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FORMULATION AND EVALUATION OF NAFTOPIDIL IMMEDIATE RELEASE TABLETS

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Abstract:
The aim and objectives of the present study is to develop a pharmaceutically stable, cost effective and quality improved formulation of Naftopidil immediate release tablets. Naftopidil immediate release tablets were formulated by using microcrystalline cellulose (diluent), Sodium starch glycollate (super disintegrant), Povidone K 30 (binder) and magnesium stearate (lubricant) and Aerosil 200 pharma (carrier/glidant).The granules were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness and drug content. The formulation F12 showed improved disintegration time when compared to innovator product. The dissolution profile of the formulation F10 and F12 was found to have equivalent percentage drug release with that of the innovator product (f_2=70.65). No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 2 months at 40° C and 75% RH. The formulation F12 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective, and pharmaceutically stable and also yields reproducible good tablets.

Key Words: *Naftopidil,Microcrystalline cellulose,Sodium starch glycollate, Povidone K 30, magnesium stearate, Aerosil 200, Superdisintegrants, Immediate Release, Dissolution Studies.*

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INTRODUCTION

Oral Drug Delivery

Oral drug delivery is the most widely utilized route of administration among all the routes of administration that has been explored for the systematic delivery of drug through different pharmaceutical dosage forms. The oral route of drug administration is the most important method of drugs for systemic affects. It can be said that at least 90% of all drugs used to produce systemic effect by are administered orally. They present wide range of comforts to manufacturer as well as the patient. A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and site of release of drugs in the body. The goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration. Oral route of drug administration is most appealing route for delivery of drugs for various dosage forms [1,2].

Immediate Release Drug Delivery System

Immediate release drug delivery system is also conventional type of drug delivery system as it is defined as – Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques [3,4].

Advantages of Immediate Release Drug Delivery Systems [5, 6]:

- Release the drug immediately.
- More flexibility for adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease.
- At the particular site of action the drug is released from the system.

MATERIALS AND METHODS

Materials Used

Naftopidil from Hetero drugs, Hyderabad. Lactose monohydrate, Micro Crystalline Cellulose(Avicel pH 101) and Micro Crystalline Cellulose(Avicel pH 102) from Mylan Laboratories. Sodium Starch Glycollate, Povidone k-30 and Light anhydrous silicic acid (Aerosil 200 pharma) from savan Pharmaceuticals, Hyderabad

Methods Used

Pre Formulation Studies

Preformulation testing is an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. It was the first step in the rational development of dosage forms.Preformulation studies described as the process of optimizing the delivery of drug though the determination of physico-chemical properties of the new compound that could affect the drug performance and development of an efficacious, stable and safe dosage form [7, 8]

Physical Appearance

Physical appearance of API (Active Pharmaceutical Ingredient) was characterized by visual observation.

Solubility Studies [9,10]

The solubility of drug is an important physicochemical property because it affects the bioavailability of the drug, the rate of drug release into the dissolution medium, and consequently, the therapeutic efficacy of the pharmaceutical product. Naftopidil is classified under class IV according to BCS i.e.; poorly soluble and poorly permeable. Solubility studies of Naftopidil were conducted at all pH ranges from 1 to 7.4. The solubility of API was determined by dissolving the highest unit dose of the drug in 500 mL of buffer adjusted between pH 1.0 and 7.4. For this purpose 0.1N HCl, Glycine buffer, Acetate buffer pH 4.5, Phosphate buffer pH 6.8, and Purified water were used. Highest dose of the drug i.e., 75mg was dissolved in 500 mL of medium and agitated on Rotary shaker for 12 hrs. Later on the insoluble drug was filtered off and the solution was analysed by UV to find out the solubility.

Melting Point

The melting point of Naftopidil was found out by capillary method using programmable melting point apparatus.

Bulk Density

Bulk density was determined by pouring gently 20 gm of sample (Naftopidil) through a glass funnel into 50 ml graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as [11].

Bulk Density *= weight of sample in gram /volume occupied by the sample*

Tapped Density

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

A sufficient number of taps should be employed to

assure reproducibility for the material in question. Volume was noted and taped density is calculated using following formula.

***Tapped Density** = Wt. of sample in gm / Tapped volume*

Compressibility Index and Hausner ratio [12, 13]:

In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. Both the compressibility index and the Hausner ratio were determined by using bulk density and the tapped density of a powder.

$$\text{Carr's index} = \frac{\text{Tapped desnity} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Angle of Repose [14]

The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane. A funnel was fixed at a height approximately of 2-4 cm over the platform. The loose powder was slowly passed along the wall of funnel, till the cone of the powder formed .Determine the angle of repose by measuring the height of the cone of powder and radius of the heap of powder.

$\text{Tan } \theta = h / r$

$\theta = \text{Tan}^{-1} h / r$

Estimation of Naftopidil

A spectrophotometric method based on the measurement of absorbance at 423 nm in 0.1N HCl was used in the present study for the estimation of Naftopidil.

Reagents

Preparation of 0.1N Hcl

8.5ml of concentrated HCl was taken in a volumetric flask and it was made up to 1000ml with distilled water.

Standard Solution

100 mg of Naftopidil pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution-1000 µg/ml), from this 10 ml of solution was taken and the volume was adjusted to 100 ml with 0.1 N HCl (100 µg/ml).

Procedure:

The above solution was subsequently diluted with 0.1N HCl to obtain the series of dilutions containing 2,4,6,8,10,12,16,20,24,30, and 100µg/ml of Naftopidil. The absorbance of the above dilutions was measured at 423 nm by using the UV-Spectrophotometer using 0.1N HCl as the blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line.

Table 1:Calibration Curve of Naftopidil in 0.1 N HCl at λ_{max} 423 nm

Concentration (µg/ml)	Absorbance
2	0.097
4	0.202
6	0.308
8	0.415
10	0.525
12	0.628
14	0.744
16	0.823

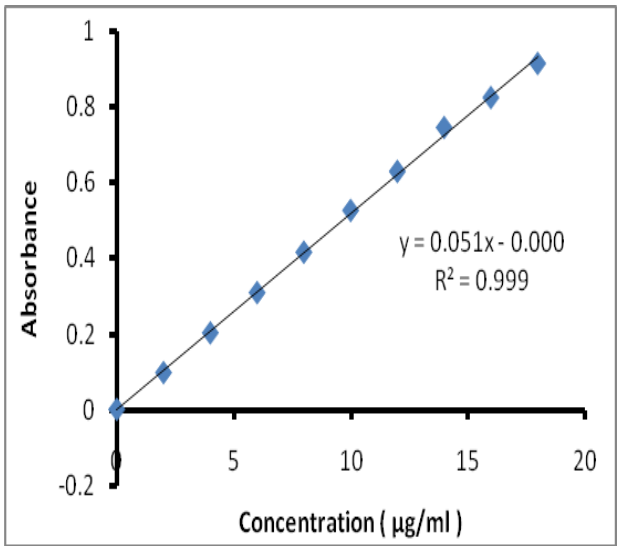

Fig 1: Calibration Curve of Naftopidil in 0.1 N HCl at λ_{max} 423 nm

Evaluation of Tablets [15-20]

The formulated tablets were evaluated for the following physicochemical characteristics:

General Appearance:

The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.

Hardness:

Hardness of the tablet was determined by using hardness tester. The desired hardness is 8-10kp.

Thickness:

Thickness of the tablets was calculated by the use of Digital Vernier calipers. Desired thickness was 7-8mm.

Weight Variation:

20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within the permissible limits or not.

$$\text{Weight variation} = \frac{(\text{Weight of tablet} - \text{Average weight})}{\text{Average weight of tablets}} \times 100$$

Not more than two of the individual weights should deviate from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

Friability test:

20 previously weighed tablets were placed in the friability apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula,

Percentage friability = initial weight-final weight /initial weight × 100.

Friability should be less than 1.

Drug Content:

20 tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of Naftopidil was transferred into a 100 ml volumetric flask and the volume is adjusted to 100ml with 0.1N HCl. Further 1ml of the above solution was diluted to 100 ml with 0.1N HCl and the absorbance of the resulting solution was observed at 423 nm.

Disintegration Test:

One tablet was placed into each tube and the assembly was suspended into the 1000ml beaker containing water maintained at 37±2ºC and is operated until no residue of the tablet under test remains on the screen of the apparatus. If one or two tablets fail to disintegrate completely, repeat the test on 12 additional tablets. If the requirement is not met less than 16 of the total of 18 tablets tested are disintegrated.

***In vitro* Dissolution Studies of Tablets:**

The compressed tablets were evaluated for dissolution release profiles.

Dissolution parameters:

Apparatus -- USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl
RPM -- 50
Sampling intervals (hrs) --5, 10, 15, 30,45,60,90 and 120 min
Temperature -- 37± 0.5 °C

Preparation of Dissolution media (0.1 N HCL):

Transfer 85ml of HCl into a suitable container and dilute to 10,000 ml with water and mix.

Blank Preparation: Dissolution medium is used as blank.

Dissolution Study: 900ml 0f 0.1N HCl was placed in the vessel and the USP apparatus –II (Paddle Method) was assembled and operated at 50 RPM. The medium was allowed to equilibrate to temp of 37± 0.5°C. Tablet was placed in the vessel and the vessel was covered. At definite time intervals, 5 ml of the fluid was withdrawn; filtered and again 5ml of the blank was replaced. Suitable dilutions were done with the dissolution fluid and the samples were analyzed spectrophotometricallyat423 nm.

RESULTS

Table 2: Composition of Naftopidil Immediate Release Tablets

S.NO	INGREDIENTS	F1	F2	F3	F4	F5	F6
A. Dry mix		Quantity (mg/tab)					
1.	Naftopidil	75.00	75.00	75.00	75.00	75.00	75.00
2.	Lactose monohydrate	130.20	180.00	195.00	189.00	195.00	175.00
3.	Microcrystalline Cellulose 101	55.80	-	-	-	-	-
4.	Aerosil 200 pharma	-	-	-	-	-	-
5.	Sodium Starch Glycollate	6.00	6.00	6.00	6.00	6.00	6.00
Continue……							

B. Binder Solution							
5.	**Povidone K30**	**9.00**	**9.00**	**9.00**	**15.00**	**9.00**	**6.00**
6.	**Purified Water**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
C. Blending							
7.	**Microcrystalline Cellulose 102**	**15.00**	**21.00**	**6.00**	**6.00**	**6.00**	**30.00**
8.	**Sodium Starch Glycollate**	**6.00**	**6.00**	**6.00**	**6.00**	**6.00**	**3.50**
9.	**Aerosil 200 pharma**	**1.50**	**1.50**	**1.50**	**1.50**	**1.50**	**3.00**
D. Lubrication							
10.	**Magnesium stearate**	**1.50**	**1.50**	**1.50**	**1.50**	**1.50**	**1.50**
Average weight (mg)		**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**

Table 3: Composition of Naftopidil Immediate Release Tablets

S.NO	INGREDIENTS	F7	F8	F9	F10	F11	F12
A. Dry mix		**Quantity (mg/tab)**					
1.	**Naftopidil**	**75.00**	**75.00**	**75.00**	**75.00**	**75.00**	**75.00**
2.	**Lactose monohydrate**	**175.00**	**175.00**	**189.00**	**150.00**	**150.00**	**150.00**
3.	**Microcrystalline Cellulose 101**	**-**	**-**	**-**	**45.00**	**45.00**	**45.00**
4.	**Aerosil 200 pharma**	**1.50**	**3.00**	**-**	**6.00**	**6.00**	**6.00**
5.	**Sodium Starch Glycollate**	**6.00**	**6.00**	**6.00**	**12.00**	**12.00**	**12.00**
B.BINDER SOLUTION							
5.	**Povidone K30**	**6.00**	**6.00**	**15.00**	**9.00**	**9.00**	**9.00**
6.	**Purified Water**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**	**q.s**
C. BLENDING							
7.	**Microcrystalline Cellulose 102**	**30.00**	**30.00**	**6.00**	**-**	**-**	**-**
8.	**Sodium Starch Glycollate**	**3.50**	**3.50**	**6.00**	**-**	**-**	**-**
9.	**Aerosil 200 pharma**	**1.50**	**1.50**	**1.50**	**-**	**-**	**-**
D. LUBRICATION							
10.	**Magnesium stearate**	**1.50**	**1.50**	**1.50**	**3.00**	**3.00**	**3.00**
Average weight (mg)		**300.00**	**300.00**	**300.00**	**300.00**	**300.00**	**300.00**

Table 4: Solubility data of Naftopidil across pH

Medium	Solubility at 25° C (mg/ml)
pH-1.2 (0.1 N HCl)	**0.1×10^{-3}**
pH-2.1(0.01 N HCl)	**11×10^{-3}**
pH-3.0 (0.001 N HCl)	**1.9×10^{-3}**
pH-4.5 (Acetate buffer)	**0.6×10^{-3}**
pH-5.0 (phthalate buffer)	**$< 0.1\times10^{-3}$**
pH-6.5 (Phosphate buffer)	**$< 0.1\times10^{-3}$**
pH-7.4 (Phosphate buffer)	**$< 0.1\times10^{-3}$**

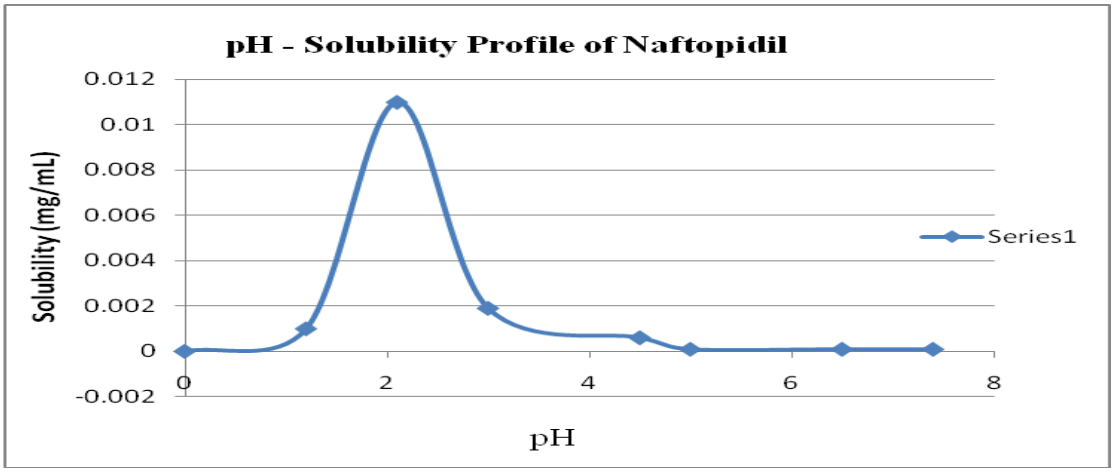

Fig 2: pH-Solubility profile of Naftopidil

Table 5: Results of Excipients Compatibility Study

S. No	Name of the Excipient	Ratio API: Expt	Initial Observation	Final observation		Conclusion
				40°C/75% RH		
				2nd week	4th week	
1	API (Naftopidil)	---	Off-White	Off-White	Off-White	Compatible
2	API+ Lactose monohydrate	1 :1	Off-White	Off-White	Off-White	Compatible
3	API + MCC 101	1 : 1	Off-White	Off-White	Off-White	Compatible
4	API + Sodium starch glycollate	1 : 1	Off-White	Off-White	Off-White	Compatible
5	API +Aerosil 200 pharma	1 : 1	Off-White	Off-White	Off-White	Compatible
6	API + Povidone	1 : 1	Off-White	Off-White	Off-White	Compatible
7	API +MCC 102	1 : 1	Off-White	Off-White	Off-White	Compatible
8	API + Magnesium stearate	1 : 1	Off-White	Off-White	Off-White	Compatible

Table 6: Flow Properties of Blends of Various Trial Batches

Formulation	Blend Property				
	B.D (gm/ml)	T.D (gm/ml)	C.I (%)	H.R	Angle of Repose
F1	0.49±0.013	0.62±0.061	20.97±2.445	1.26±0.028	44.91±2.05
F2	0.613±0.008	0.795±0.025	22.95±0.009	1.298±0.009	26.52±1.32
F3	0.66±0.003	0.75±0.165	9.56±0.009	1.18±0.165	29.56±1.64
F4	0.78±0.012	0.86±0.231	9.36±0.156	1.14±0.156	27.46±1.52
F5	0.72±0.011	0.79±0.013	9.24±1.447	1.10±0.018	28.41±1.69
F6	0.62±0.028	0.69±0.009	7.91±0.124	1.08±0.015	29.25±1.39
F7	0.68±0.009	0.74±0.011	8.20±0.098	1.89±0.001	28.54±0.42
F8	0.70±0.089	0.77±0.011	8.29±0.089	1.09±0.021	29.96±2.18
F9	0.62±0.015	0.67± 0.006	7.60±0.075	1.08±0.005	29.93±1.70
F10	0.544±0.014	0.697±0.018	22±0.224	1.282±0.011	28.47±0.70
F11	0.58±0.012	0.76±0.231	8.36±0.156	1.24±0.156	24.46±1.52
F12	0.584±0.015	0.735±0.015	20.513±0.226	1.258±0.014	26±0.014

Table 7: Physical Evaluation of Tablets of Various Trial Batches

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F 12
1	Weight variation	1.65	1.57	1.42	1.54	1.18	1.35	1.44	1.23	1.48	1.54	1.63	1.38
2	Hardness (KP)	8.8	8.4	8.2	9.4	9.1	8.8	9.4	8.8	8.5	8.8	9.0	8.6
3	Thickness (mm)	4.41	4.40	4.50	4.37	4.37	4.85	4.89	4.90	4.93	4.12	4.02	4.14
4	Friability %	0.05	0.12	0.10	0.18	0.12	0.07	0.06	0.14	0.15	0.18	0.10	0.15
5	Disintegration time	3min 25sec	2min 30sec	2min 24sec	1min 29sec	1min 45sec	1min 20sec	1min 30sec	1min 40sec	1min 20sec	1min 18sec	1min 10sec	1min 10sec

Table 8: Chemical Evaluation of Tablets of Various Trial Batches

S No	Parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9	F 10	F 11	F12
1	Assay (%)	99.9	98.6	98.5	100.7	98.7	99.5	98.7	99.6	100.6	98.7	98.9	98.7
2	Dissolution study(NLT 75% in 45 mins)	63.9	62.4	59.6	63.6	60.0	72.8	58.7	67.4	65.7	85.5	75.7	86.7

Table 9: Dissolution Profile of Naftopidil IR Tablets (FLIVAS)

TIME (min)	CUMULATIVE % DRUG DISSOLVED
0	0
5	64.6
10	71.6
15	80.9
30	86.4
45	88.2
60	91.4
90	93.2
120	94.8

Table 10: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F1	F2
0	0	0
5	44.0	40.1
10	49.5	47.5
15	53.9	53.0
30	61.4	58.4
45	63.9	62.4
60	70.0	67.4
90	74.3	72.4
120	79.4	76.2

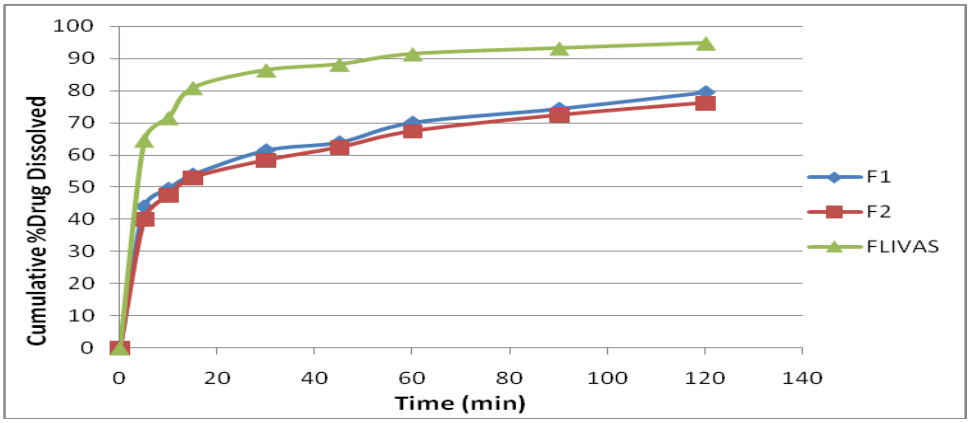

Fig 3: Dissolution profile of Naftopidil Immediate Release tablets (F1, F2)

Table 11: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F3	F4
0	0	0
5	40.8	41.8
10	45.6	47.1
15	49.3	50.7
30	55.8	57.9
45	59.6	63.6
60	62.4	69.6
90	66.9	75.4
120	70.5	77.8

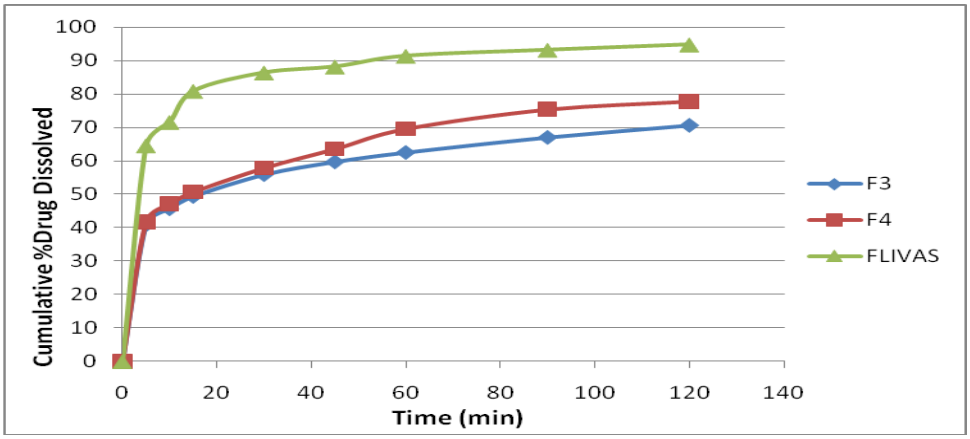

Fig 4: Dissolution profile of Naftopidil Immediate Release tablets (F3, F4)

Table 12: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F5	F6
0	0	0
5	39.8	49.2
10	43.7	57.6
15	49.1	59.7
30	54.8	67.7
45	60.0	72.8
60	62.8	77.8
90	68.3	77.5
120	70.3	77.6

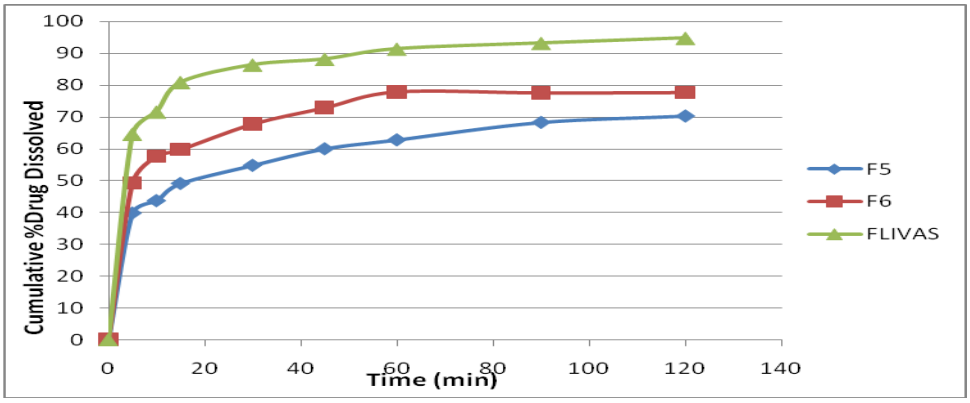

Fig 5: Dissolution profile of Naftopidil Immediate Release tablets (F5, F6)

Table 13: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F7	F8
0	0	0
5	42.0	52.1
10	48.3	56.8
15	51.7	60.3
30	57.5	65.5
45	58.7	67.4
60	60.8	72.1
90	65.3	76.0
120	69.3	79.9

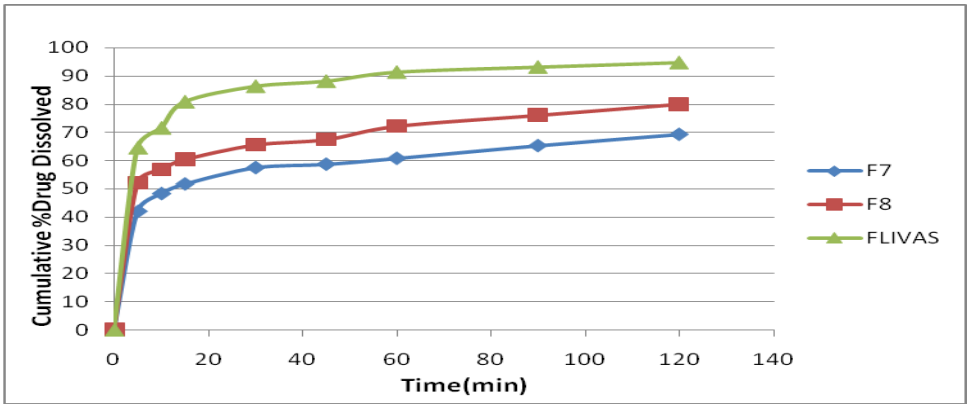

Fig6: Dissolution profile of Naftopidil Immediate Release tablets (F7, F8)

Table 14: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F9	F10
0	0	0
5	40.7	70.0
10	46.2	76.8
15	51.4	78.8
30	58.9	80.1
45	65.7	85.5
60	70.1	86.4
90	77.6	85.9
120	78.3	86.8

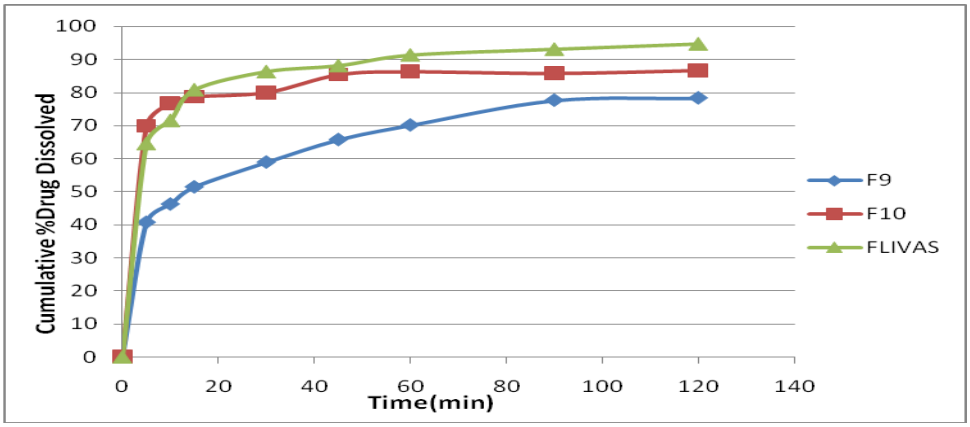

Fig7: Dissolution profile of Naftopidil Immediate Release tablets (F9, F10)

Table 15: Dissolution Profile of Naftopidil IR Tablets

TIME (min)	CUMULATIVE PERCENT DRUG DISSOLVED (n=3±SD)	
	F11	F12
0	0	0
5	57.2	70.5
10	63.2	77.2
15	65.6	79.0
30	72.0	80.9
45	75.7	86.1
60	78.4	86.8
90	83.6	86.2
120	85.9	85.5

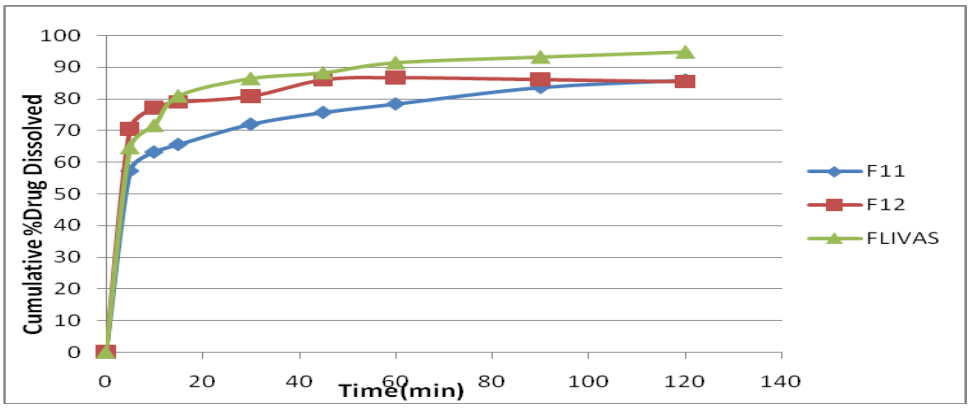

Fig 8: Dissolution profile of Naftopidil Immediate Release tablets (F11, F12)

Accelerated stability data

Table 16: Comparative dissolution profile of F12 tablets after 15 Days stability with initial tablets

TIME	INITIAL	15 DAYS
0	0	0
5	70.5	65
10	77.2	73.5
15	79	77.8
30	80.9	79.2
45	86.1	84.6
60	86.8	85
90	86.2	84.7
120	85.5	84.4

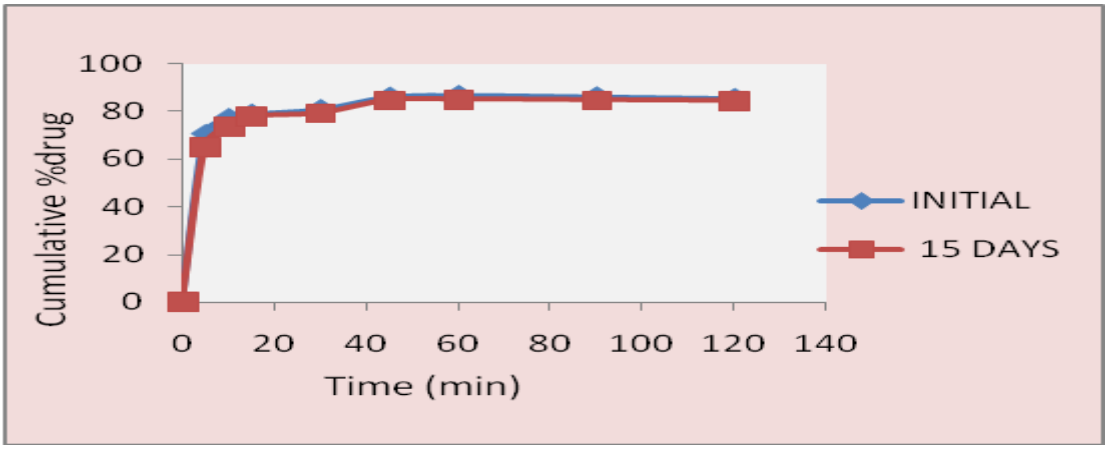

Fig 9: dissolution profile after 15 days stability

Table 17:Comparative dissolution profile after 1 month stability of F12

TIME	INITIAL	1MONTH
0	0	0
5	70.5	62
10	77.2	72.5
15	79	77.8
30	80.9	79.2
45	86.1	84.6
60	86.8	85
90	86.2	84.7
120	85.5	84.4

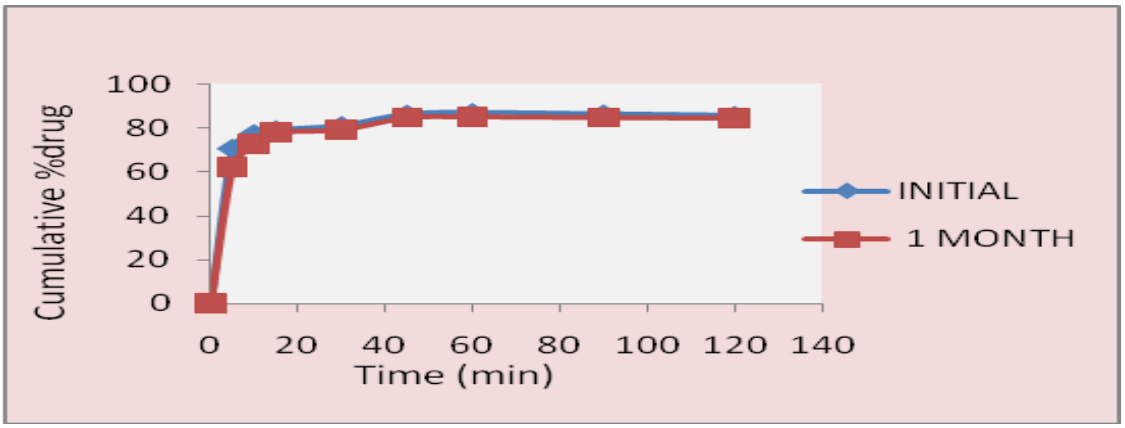

Fig 10: Dissolution Profile after 1 Month Stability

Table 18: Comparative Dissolution Profile after 2 Month Stability of F12

TIME	INITIAL	2MONTH
0	0	0
5	70.5	58
10	77.2	71.9
15	79	72.8
30	80.9	75.7
45	86.1	80.6
60	86.8	83
90	86.2	83.7
120	85.5	82.4

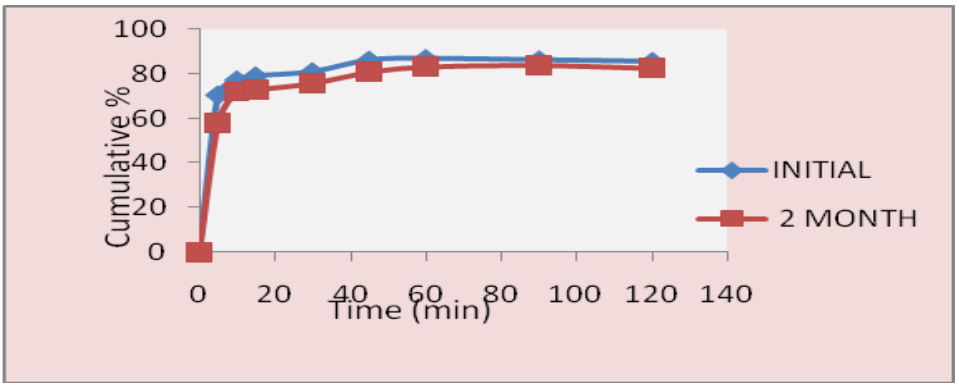

Fig 11: Dissolution Profile after 2 Month Stability

SUMMARY AND CONCLUSION

This dissertation work was done with an aim to design an immediate release oral dosage form of Naftopidil and evaluation of the tablets including *in vitro* drug release studies.Naftopidil immediate release tablets were formulated by using microcrystalline cellulose (diluent), Sodium starch glycollate (super disintegrant), Povidone K 30 (binder) and magnesium stearate (lubricant) and Aerosil 200 pharma (carrier/glidant).

The granules were compressed into tablets and were analyzed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness and drug content. The formulation F12 showed improved disintegration time when compared to innovator product. The dissolution profile of the formulation F10 and F12 was found to have equivalent percentage drug release with that of the innovator product (f_2=70.65)

No significant change was observed in the drug content, physical properties and dissolution rate of these tablets after the storage period of 2 months at 40° C and 75%RH.

The formulation F12 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective, and pharmaceutically stable and also yields reproducible good tablets.

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