**International Journal of Farmacia (IJF)**

***IJF |Vol.10 | Issue 4 | Oct - Dec -2024***
**www.ijfjournal.com**
DOI : https://doi.org/10.61096/ijf.v10.iss4.2024.132-138

**ISSN: 2231-3656**

**Research**

# Development And Evaluation Of Naftopidil Solid Dispersion Tablets

**Shaikh Mohd Jafar[1*], Dr.J.Ramesh[1]**

[1]*Department Of Pharmaceutics, Omega College Of Pharmacy, Edulabad, Hyderabad (Telangana)*

*Author for Correspondence: Shaikh Mohd Jafar
Email: mdjafar1198@gmail.com

Published on: 28 Oct 2024

Published by:
DrSriram Publications



**Abstract**

The aim of the present study is to Development and evaluate solid dispersion of Naftopidil by using various polymers with different ratios and formulating its tablet. Solid dispersion is an effective way of improving the dissolution rate of poorly watersoluble drugs. Naftopidil were prepared by different methods and evaluated with a view to increase its water solubility and hence to improve the dissolution profile. Solid dispersions were evaluated for solubility and % practical yield. Solid dispersion showing maximum solubility were selected and formulated into tablet. The tablets were exposed to routine qualitycontrolled tests like hardness, friability, weight variation and disintegration. The dissolution profiles of these formulations were studied in 6.8 phosphate buffer and compared to marketed formulation as well as pure drug. At the end of 60min formulation N5 gave the highest drug release that is 99.71% compared to all the formulation. N5 formulation consider as a optimized formulation Naftopidil was significantly improved by preparing solid dispersion.

**Keywords:** Naftopidil, Solid dispersion method.

## INTRODUCTION

The enhancements of oral bioavailability of such poorly water-soluble drugs often show poor bioavailability because of low and erratic levels of absorption. Drugs that undergo dissolution rate limited gastrointestinal absorption generally show improved dissolution and bio availability as a result of reduction in particle size. However, micronizing of drugs often leads to aggregation and agglomeration of particles, which results in poor wettability. Solid dispersions of poorly water-soluble drugs with water-soluble carriers have been reduced the incidence of these problems and enhanced dissolution. The development of solid dispersions as a practically viable method to enhance bioavailability of poorly water-soluble drugs overcame the limitations of previous approaches such as salt formation, solubilization by cosolvents, and particle size reduction. Studies revealed that drugs in solid dispersion need not necessarily exist in the micronized state. A fraction of the drug might molecularly disperse in the matrix, there by forming a solid dispersion. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles.

The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water soluble drugs. In addition, in solid dispersions, a portion of drug dissolves immediately to saturate the gastrointestinal tract fluid, and excess drug precipitates as fine colloidal particles or oily globules of submicron size. solid dispersion technique was firstly demonstrated by Sekiguchi and Obi. They proposed the faster absorption of poorly water-soluble drugs such as sulfathiazole by the formation of eutectic mixture with a water-soluble and physiologically inert carries like urea. Upon exposure to aqueous fluids the active drug released into fluids is fine, dispersed particles because of fine dispersion of the drug in the solid eutectic mixture and the faster dissolution of the soluble matrix. The eutectic mixture contained 52 per cent w/w of sulfathiazole and 48 per cent w/w of urea. Thepossibility of using

solid solution approach in which a drug is molecularly dispersed in soluble carrier was subsequently introduced. A solid dispersion technique has been used by various researchers who have reported encouraging results with different drugs The first drug whose rate and extent of absorption was significantly enhanced using the solid dispersion technique was sulfathiazole by Sekiguchi and Obi (Sekiguchi, 1961). Technique for the preparation of solid dispersions, Lyophilization has also been thought of as a molecular mixing technique where the drug and carrier were co-dissolved in cyclohexanol, frozen and then sublimed under vacuum to obtain a lyophilized molecular dispersion.[1,2]

Numerous solid dispersion systems have been demonstrated in the pharmaceutical literature to improve the dissolution properties of poorly water-soluble drugs. Other methods, such as salt formation, complexation with cyclodextrins, solubilization of drugs in solvent(s), and particle size reduction have also been utilized to improve the dissolution properties of poorly water-soluble drugs; however, there are substantial limitations with each of these techniques. On the other hand, formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs.

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity. Therefore efforts to increase drug dissolution of drug are often needed. Methods available to improve dissolution include salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and it involves dispersion of one or more active ingredients in aninner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method [3]. The technique has been used for a wide variety of poorly aqueous soluble drug. Poorly soluble drugs represent a problem for their scarce availability related to their low dissolution rate. The major drawback of low aqueous solubility is delays its absorption from the gastrointestinal tract. Solubility behavior of a drug is one of the key determinants of its oral bioavailability. Noyesh Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral availability.[4]

$$\frac{DC}{DT} = \frac{AD(CS - C)}{H}$$

Where,

dC/dt - is the rate of dissolution, A -is the surface area available for dissolution, D - is the diffusion coefficient of the compound, Cs- is the solubility of the compound in the dissolution medium, C -is the concentration of drug in the medium at time t and h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound. To increase the dissolution rate from equation the following approaches are available.

- To increases the surface area available for dissolution Decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness.
- Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.
- Drug administered in fed state is a way to improve the dissolution rate.

Of these possibilities, changes in the hydrodynamics are difficult to invoke in-vivo and the maintenance of sink conditions will depend on how permeable the gastrointestinal mucosa is to the compound as well as on the composition and volume of the luminal Fluids. Although some research effort has been directed towards permeability enhancement using appropriate excipients, results to date have not been particularly encouraging. Administration of the drug in the fed state may be an option to improve the dissolution rate and also to increase the time available for dissolution; the likely magnitude of the food effect can be forecasted from dissolution tests in biorelevant media. [5]

The approaches that have commonly been used to overcome drawbacks associated with poorly water-soluble drugs, in general includes micronization, salt formation, use of surfactant and use of pro- drug [6] , however all these techniques have certain limitations. Techniques that have commonly been used to improve dissolution and bioavailability of poorly water-soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions. Chiou and Riegelman outlined 6 types of drug carrier interactions in solid-state dispersions: simple eutectic mixtures, solid solutions, glass solutions and glass suspensions, amorphous precipitates, and compound or complex formation. Other factors such as increased wettability, solubilization of the drug by the carrier at the diffusion layer, and the reduction or absence of aggregation and agglomeration may also contribute to increased dissolution. Micronization has several disadvantages, the main one being the limited opportunity to control important characters of the final particle such as size, shape, morphology, surface properties and electrostatic charges. In addition micronization is a high-energy process, which causes disruptions in the drug s crystal lattice, resulting in the presence of disordered or amorphous regions in the final product. The amorphous regions are thermodynamically unstable and are therefore susceptible to recrystallization upon storage, particularly in hot and humid conditions [7,8,9]. All poorly water-soluble drugs are not suitable for improving their solubility by salt formation. The dissolution rate of a particular salt is usually different form that of parent compound. However sodium and potassium salts of weak acids dissolve more rapidly than the free salts. Potential disadvantages of salt forms include high reactivity with atmospheric carbon dioxide and water resulting in precipitation of poorly water-soluble drug, epigastric distress due to high alkalinity.

Use of co-solvents or surfactants to improve dissolution rate pose problems, such as patient compliance and commercialization. Even though particle size reduction increases the dissolution rate, the formed fine powders showing poor wettability and flow properties. Solid dispersion technique has come into existence to eliminate all these problems. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches.[10,11]

**Solid dispersion**

Chiou and Riegelman defined the term solid dispersion as "a dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers bymelting of their physical mixtures" [13].The term solid dispersion refers to the dispersion ofone or more active ingredient in an inert carrier or matrix at solid state prepared by melting (fusion), solvent, or the melting solvent method. Suggested that the drug was present in a eutectic mixture in a microcrystalline state [9], after few years Goldberg et.al. reported that all drug in solid dispersion might not necessarily be presents in a microcrystalline state, a certain fraction of the drug might be molecular dispersion in the matrix, thereby forming a solid solution. Once the solid dispersion was exposed to aqueous media & the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water soluble drugs were expected to be high. The commercial use of such systems has been limited primarily because of manufacturing problems with solid dispersion systems may be overcome by using surface active and self-emulsifying carriers. The carriers are melted at elevated temperatures and the drugs are dissolved in molten carriers. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles(clusters) or in crystalline particles. Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the melting (fusion), solvent or melting solvent method. The dispersion of a drug or drugs in a solid diluent or diluents by traditional mechanical mixing is not included in this category. The solid dispersion, a first stated by Mayersohn and Gibaldi.

## MATERIALS AND METHODS

Naftopidil-Provided by SURA LABS, Dilsukhnagar, Hyderabad, PEG 6000-Nihar traders pvt Ltd, Croscarmellose-Nihar traders pvt Ltd, Sodium starch glycolate-Nihar traders pvt Ltd, Ac-di-sol-Nihar traders pvt Ltd, Magnesium stearate-Himedia Laboratories, Talc-Nice chemicals Ltd, MCC-Nihar traders pvt Ltd.

## METHODOLOGY

**Determination of Wavelength**

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

**Determination of Calibration Curve**

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

**Formulation Development**

**Formulation development for solid dispersion**

Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Naftopidil and Water soluble Disintegrants such as Croscarmellose, Sodium starch glycolate, Ac-di-sol. were selected as carrier PEG 6000. Drug and Disintegrants were taken in 1:1 ratio stated in the formulation chart (Table 7.1 ). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of super disintegrates, diluents, lubricant and glidant. The blend was evaluated for precompression parameters.

**Table 1: Formulation of solid dispersion showing various compositions (Ratios only)**

| Ingredients | SD1 | SD2 | SD3 |
|---|---|---|---|
| Naftopidil | 50 | 50 | 50 |
| PEG 6000 | 15 | 30 | 45 |

**Table 2: Formulation of tablet by using solid dispersion**

| Ingredients | FORMULATION CHART | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | N9 |
| **Equivalent to (95mg)** | 180 | 265 | 350 | 160 | 265 | 350 | 180 | 265 | 350 |
| Croscarmellose | 25 | 50 | 75 | - | - | - | - | - | - |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Sodium starch glycolate | - | - | - | 30 | 60 | 90 | - | - | - |
| Ac-di-sol | - | - | - | - | - | - | 35 | 70 | 105 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| MCC | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| **Total weight** | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |

## RESULT AND DISCUSSION

**Analytical Method Development**

**Construction of calibration curve for Naftopidil**

The λmax of phosphate buffer pH 6.8 of Naftopidil were found to be at 232 nm. Standard graphs of Naftopidil in phosphate buffer pH 6.8 were shown in Table 8.1. Good linearity was observed with concentration verses absorbance. Its $R^2$ value in phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

**Table 3: calibration curve of Naftopidil in phosphate buffer pH 6.8**

| Concentration(µg/mL) | Absorbance |
|---|---|
| 0 | 0 |
| 5 | 0.115 |
| 10 | 0.221 |
| 15 | 0.334 |
| 20 | 0.439 |
| 25 | 0.546 |

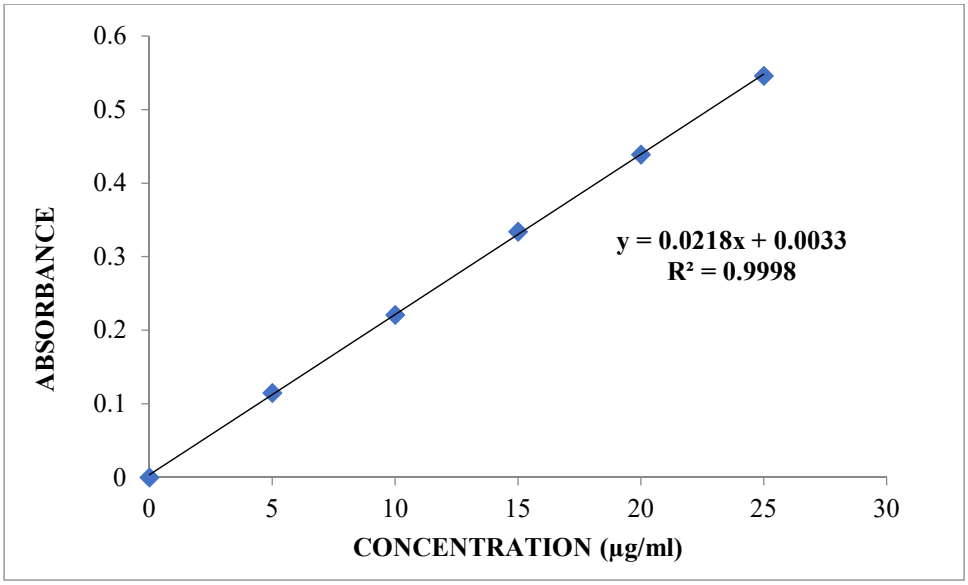


**Fig 1: Calibration curve of Naftopidil in phosphate buffer pH 6.8**

**Micromeritic properties**

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. Angle of repose was less than 38°65, Carr's index values were 9.40±0.13 to 10.34±0.13 for the pre compression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.145 for all the batches indicating good flow properties.

**Table 4: 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 |
|---|---|---|---|---|---|
| N1 | 26.43◦ | 0.54±0.03 | 0.60±0.02 | 9.40±0.13 | 1.10±0.01 |
| N2 | 26.45◦ | 0.53±0.03 | 0.58±0.03 | 10.13±0.02 | 1.12±0.01 |

| | | | | | |
|---|---|---|---|---|---|
| N3 | 26.21◦ | 0.56±0.01 | 0.63±0.01 | 9.93±0.11 | 1.13±0.03 |
| N4 | 25.31◦ | 0.59±0.03 | 0.64±0.04 | 10.12±0.34 | 1.11±0.06 |
| N5 | 27.12 | 0.58±0.03 | 0.63±0.03 | 10.34±0.13 | 1.17±0.03 |
| N6 | 25.40◦ | 0.51±0.01 | 0.61±0.06 | 10.11±0.02 | 1.16±0.01 |
| N7 | 25.31◦ | 0.54±0.02 | 0.58±0.03 | 10.01±0.19 | 1.13±0.06 |
| N8 | 26.43◦ | 0.54±0.03 | 0.60±0.02 | 9.40±0.13 | 1.10±0.01 |
| N9 | 25.15◦ | 0.53±0.01 | 0.59±0.01 | 9.43±0.12 | 1.09±0.02 |

**Post compression parameters**

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 different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 4.43 to 4.93 kg/cm$^2$ and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 3.28 to 3.88 mm. All the formulations satisfied the content of the drug as they contained 97.08 – 99.86 % of Naftopidil and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

**Table 5: Evaluation of post compression parameters of solid dispersion tablet**

| Formulation code | Average Weight (mg) | Thickness (mm) | Hardness (kg/cm$^2$) | Friability (%loss) | Disintegration time (sec) | Content uniformity (%) |
|---|---|---|---|---|---|---|
| N1 | 499.12 | 3.48 | 4.43 | 0.25 | 2.23 | 99.41 |
| N2 | 498.38 | 3.61 | 4.58 | 0.43 | 1.85 | 98.22 |
| N3 | 501.22 | 3.88 | 4.62 | 0.36 | 2.46 | 97.08 |
| N4 | 497.08 | 3.28 | 4.76 | 0.49 | 2.62 | 99.12 |
| N5 | 500.12 | 3.58 | 4.93 | 0.51 | 1.98 | 99.44 |
| N6 | 499.69 | 3.44 | 4.38 | 0.39 | 2.12 | 98.92 |
| N7 | 498.78 | 3.51 | 4.83 | 0.67 | 2.36 | 97.43 |
| N8 | 499.63 | 3.53 | 4.76 | 0.55 | 2.88 | 99.86 |
| N9 | 496.77 | 3.73 | 4.51 | 0.29 | 2.59 | 98.35 |

From the above pre and post compression of solid dispersion tablets of all the required evaluation tests were found to be within limit. Less disintegration time is F3 formulation i.e., 25 seconds.

***In vitro* Dissolution Studies**

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 de solid dispersion tablets showed better release in phosphate buffer pH 6, in that N5 showed good drug release i.e., 99.71 at 60 minutes.

**Table 6: *In vitro* dissolution studies of formulated solid dispersion tablets**

| Time(min) | N1 | N2 | N3 | N4 | N5 | N6 | N7 | N8 | N9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5 | 24.23 | 26.62 | 29.05 | 39.44 | 33.63 | 41.81 | 31.12 | 28.63 | 36.35 |
| 10 | 31.11 | 40.25 | 38.87 | 46.22 | 49.08 | 49.53 | 43.93 | 43.91 | 49.28 |
| 15 | 35.79 | 46.86 | 47.71 | 59.43 | 56.72 | 55.41 | 48.85 | 51.42 | 58.47 |
| 20 | 49.53 | 52.43 | 57.09 | 64.23 | 64.91 | 68.76 | 57.08 | 57.65 | 63.22 |
| 30 | 58.31 | 60.91 | 70.15 | 69.42 | 81.01 | 78.59 | 71.43 | 64.18 | 78.18 |
| 45 | 62.92 | 68.32 | 75.45 | 89.66 | 88.74 | 88.22 | 87.16 | 76.64 | 82.53 |
| 60 | 78.95 | 73.17 | 82.23 | 94.17 | 99.71 | 97.09 | 92.75 | 85.37 | 88.47 |

From the above graphs it was revealed that N5 formulation was optimized formulation. Why because in that N5 showed good drug release i.e., 99.71% at 60 minutes. And less disintegration time is N5 formulation i.e., 1.98 seconds. Hence N5 formulation considered as optimized formulation.

**Drug Excipient Interactions**

**Fourier transform infrared (FTIR) spectroscopy studies**

The pure drug and the optimised formulation (N5) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients.

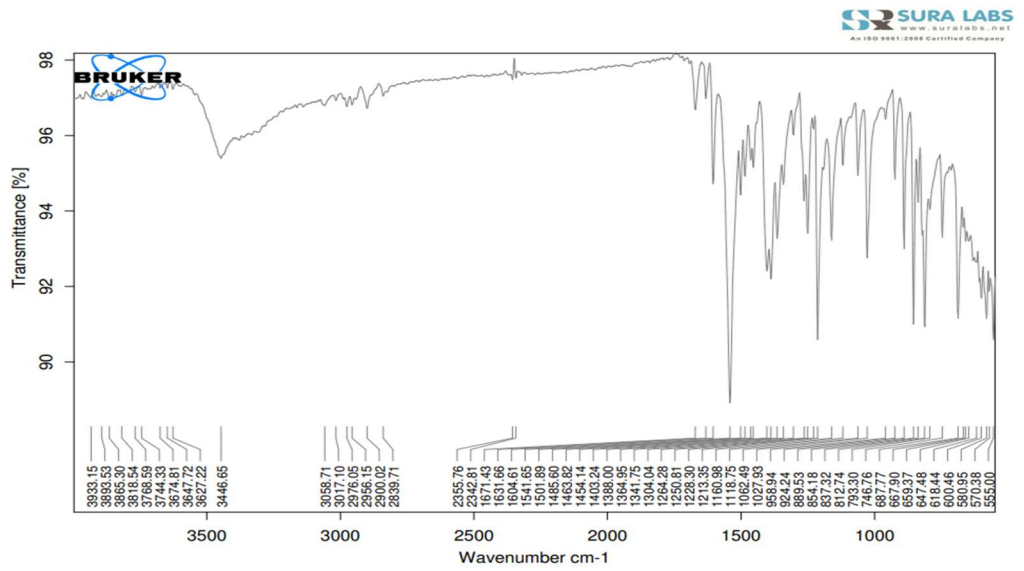


**Fig 2: FT-IR Spectrum of Naftopidil pure drug**

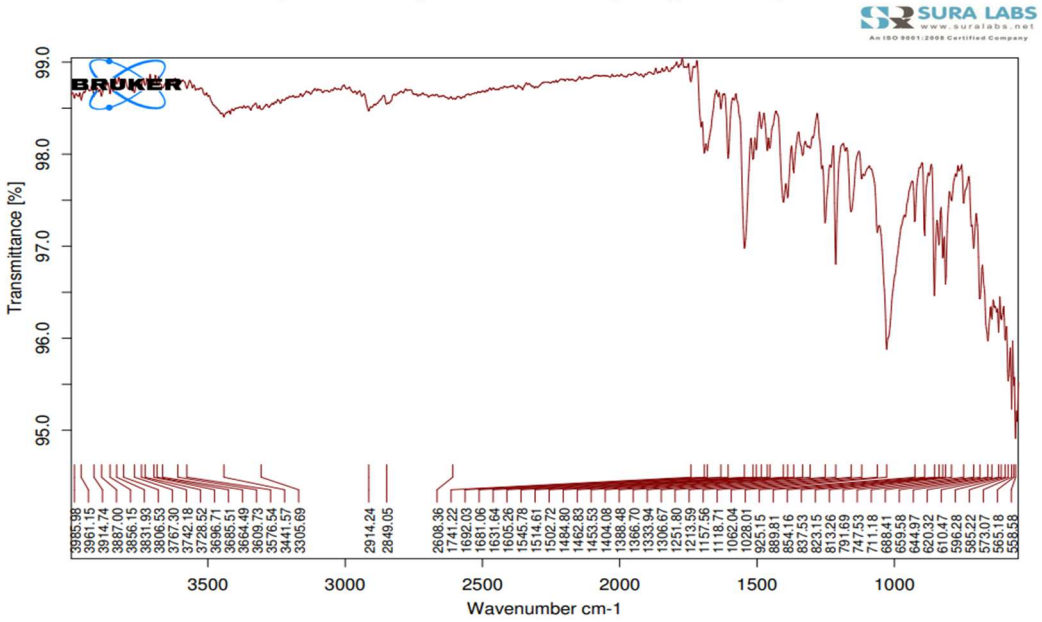


**Fig 3: FT-IR Spectrum of Optimised Formulation**

## CONCLUSION

Total Nine Formulations (N1 – N9) were prepared using with different polymers. All these ratios were compatibility with drug and showed good results in increasing manner and dissolution profile of Naftopidil drug. N5 batch showed drug content 99.86 % yield and the highest drug release 99.71% optimized solid dispersion batch was subjected to accelerated storage conditions. At regular intervals the solid dispersions was characterized for physical appearance, drug content and in vitro drug release. There was no change in the physical appearance of solid dispersion during the study period.

## BIBLIOGRAPHY

1. Sameer Singh, Raviraj Singh Baghe and Lalit Yadav. A review on solid dispersion. Int. J. of Pharm. & Life Sci. (IJPLS), Vol. 2, Issue 9: Sep.: 2011, 1078-1095.
2. Noyes, A.A., and Whitney W.R., (1897). The rate of solution of solid substances in their own solutions, J. Am. Chem. Soc., 19: 930-934.
3. Sengodan guruswamy, V., and Mishra, D.N., 2006. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. The Pharmaceutic. Soc. Jap., 126(2): 93-97.

4. Van Drooge, D.J. et al. (2006). Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int. J. Pharm,. 310: 220–229.
5. Galia, E., Nicolaides, E., HoÈrter, D., LoÈbenberg, R., Reppas, C., and Dressman, J.B., (1998). Evaluation of various dissolution media for predicting in vivo performance of class I and II drugs. Pharm. Res., 15: 698-705.
6. Hancock, B.C., and Zogra, G., (1997). Characteristics and significance of the amorphous state in pharmaceutical systems (review). J. Pharm. Sci., 86: 1-12.
7. Hoerter, D., and Dressman, J.B., (1997). Influence of physicochemical properties on dissolution of drugs in the gastrointestinal tract (review). Adv. Drug Delivery Rev., 25-14.
8. Loftsson, T., and Brewster, M.E., (1996). Pharmaceutical application of cyclodextrins. 1.
9. Drug solubilisation and stabilization (review). J. Pharm. Sci., 85: 1010-1025.
10. Sekiguchi, K., and Obi, N., (1961). Studies on absorption of eutectic mixtures. I. A comparison of the behavior of eutectic mixtures of sulphathiazole and that of ordinary sulphathiazole in man. Chem. Pharm. Bull., 9: 866-872.
11. Taylor, L.S., and Zogra, G., (1997). Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. Pharm. Res., 14: 1691-1698.
12. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1966). Increasing dissolution rates and gastrointestinal absorption of drugs via solid solutions and eutectic mixtures II ± experimental evaluation of a eutectic mixture: urea±acetaminophen system. J. Pharm. Sci., 55: 482-487.
13. Chiou, W.L., and Rielman, S., (1971). Pharmaceutical application of solid dispersionsystem. J.Pharm.Sci., 60: 1281-1302.
14. Goldberg, A.H., Gibaldi, M., and Kanig, J.L., (1965). Increasing dissolution rates andgastrointestinal absorption of drugs via solidsolutions and eutectic mixtures I theoretical considerations and discussion of the literature. J. Pharm. Sci., 54: 1145-1148.
15. Kreuter, J., Kreuter, J., and Herzfeldt, C.D., (1999).Grundlagen der Arznei-formenlehre Galenik, 2, Springer, Frankfurt am Main. 262-274.