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ENHANCEMENT OF SOLUBILITY OF NAFTOPIDIL USING SOLID DISPERSION TECHNIQUE

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ABSTRACT

The present study was carried out on Naftopidil by employing solid dispersion technique. The λmax of phosphate buffer pH 6.8 of Naftopidil were found to be at 282 nm. The pure drug the optimised Solid dispersion formulations were subjected to FTIR studies. The results were showed that there's no interaction between the drug and excipients. The micrometric properties of blend of Naftopidil solid dispersion were characterized with respect to Angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. All the Values of batches indicating good flow properties. All the tablets of various batches complied with the official demand of weight variation as their weight variation passes the bounds. The hardness of the tablets ranged from 2.5±0.03 to 2.75±0.01 kg/cm2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.01±0.32 to 3.06±0.54 mm. All the formulations satisfied the content of the drug as they contained 97.1 -101.4 % of Naftopidil and good uniformity in drug content was observed. Thus all the physical attributes of the ready tablets were found to be much among management limits. The dissolution profile of Naftopidil tablets were compared between solid dispersion tablets. The Naftopidil solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F8 showed good drug release i.e., 99.74 at 60 minutes. F8 formulation was taken as optimised formulation.

KEYWORDS

Naftopidil and Solid dispersion tablets.

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INTRODUCTON

Improvements in oral bioavailability of these poorly water soluble drugs often show poor bioavailability due to low and irregular uptake levels. Drugs that have limited gastrointestinal absorption with a dissolving index usually show better dissolution and bioavailability because of the reduction in particle size. However, micronization of drugs often leads to aggregation and agglomeration of the particles, resulting in poor wettability. Solid dispersions of

poorly water-soluble drugs with water-soluble carriers have reduced the incidence of these problems and improved dissolution. The development of solid dispersions as a practically viable method for improving the bioavailability of poorly water-soluble drugs exceeded the limitations of previous approaches, such as salt formation, co-solvent solubilization and particle size reduction. . Studies have shown that solid dispersion drugs do not need to exist in the micronized state. A fraction of the drug could be molecularly dispersed in the matrix, thereby forming a solid dispersion. When the solid dispersion is exposed to an aqueous medium, the carrier dissolves and the drug is released as fine colloidal particles.

The increase in the resulting surface results in a higher rate of dissolution and bioavailability of drugs that are poorly soluble in water. In addition, in the solid dispersions, a portion of the drug dissolves immediately to saturate the liquid of the gastrointestinal tract, and the excess drug precipitates as fine colloidal particles or oily globules smaller than the minimum size. The solid dispersion technique was demonstrated for the first time by Sekiguchi and Obi. They proposed a more rapid absorption of drugs that are poorly soluble in water, such as sulfathiazole, forming a eutectic mixture with a assimilable substance soluble in water and physiologically inert. When exposed to aqueous fluids, the active drug released in the fluids is dispersed into fine particles due to the fine dispersion of the drug in the solid eutectic mixture and also the quicker dissolution of the soluble matrix. It contained 52% w / w sulfathiazole and 48% w / w urea. Then there is the possibility of using a solid solution approach in which a drug is dispersed at the molecular level in a soluble vehicle. Several researchers have used a solid dispersion technique that has reported encouraging results with different drugs. By Sekiguchi and Obi (Sekiguchi, 1961). A technique for preparing solid dispersions, lyophilization was also considered a molecular mixing technique in which the drug and the vehicle were dissolved in cyclohexanol, frozen and then sublimed in vacuo to obtain a lyophilized molecular dispersion[1,2].

Many solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolving properties of poorly water-soluble drugs. Other methods have also been used, such as salt formation, complexation with cyclodextrins, solubilization of drugs in one or more solvents and reduction of particle size to improve the dissolution properties of poorly soluble drugs. The water; However, each of these techniques has significant limitations. On the other hand, solid dispersion drug formulation offers a variety of treatment options and excipients that allow flexibility in the formulation of oral delivery systems for poorly water soluble drugs.

MATERIAL AND METHODS

Naftopidil was Procured from Hetero labs, Hyderabad, gift sample Provided by Sura Labs, Dilsukhnagar. Polaxomer 407, Hydroxypropyl β-Cyclodextrin Signet labs Mumbai, India. Urea, PEG 6000, Mannitol Nihar traders pvt Ltd. Magnesium Stearate Himedia Laboratories. Aerosil Nice chemicals Ltd.

Methods

Formulation development for solid dispersion

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Naftopidil and Water soluble polymers such as Polaxomer, PEG 4000, Urea were selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart (Table). The ready solid dispersions were skillful the sieve no twenty to urge uniform sized particles. The solid dipersions were mixed with required quantities of super disintegrants, diluent, lubricant and glidant. The blend was evaluated for precompression parameters.

EVALUATION PARAMETERS

Fourier Transform Infrared (FTIR) spectroscopy

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FTIR analysis of the Pure drug and optimised formulation were carried out using an FTIR spectrophotometer (Bruker FT-IR - Germany).

Micrometric Properties

Angle of repose

The angle of repose of was determined by fixed funnel method. The accurately weighed physical mixtures were taken in a funnel. The height of the funnel was adjusted to 2cm, the tip of the funnel just touches the apex of the heap of the powder. The powder was allowed to flow through the funnel into the surface. The height and diameter of the powder cone was measured and angle of repose was calculated.

Tan θ= h/r

Where, θ is the angle of repose

h is that the height in cm, r is the radius in cm

Bulk Density

Bulk density measurements were carried by inserting a set weight of powder during a graduate, and the volume occupied was measured. The bulk volume (Vb) and weight of the powder were measured and the initial bulk density was calculated by using following formula.

Db= M/ Vb

Where,

M = Weight of powder

Vb= Bulk volume of powder

Tapped density

The measuring cylinder containing weighed mass of powder. The cylinder was then abroach at a continuing speed till a continuing volume was obtained. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the powder was measured. The tapped density was calculated using following formula.

D t = M/ Vt

Where,

M = weight of powder

Vt= tapped volume of powder

Carr's Index (%)

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these influence the compressibility index. The simple method for measurement of free flow of powder is Carr's Index, a sign of the easiness with which a material can be induced to flow is given by Carr's Index (CI) that is calculated as follows:

CI (%) = [(Tapped density - Bulk density) / abroach density] x a hundred

Hausner Ratio

Hausner magnitude relation is AN indirect index of easy powder flow. It is calculated by the following formula.

Hausner's Ratio=Tapped density / Bulk density

Evaluation of Naftopidil tablets

Weight variation

Twenty tablets were arbitrarily selected from every batch and severally weighed. The average weight and variance 3 batches were calculated. It passes the check for weight variation check if less than 2 of the individual pill weights deviate from the typical weight by over the allowed proportion deviation and none deviate by over doubly the proportion shown. It was calculated on an electronic weighing balance.

Thickness

The thickness of Naftopidil tablets was determined by using digital micrometer. Ten individual tablets from every batch were used and also the results averaged.

Hardness

The hardness of the tablets determined by mistreatment Monsanto hardness tester. Six individual tablets from each batch were taken and results averaged.

Friability

The crumbliness values of the tablets were determined employing a Roche-type friabilator. Accurately weighed six tablets were placed in Roche friabilator and turned at twenty five rate for four min. Percentage friability was calculated using the following equation.

Friability = ([WO – W] /WO) □ 100

Where,

WO = weight of the tablet at time zero before revolutions.

W = weight of the pill once a hundred revolutions.

Disintegration test

Six tablets were taken arbitrarily from every batch and placed in USP disintegration equipment baskets equipment was last ten minutes and also the basket

was carry from the fluid and observed for disintegration of tablets.

Content of uniformity

The tablets were individually weighed and crushed. The quantity of powder equivalent to mass of the one tablet was extracted in 10ml of methanol and then made up 100ml with phosphate buffer pH 6.8, shaken for 30mins. The solution was filtered through whattmen filter paper. The drug content was determined by UV spectrometer at respective wavelength for Naftopidil after suitable dilution with phosphate buffer pH 6.8.

In vitro Dissolution Study

Drug release from formulated Naftopidil tablets was determined by using USP dissolution test apparatus II (Paddle apparatus). The tablets were place in 900 ml of dissolution medium as phosphate buffer pH 6.8 maintained at 37 ± 0.5 °C and 50 rpm. At appropriate intervals (5, 10, 15, 30, 45 and 60) 5ml of the samples were taken and the dissolution media was then replaced by 5ml of fresh dissolution fluid to maintain a constant volume. After proper dilution, the samples were then analyzed at respective wavelength by UV-spectrophotometer. The concentration was calculated by using calibration curve.

RESULTS

Fourier transform infrared (FTIR) spectroscopy studies

The pure drug and the optimised formulation (F8) were subjected to FTIR studies. The results were showed that there's no interaction between the drug and excipients.

Micromeritic properties

The micrometric properties of blend of Naftopidil soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 390, Carr's index values were 14.87 to 15.64 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.198 for all the batches indicating good flow properties.

DISCUSSION

The Solid Dispersion tablets of were prepared by solvent evaporation method. The pure drug and were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients. The micrometric properties of blend of Naftopidil soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 390, Carr's index values were 14.87 to 15.64 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.198 for all the batches indicating good flow properties. The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of various batches complied with the official demand of weight variation as their weight variation passes the boundaries. The hardness of the tablets ranged from 2.5±0.03 to 2.75±0.01 kg/cm2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.01±0.32 to 3.06±0.54 mm. All the formulations satisfied the content of the drug as they contained 97.1 -101.4 % of Naftopidil and good uniformity in drug content was observed. Thus all the physical attributes of the ready tablets were found to be much at intervals management limits.

The *in vitro* drug release graphs it was revealed that F8 formulation was optimised formulation. Why because in that F8 showed good drug release i.e., 99.74% at 60 minutes. And less disintegration time is F8 formulation i.e., 30 seconds. Hence F8 formulation considered as optimised formulation.

Table No.1: Formulation of tablets by using solid dispersion

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Naftopidil 50 mg Equivalent	SD1 (100m)	SD2 (200mg)	SD3 (300 mg)	SD4 (400 mg)	SD5 (100m)	SD6 (200m g)	SD7 (300 mg)	SD8 (400 mg)	SD9 (100m g)	SD10 (200m)	SD11 (300 mg)	SD12 (400 mg)
Cross Caramellose Sodium	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Hydroxypropyl β-Cyclodextrin	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5
Aerosil	5	5	5	5	5	5	5	5	5	5	5	5
Mannitol	325	225	125	25	325	225	125	25	325	225	125	25
Total weight	450	450	450	450	450	450	450	450	450	450	450	450

Table No.2: Evaluation of pre compression parameters of solid dispersion blend

Formulation Code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio
F1	35.24±0.07	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07
F2	36.27±0.06	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06
F3	34.65±0.08	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13
F4	33.54±0.04	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02
F5	32.21±0.01	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03
F6	39.23±0.01	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21
F7	31.10±0.02	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01
F8	32.19±0.02	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03
F9	33.28±0.01	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15
F10	30.86±0.03	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01
F11	31.24±0.04	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02
F12	30.48±0.02	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01

Table No.3: Evaluation of post compression parameters of solid dispersion tablets

Formulation code	Average Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disintegration time (sec)	Content uniformity (%)
F1	448.12	3.01±0.32	2.63±0.05	0.52±0.08	32±0.07	97.1±0.13
F2	450.1	3.06±0.54	2.52±0.03	0.45±0.06	54±0.14	101.2±0.15
F3	449.8	3.05±0.63	2.65±0.02	0.63±0.05	63±1.3	101.4±0.25
F4	449.10	3.04±0.45	2.45±0.01	0.45±0.01	60±0.09	99.6±0.42
F5	448.06	3.02±0.35	2.65±0.02	0.35±0.025	51±0.13	98.8±0.32
F6	446.34	3.00±0.63	2.65±0.01	0.36±0.03	49±0.09	99.3±0.15
F7	449.25	3.01±0.63	2.60±0.03	0.29±0.009	38±0.15	98.7±0.21
F8	447.68	3.05±0.47	2.75±0.01	0.65±0.02	24±0.02	100.1±0.32
F9	449.55	3.03±0.42	2.5±0.03	0.34±0.01	32±0.01	98.45±0.12
F10	450.00	3.01±0.45	2.60±0.14	0.48±0.02	29±0.03	99.4±0.35
F11	448.47	3.05±0.47	2.70±0.03	0.54±0.04	42±0.03	98.2±0.14
F12	449.75	3.02±0.63	2.65±0.024	0.42±0.02	56±0.02	99.97±0.15

Table No.4: *In vitro* dissolution studies of formulated solid dispersion tablets

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
5	29.86	27.30	25.10	20.98	17.88	21.32	28.11	31.98	30.14	33.61	27.02	20.14
10	41.72	39.58	36.29	32.48	29.14	35.65	40.28	44.60	45.69	49.21	40.13	38.00
15	56.75	55.10	53.44	50.77	49.55	53.87	58.62	60.53	57.36	59.98	52.07	49.21
20	65.35	63.08	60.74	58.41	60.10	64.29	69.10	70.55	68.91	69.83	62.42	57.94
30	79.94	75.64	71.22	71.55	69.25	76.81	77.98	81.41	76.20	77.30	74.11	70.60
45	89.24	86.40	82.91	80.11	75.69	85.49	90.01	92.06	88.10	90.11	80.91	79.96
60	97.29	95.31	90.62	87.90	89.31	92.69	94.79	99.74	97.99	98.68	94.26	90.16

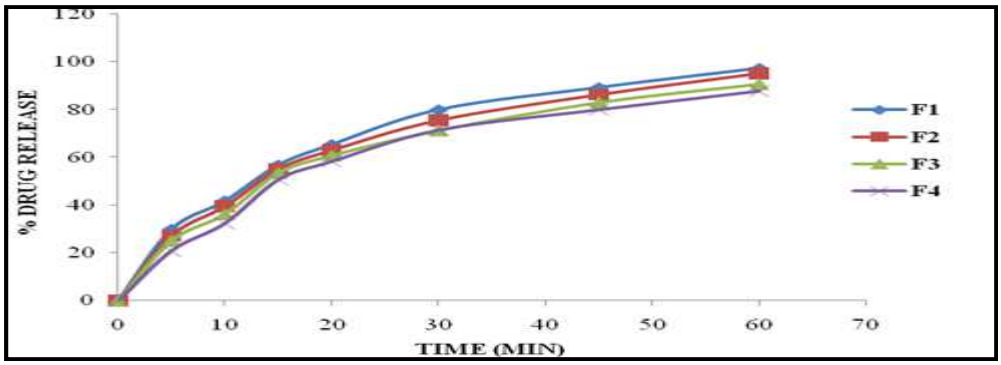

Figure No.1: *In vitro* dissolution studies of formulated solid dispersion tablets by using Polaxomer 407

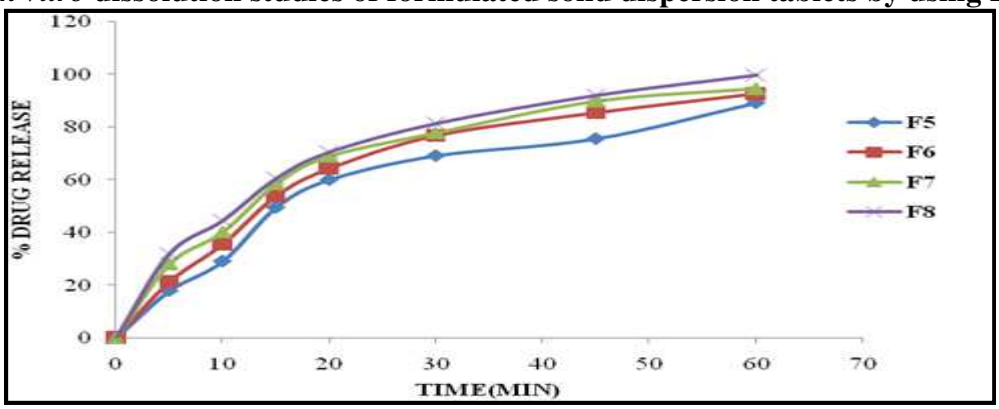

Figure No.2: *In vitro* dissolution studies of formulated solid dispersion tablets by using Urea

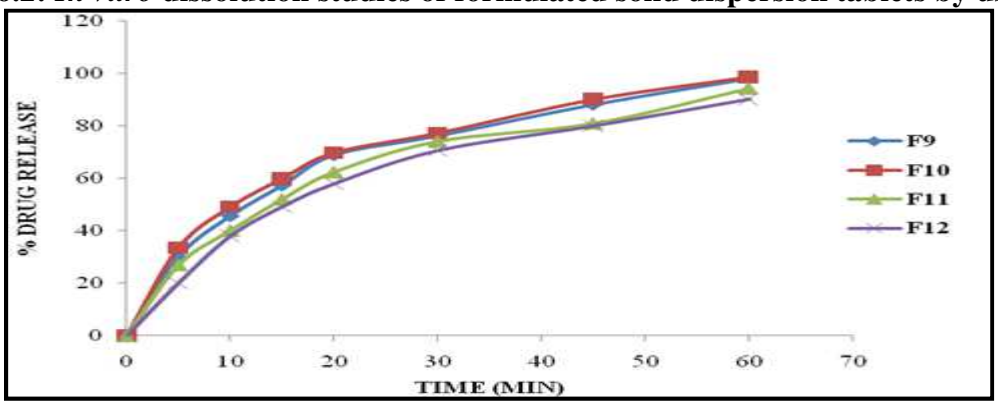

Figure No.3: *In vitro* dissolution studies of formulated solid dispersion tablets by using PEG 6000

CONCLUSION

The present study was carried out on Naftopidil by employing solid dispersion technique. The λmax of phosphate buffer pH 6.8 of Naftopidil were found to be at 282 nm. Standard graph of Naftopidil in phosphate buffer pH 6.8 was plotted. Good linearity was observed with concentration verses absorbance. Its R2 value in phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer - Lambert" law. The optimized Solid dispersion formulations, pure drug were subjected to FTIR studies. The results were showed that there's no interaction between the drug and excipients. The micrometric properties of blend of Naftopidil soild dispersion were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 390, Carr's index values were 14.87 to 15.64 for the pre compression blend of all the batches indicating good to fair flowability and compressibility. Hausner's ratio was less than 1.198 for all the batches indicating good flow properties. The results of the weight variation, hardness, thickness, friability, and drug content of the solid dispersion tablets were given in Table. All the tablets of various batches complied with the official demand of weight variation as their weight variation passes the bounds. The hardness of the tablets ranged from 2.5±0.03 to 2.75±0.01 kg/cm2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.01±0.32 to 3.06±0.54 mm. All the formulations satisfied the content of the drug as they contained 97.1 -101.4 % of Naftopidil and good uniformity in drug content was observed. Thus all the physical attributes of the ready tablets were found to be much at intervals management limits. All the solid dispersion formulations of Naftopidil were subjected to in vitro dissolution studies, these studies were carried out using phosphate buffer pH 6.8 by using dissolution apparatus type II. The dissolution profile of Naftopidil tablets were compared between solid dispersion tablets. The Naftopidil solid dispersion tablets showed better release in phosphate buffer pH 6.8, in that F8 showed good drug release i.e., 99.74% at 60 minutes. F8 formulation was taken as optimised formulation.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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