a Roche friabilator [8]. For determination of disintegration time, one tablet was placed in each tube of disintegration test apparatus. Wetting time was measured by placing a tablet on a piece of tissue folded twice, and was placed in a petri dish containing 6 ml of simulated saliva pH 6.8 and the time for complete wetting was measured. Three tablets from each batch were used [9]. The physical properties are shown in table 2.

In vitro drug release studies:

The in- vitro drug release studies was carried out using USP XXIV dissolution apparatus type II (paddle) at 50 rpm. The dissolution medium consisted of the 900 ml phosphate buffer pH 4, maintained at 37°C±0.5°C. 5 ml of samples were withdrawn every 5 minute interval and analyzed spectrophotometrically at 280 nm using a UV-visible double beam spectrophotometer (Shimadzu, Japan, Model-1701) after suitable dilution. Fresh dissolution medium was replaced after each withdrawal. The study was performed in triplicate.

Differential scanning calorimetry studies:

DSC study was carried out using DSC-60 instrument (M/s Shimadzu, Japan) to check the compatibility of ingredients. DSC thermo grams of pure drug (Naftopidil), SSG, HPC LH 11 and Crospovidone XL, Aerosil 200, L-menthol, Mannitol, Magnesium Stearate and Talc were individually taken for their identical endothermic reaction. Finally physical mixture of all above ingredients was scanned for DSC.

Stability studies: [10]

The optimized naftopidil ODT formulation (batch F7) was packed and subjected to accelerated stability studies as per ICH guidelines (40°C±2°C/75%RH±5%RH) for 3 months. The sample were withdrawn after 3 months and evaluated for the different physico-chemical parameters viz. weight variation, hardness, disintegration time, wetting time and in vitro drug release studies.

Comparison of optimized batch (F7) with Innovator tablet:

The optimized batch (F7) was compared with innovator ODT of Naftopidil (Flivas ODT, Asahi Kasei Pharmaceuticals) for disintegration time, wetting time, hardness, friability and In vitro drug release profile.

RESULTS AND DISCUSSIONS

In the present investigation, ODT formulations were prepared by using wet granulation method. The optimization of concentration and type of superdisintegrating agent was carried out by formulating and evaluating several batches on the basis of trial and error method. Super disintegrating agents SSG and Crospovidone XL were used in this study.

The physical properties of different batches of developed orally disintegrating tablet are given in table 2. The average percentage deviation of

20 tablets of each formulation was less than (5 %), and hence all formulations passed the test for uniformity of weight as per official requirements (Pharmacopoeia of India, 2010). The hardness of the tablets of all the formulations ranged from **(**4.0 ± 1.0 to 5.33 ± 0.57) kg/cm^2, friability (0.30 to 0.80 %), wetting time (26 to 46 sec), and disintegration time (20 to 37 sec). All were found within the acceptable official limits. The formulation batch F7 was found to have the minimum disintegration and wetting time (20 and 26 sec. respectively) containing the combination of crospovidone XL and sodium starch glycolate as superdisintegrants.

Table 2: Physical properties of batches F1 to F7

Batches	Weight Variation Test (mg)** (Mean ± S.D.)	Hardness (kg/ cm^2)* (Mean ± S.D.)	Friability (%)	Wetting time (sec)	Disintegration time (sec)
F1	301± 2.84	4.66± 0.52	0.42	45	30
F2	302± 2.44	4.33± 0.57	0.78	37	32
F3	300± 3.46	4.33± 0.57	0.8	39	37
F4	302± 3.85	4.0± 1.0	0.3	46	37
F5	300± 1.54	4.66± 0.52	0.4	29	21
F6	301± 4.22	4.33± 0.57	0.56	46	32
F7	302± 2.12	5.33± 0.57	0.67	26	20

**n=20, *n=3

The data obtained from in-vitro release studies for formulation batches F1 to F7 are shown in the figure 1 & table 3 respectively. Among the tablet formulation employing various combination of SSG (3-5%) and crospovidone (3-9 %) as superdisintegrants. The formulation F7 containing 5% w/w SSG and 6 % w/w crospovidone XL (1% intragranular and 5 % extragranular) was found to be promising and has displayed disintegration time 20 sec, wetting time of 26 sec and an in vitro drug release of 97.98 % in 60 minutes.

Table 3: In-vitro dissolution Profile of formulation batches F1 to F7

Time (Min.)	Cumulative % drug release (Mean ± S. D; n = 3)						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
5	8.9±0.92	25.6±0.84	22.6±0.78	35.9±1.28	52.98±0.84	34.25±0.46	77.35±1.42
10	15.6±1.84	32.4±1.23	28.9±1.54	57.58±1.36	82.96±1.36	59.56±1.46	92.38±0.64
15	18.9±0.76	39.48±0.94	43.5±0.85	62.58±0.86	91.23±1.24	61.23±0.86	94.65±0.68
20	23.4±1.56	43.78±1.46	45.9±0.82	64.98±0.96	91.89±0.44	63.45±1.26	95.21±0.58
30	26.8±1.43	51.25±1.38	46.37±1.36	67.99±1.43	92.58±1.74	65.58±0.72	97.36±0.79
40	32.5±1.12	55.68±0.86	49.87±0.78	68.98±1.12	92.88±1.54	69.62±1.22	97.58±1.08
50	36.12±0.48	59.98±1.62	50.18±0.79	70.14±1.76	93.26±0.98	73.45±0.84	97.86±0.36
60	36.6±1.72	65.1±1.24	51.3±1.54	71.5±1.24	93.6±1.62	74.52±0.46	97.98±0.28

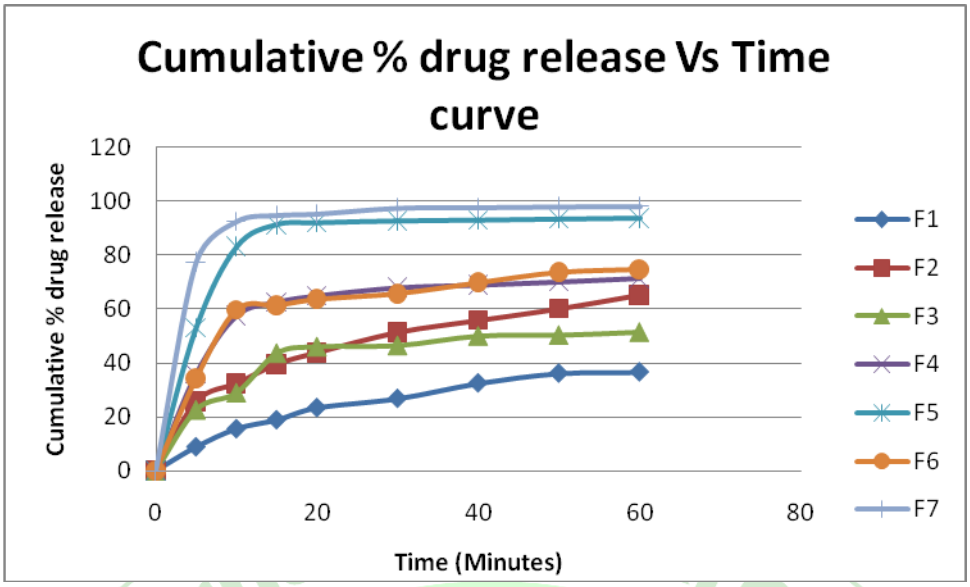

Figure 1: In-vitro dissolution Profile of formulation batches F1 to F7

Differential Scanning Calorimetry (DSC) Studies:

DSC curves obtained for pure Naftopidil, SSG, HPC LH 11, Crospovidone XL, Mannitol, L-menthol, Aerosil 200, Magnesium Stearate and physical mixture of all ingredients are shown in figure 2. Pure powdered Naftopidil showed a sharp melting endotherm at 197.41 °C. DSC scan of Mannitol, L-menthol, Aerosil 200 showed sharp endotherm at 168.30°C, 191.80°C & 254.86°C, 194.10°C & 104.11°C respectively due to melting whereas during scanning of SSG, HPC LH-11, Crospovidone XL and Magnesium stearate, melting endotherm at 86.46°C, 96.11°C, 88.52°C, 96.25°C and 116.14°C were observed respectively. DSC thermograms of physical mixture of drug and excipients showed the melting peak of the drug at 197.41°C and broad endothermic peak at 116.94°C. Physical mixture of all above ingredients showed their identical peaks at defined temperature range. Presence of all peaks indicates that all ingredients are compatible with drug and there is no incompatibility between the selected ingredients and drug.

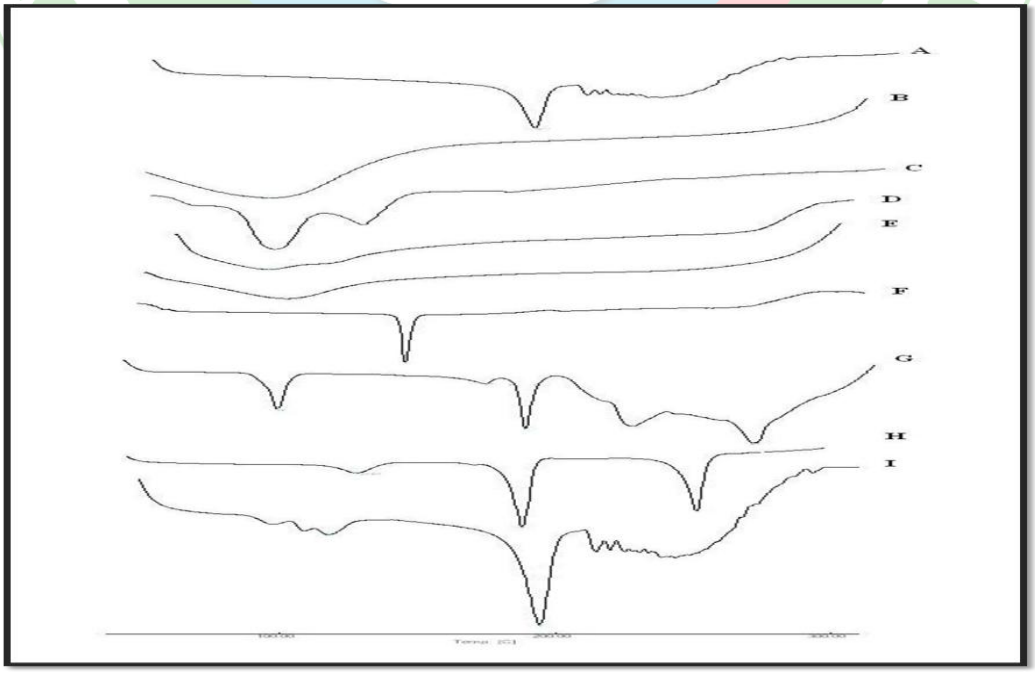

Figure 2: DSC thermograms of A-Naftopidil, B-Crospovidone-XL, C-Mg.stearate, D-S.S.G, E-Aerosil 200, F-Mannitol, G-HPC LH-11, H-L-Menthol, I-Physical mixture

Stability Studies

According to ICH guidelines , three months accelerated study (40°C±2°C/75%±5%RH) for the optimized formulation (batch F7) showed negligible change over time for the parameters like In-vitro drug release profile, disintegration time and wetting time. Results are shown in table 4 and figure 3 respectively.

Table 4: Results of stability study of optimized batch (F7)

Time (Min.)	Dissolution of F7 (Initial)	Dissolution of F7 (After storage at 40° C and 75%RH for 3 months)
0	0	0
5	77.35	75.56
10	92.38	91.35
15	94.65	93.3
20	95.21	94.79
30	97.36	95.34
45	97.86	97.23
60	97.98	97.7
90	98.21	98.01
120	98.35	98.23
135	98.45	98.28
180	98.66	98.34
Disintegration time	**20 sec**	**21 sec**
Wetting time	**26 sec**	**28 sec**

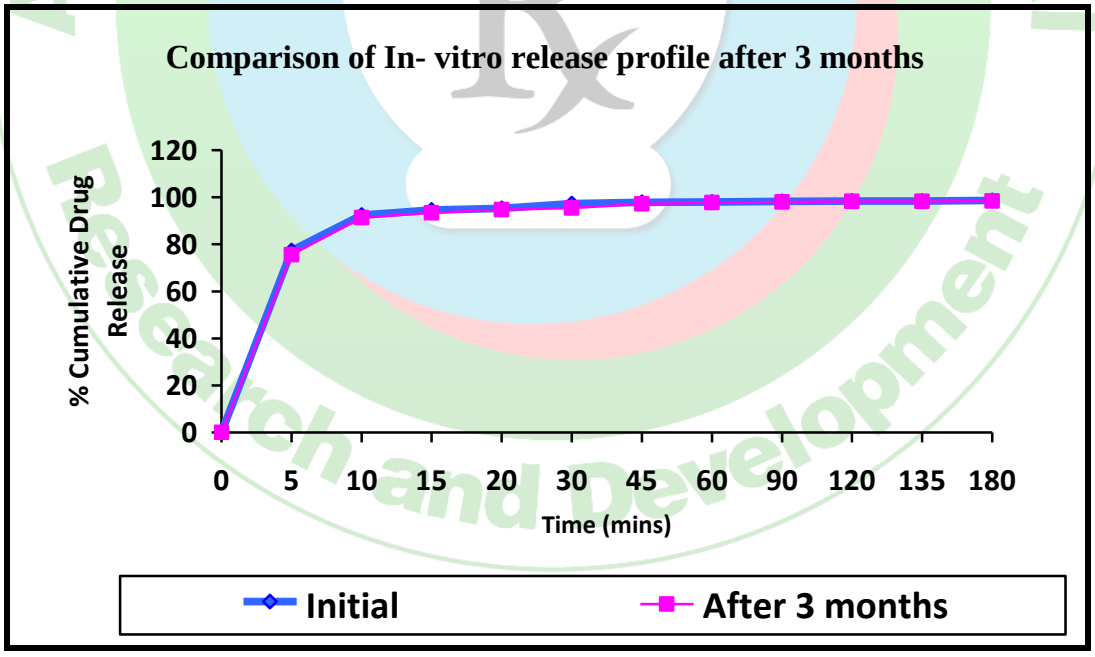

Figure 3: Stability comparison between initial sample & after 3months sample of F7

Comparison of optimized batch (F7) with Innovator tablet:

The comparison of optimized formulation batch F7 with innovator tablet ((Flivas ODT) are shown in Table 5. These values indicated that the formulation batch F7 was similar to that of innovator product.

Table 5: Comparison of optimized batch F7 with Innovator tablet

Batch	Disintegration time (sec)	Wetting time (sec)	Hardness Kg/ cm^2	Friability (%)	Cumulative % drug release (60 min.)
F7	20	26	5.33	0.67	97.98
Innovator (Flivas ODT)	20	25	5.66	0.52	94.70

CONCLUSION:

Orally disintegrating tablet is a promising approach with a view of obtaining faster action of the drug and would be advantageous in comparison to currently available conventional forms. The dosage form had a good balance over disintegration time and mechanical strength. Amongst all the formulation F7 prepared by the combination of crospovidone XL 6% and sodium starch glycolate 5% showed least disintegration time and faster dissolution. Thus, it can conclude that the combination of superdisintegrants is a promising approach to prepare orally disintegrating tablets of poorly soluble antihypertensive drug naftopidil.

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