PREPARATION AND CHARACTERIZATION OF SOLID DISPERSION OF NORFLOXACIN USING MIXED HYDROTROPIC SOLUBILIZATION TECHNIQUE

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ABSTRACT
For the drugs having dissolution rate limited absorption improvement of aqueous solubility are prerequisite to enhance their therapeutic efficacy. In the present research solid dispersion of slightly aqueous soluble drug Norfloxacin was prepared using mixed hydrotropic solubilization technique. Different blends of sodium citrate, niacinamide and polyethylene glycol 4000 were used used for the preparation of solid dispersion. When Norfloxacin was mixed with Hydrotropic agents blend (1:1:1 of sodium citrate, niacinamide and polyethylene glycol 4000) highest solubility was obtained. Therefore it was selected for further evaluations such as scanning electron microscopy, *in vitro* dissolution study, differential scanning calorimetry and X ray diffraction analysis. Stability study of mixed hydrotropic solid dispersions also carried out according to ICH guidelines The surface characteristics of solid dispersion showed rough, disordered and intact structures, which subsequently help to dissolve Norfloxacin when comes in contact with aqueous fluid. The X.R.D. pattern of Norfloxacin showed intense and sharp peaks that prove crystalline nature of Norfloxacin. Differential scanning calorimetry indicated complete dispersion of Norfloxacin in the mixture of hydrotropic solvents. *In vitro* dissolution study indicated fastest drug release from solid dispersion and slowest drug release from bulk Norfloxacin. It was also observed that on increasing the concentration of solubilizing agent dissolution behavior was improved. The quick onset of action and better extent of absorption is expected after oral administration of these hydrotropic solid dispersions due to high initial rate of dissolution from hydrotropic solid dispersion as compared to initial rate of dissolution from bulk drug Norfloxacin alone. Stability studies indicated good chemical stability of all formulations at higher temperature.

Kew words: Hydrotropic solubilization, Norfloxacin, solid dispersion.

INTRODUCTION
High Throughput Screening technique optimizes the drug solely on binding site properties. It may lead to attainment of lead compounds with higher molecular mass and water insolubility[1, 2, 3; 4]. Dissolution rate limited absorption is the result of poor aqueous solubility of the drug. This fact was revealed from various literature reports. Improvement of aqueous solubility in such a case is a valuable assignment to improve therapeutic efficacy[5].

For the present research work Norfloxacin, a slightly water soluble drug was selected. Norfloxacin is a quinoline antibiotic. It is used to treat several bacterial infections. Solubility of Norfloxacin was increased by using mixed hydrotropic solid dispersion method. Solid dispersion technology is one of the important methods of increasing the dissolution rate and hence the rate of absorption and/or total bioavailability of poorly water soluble drugs. The common popular methods for the preparation of solid dispersions are solvent evaporation, fusion, and fusion-solvent methods.

Use of organic solvent has been totally eliminated in newly developed mixed hydrotropic solid dispersion technology. Hydrotropic agents are non-micelle-forming substances, either liquids or solids, organic or inorganic having capability of solubilizing poorly aqueous soluble compounds. Conventional Neuberg's hydrotropic salts (proto-type, sodium benzoate) are usually made up of two necessary portions, an anionic group and a hydrophobic aromatic ring or ring system. The anionic group is responsible for high aqueous solubility, which is a essential for a hydrotropic substance.

In this method mixture of two or more hydrotropic agents were used which may give remarkable synergistic enhancement effect on solubility of poorly water soluble drugs. This technique is very helpful in the formulation of dosage forms of poorly water soluble drugs to reduce the concentration of individual hydrotropic agents thus to minimize their side effects. Other advantages of this method are the solvent character is independent of pH, has high selectivity and does not require emulsification. Chemical modification of hydrophobic drugs, use of organic solvents, or preparation of emulsion system is not required in this technique. Sodium benzoate, sodium acetate, sodium bicarbonate, sodium chloride, sodium gluconate, thiourea, trisodium citrate and urea have been employed to enhance the aqueous solubility of many poorly water soluble drugs[6].

MATERIALS AND METHODS

MATERIALS

PEG 4000, niacinamide, sodium citrate and other chemicals were purchased from Vijay Scientific Centre, Gwalior. Norfloxacin was found as a gift sample from Viva Laboratories Pvt. Ltd., Ahmedabad.

METHODS

Solubilization studies

Determination of equilibrium solubility of Norfloxacin in distilled water[7]

Sufficient excess amount of Norfloxacin was added to screw capped amber colored glass vials containing 10 ml of distilled water. The vial was shaken mechanically for 12 hours at room temperature in rotatory flask shaker (Jyoti scientific industries, India). The solution was allowed to equilibrate for next 24 hours and then centrifuged for 5 minutes at 2000 rpm using a centrifuge (Remi Instruments Limited, Mumbai, India). The supernatant of vial was filtered through what man filter paper # 1. An aliquot of filtrate was diluted suitably with distilled water and analyzed spectrophotometrically at 272 nm (corresponding λ_{max} of Norfloxacin).[7]

Selection of hydrotropic agents

Several hydrotropic agents, sodium benzoate, sodium citrate, sodium acetate, PEG 4000, urea, niacinamide and sodium ascorbate with moderately high concentrations (10-40%) were tried out on the basis of literature survey. In order to select suitable hydrotropic agents for sufficient enhancement in solubility an approximate solubility determination method was used.

Twenty five ml of hydrotropic solution was taken in a 50 ml glass bottle and gross weight (including the cap) was noted. Then, few mg (by visual observation) of fine powder of Norfloxacin was transferred to the bottle. This bottle was shaken vigorously (by hand). When drug got dissolved, more drug (few mg by visual observation) was transferred to the bottle and again the bottle was shaken vigorously. Same step was performed repeated till some excess drug remained undissolved (after constant vigorous shaking for 10 minutes). Then again gross weight was noted. Approximate solubility and solubility enhancement ratios (solubility in hydrotropic solution/solubility in distilled water) were calculated using the value of difference in two readings (of weight),. When the solubility enhancement ratio determined was at least 5, such hydrotropic solution was selected for the drug for further studies.

Determination of equilibrium solubility of drug in different concentration of hydrotropic agent solutions

Aqueous solutions of selected hydrotropic agents (sodium citrate, niacinamide and PEG 4000) of known concentrations (10%, 20%, 30%, and 40%) were prepared in distilled water. Equilibrium solubility of Norfloxacin was determined using the method mentioned previously for the determination of equilibrium solubility in distilled water.

Determination of equilibrium solubility of drug in blends of hydrotropic agents

Aqueous solubility of Norfloxacin was determined in different blends of hydrotropic agents using the equilibrium solubility method.

$$\text{Solubility enhancement ratio} = \frac{\text{Solubility in particular hydrotropic solution}}{\text{Solubility in water}}$$

Blend CNP (sodium citrate, niacinamide and PEG 4000) (1:1:1) was found to be most effective in increasing aqueous solubility of Norfloxacin. Therefore it was selected to prepare physical mixture and solid dispersion of Norfloxacin.

Formulation Development

Preparation of Physical mixture of Norfloxacin

Norfloxacin and blend of hydrotropic agents CNP (1:1:1) were accurately weighed and transferred to a glass pestle and mortar and mixed for 10 min with intensive trituration. Then, powder mass was shifted through sieve number 60. After this, the physical mixture was kept in desiccator for 24 h and then stored in air-tight glass bottles. Composition of physical mixture is given in table 1.

Table 1: Composition of physical mixture of Norfloxacin

Formulation code	Ratio of Norfloxacin: blend CNP	Quantity of Norfloxacin (g)	Quantity of hydrotropic agents (g)		
			Sodium citrate	Niacinamide	PEG 4000
PM	1:10	2	6.66	6.66	6.66

Preparation of solid dispersion of Norfloxacin[8]

The hydrotropic agents were dissolved in minimum possible quantity of distilled water Norfloxacin was weighed and added to the beaker. This mixture now placed on a magnetic stirrer and then stirred until most of the water gets evaporated. Now this mix was spread on several watch glasses to accelerate the drying of hydrotropic mixture. After drying, the hydrotropic mixture, it was scrapped with the help of a spatula and the mixture was transferred to desiccator to remove the remaining moisture. The hydrotropic mixture was stored in amber colored screw capped bottles until further evaluation. Composition of solid dispersion prepared using different ratio of Norfloxacin and hydrotropic agents is given in table 2.

Table 2: Composition of solid dispersion formulations of Norfloxacin

S. No.	Formulation code	Ratio of drug: blend CNP	Quantity of drug (g)	Quantity of hydrotropes (g)		
				Sodium citrate	Niacinamide	PEG 4000
1	NF1	1:6	2	4	4	4
2	NF2	1:8	2	5.33	5.33	5.33
3	NF3	1:10	2	6.66	666	6.66

Evaluation

Percentage Yield[9]

Percentage yield (%) of mixed hydrotropic solid dispersions were calculated to know about percent yield or efficiency of any method, thus it helps in selection of appropriate method of production of solid dispersion. It was calculated using the following formula:

$$\% \text{ Percentage yield} = \frac{Practical\ Yield}{Theoreticla\ yield} \times 100$$

Particle size analysis: [10]

An optical microscopic method was used for the determination of the size distribution in terms of average diameter (d_{avg}) of the mixed hydrotropic solid dispersions. A compound microscope fitted with a calibrated ocular micrometer and a stage micrometer slide was used to count at least 100 particles.

Drug content: [11]

The 25 mg of powdered mixed hydrotropic solid dispersion was accurately weighed and transferred to a 25 mL volumetric flask. About 15 mL of simulated gastric fluid (pH 1.2) was added and flask was shaken to dissolve the formulation completely. Then, volume was made up to the mark with simulated gastric fluid (pH 1.2). Then 1 mL of this solution was placed in a 50 mL volumetric flask and then the volume was made up to the mark with simulated gastric fluid (pH 1.2) and absorbance of this solution was measured at wavelength of 277 nm against blank. Corresponding equation of regressed line was used for the quantitative estimation.

Bulk density[11]

Bulk density was determined by pouring the weighed quantity of mixed hydrrotropic solid dispersion powder into a measuring cylinder and the volume was measured. It is expressed in gm/mL and is given by following formula. It is expressed in gm/ml.

$$\text{Bulk density} = \frac{Mass\ of\ powder}{Bulk\ volume\ of\ powder}$$

Tapped density[11]

Tapped density was determined by using graduated cylinder. An accurately weighed powdered sample of mixed hydrotropic solid dispersion was carefully added to the graduated cylinder with the help of funnel. The starting volume was measured and the sample was tapped on a horizontal base. Tapping was continued until no further change in powdered sample volume was seen. Tapped density was calculated using the following formula. It is expressed in gm/ml.

$$\text{Tapped density} = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ powder}$$

Carr's Index (I) [11]

It indicates the ease with which a material can be induced to flow and powder compressibility. It is expressed in percentage and is determined by the formula:

$$I = \frac{Dt - Db}{Dt} \times 100$$

Where, D_t = Tapped density of the powdered sample

D_b = Bulk density of the powdered sample.

Angle of Repose[12]

Funnel method was used for the determination of angle of repose. A funnel was fixed at a height of approximately of 2-4 cm over the platform. The mixed hydrotropic solid dispersion samples were passed slowly along with the wall of funnel, till the conical pile of the powder formed. For the measuremet of angle of repose height of the cone of powder and radius of the heap of the powder was measured. Angle of repose is determined by the following formula:

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

Where, θ = angle of repose, h = height of the cone, r = radius of heap.

Scanning Electron Microscopy (SEM) [13]

The surface morphology of Norfloxacin, hydrotropic agents and mixed hydrotropic solid dispersion of Norfloxacin (NF3) was determined using an analytical scanning electron microscope (LEO-435VP, Leo Co.

Ltd, UK). The samples were lightly dredged on a double-sided adhesive tape adhered to an aluminum stub. The stubs were then coated with platinum to a thickness of about 10Å under an argon atmosphere using a gold-sputter module in a high-vacuum evaporator. Subsequently, the stubs containing the coated samples were set in the scanning electron microscope chamber. The coated sample was then randomly scanned and photomicrographs were taken.

In vitro dissolution study[14]

In vitro dissolution studies of Norfloxacin, physical mixture and mixed hydrotropic solid dispersions of Norfloxacin were carried out in a USP standard dissolution test apparatus-II (Jyoti scientific industries, India), employing a paddle stirrer at 75 rpm using 900 mL of simulated gastric fluid (pH 1.2) at 37±0.5ºC as dissolution medium. Samples were collected at 10, 20, 30, 40, 50 and 60 minutes. The dissolved Norfloxacin in medium was measured using UV spectrophotometer at 277 nm.

Differential scanning calorimetry[15]

DSC analysis was performed by using a differential scanning calorimeter (Jade, PerkinElmer, USA). Powdered samples of 4.3 mg (Norfloxacin pure, solid dispersion NF3 and hydrotropic agents) weight were heated in hermetically sealed aluminum pans over a temperature range of 30-300°C at a constant rate of 10°C/min.

X-ray diffraction analysis[16]

The powder X-ray diffraction spectra of Norfloxacin, mixed hydrotropic solid dispersion of Norfloxacin NF3 and the hydrotropic agents were obtained using RU-H R, Horizontal Rotaflex rotating anode X-ray generator instrument, Rigaku (Rigaku International Corporation, Tokyo, Japan). The sample was spread on a graticule and pressed in such a way that sample did not fall on keeping the graticule vertical. The graticule was placed in sample holder and exposed to C K -radiation (40 KV, 50 MA), 2θ=5° to 40° at a scanning speed 4°/min and step size 0.02° 2θ.

Stability studies of drug formulations[17,18,19]

The stability of a product may be characterized as the degree to which a product holds, within specified limits, all through its period of storage and utilize, the same properties and characteristics hold at the time of its packaging. The characteristics incorporate physical, chemical, microbiological, therapeutic and toxic properties and all are required to stay within acceptable limits till the time of use of the product by a patient. Stability study show the way in which quality of a drug substance or drug product changes with time under the effect of various environmental factors, such as temperature, humidity and light. It measures and documents the ability of a product to hold its potency prior to its predicted expiration date. For the determination of acceptable shelf-life, proper storage conditions and suitable packaging these data are utilized. Stability study is performed at all stages of the development, production and marketing process for quality control and monitoring purposes.

All medicated products decompose with time. Instabilities in modern formulations are often detectable only after considerable storage periods under normal conditions. To assess the stability of a formulated product it is usual to expose it to 'high stresses, i.e. conditions of temperature, humidity and light intensity that are known from experience to be likely causes of breakdown. High stress conditions enhance the deterioration of the product and therefore reduce the time required for testing. It must be emphasized that extrapolations to normal' storage conditions must be made with care and that the formulator must be beyond any doubt that such extrapolations are valid. It is advisable therefore to run concurrently a batch under expected normal conditions to confirm later that these assumptions are valid. Good formulations will invariably break down more slowly than poor ones.

Chemical Stability study of Hydrotropic Solid Dispersions and Physical mixtures of Drugs

Different mixed hydrotropic solid formulations of Norfloxacin were subjected to chemical stability testing. Powders of various formulations were kept in 10 ml colourless glass vials and vials were plugged and sealed. Vials were kept at room temperature, at 55ºC in oven and at 40ºC with 75% RH in ICH certified stability chamber. The samples were withdrawn at different time intervals and drug contents were determined spectrophotometrically. To calculate the drug content, the formulations were analyzed by the same procedures which were applied to determine their drug contents after their formulations. The initial drug content for each formulation was considered as 100.00%.

RESULTS AND DISCUSSION

Solubilization studies

Determination of equilibrium solubility of drug in distilled water

Solubility of Norfloxacin in distilled water was found to be 0.25 mg/ml.

Selection of ratios of drug and hydrotropic agents for formulation development

On the basis of the results obtained from the approximate solubility determination study, the following three hydrotropes were selected.

a) Sodium citrate
b) Niacinamide
c) PEG 4000

Determination of equilibrium solubility of Norfloxacin in different concentration of hydrotropic agent solutions

Table 3: Equilibrium solubility data of Norfloxacin in different concentration of hydrotropic solution

Name of hydrotropic agent	Particular	10 %	20 %	30 %	40 %
SC	Equilibrium solubility	1.06	1.54	1.64	1.93
	Solubility enhancement	35.33	51.3	54.6	64.33
NM	Equilibrium solubility	0.54	0.84	1.21	1.44
	Solubility enhancement	18	28	40.3	48
P4	Equilibrium solubility	1.03	1.91	2.96	4.03
	Solubility enhancement	34.33	63.6	98.6	144.3

Table 4: Equilibrium solubility data of Norfloxacin in different hydrotropic blends

Name and concentration of hydrotropic agent	Equilibrium solubility	Solubility enhancement ratio
SC (20%) + NM (20 %)	2.41	80.33
SC (20%) + P4 (20%)	5.23	174.33
NM (20 %) + P4 (20%)	3.69	123
SC (13.3 %) + NM (13.3 %) + P4 (13.3%)	6.04	201.33

Equilibrium solubility data revealed that highest solubility was obtained in case of mixture of all there hydrotropic agents (sodium citrate, niacinamide and PEG 4000 in the ratio of 1:1:1).

Table 5: Percentage yield, average particle size and drug content of solid dispersion of Norfloxacin

Solid dispersion formulation	Percentage yield (%)	Average particle size in µm	Drug content (%)
NF1	98	52.4	97.4

NF2	97.2	60.1	96
NF3	98.5	58.7	97

Table 6: Flow characteristics of solid dispersion of Norfloxacin

Solid dispersion formulation	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Angle of repose (°)
NF1	0.78	0.94	17.02	24.2
NF2	0.74	0.89	16.82	21.3
NF3	0.73	0.88	17.04	21.6

Values of Carr's index and angle of repose revealed good flow properties of all three formulations.

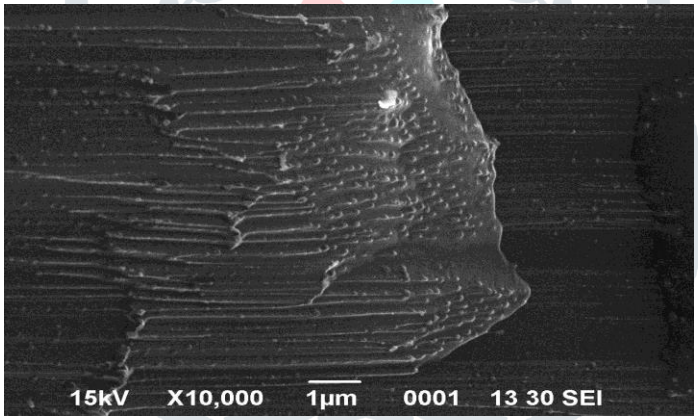


Fig. 1: Scanning electron micrograph of Norfloxacin

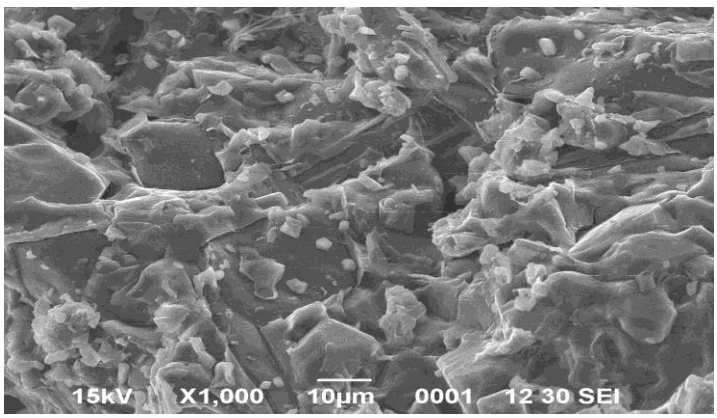


Fig. 2: Scanning electron micrograph of Niacinamide

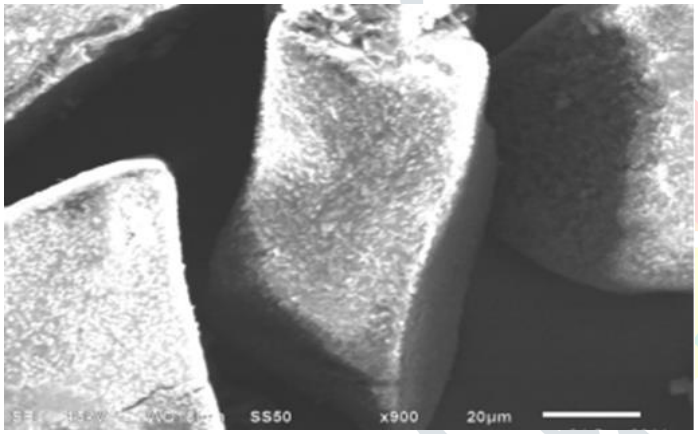


Fig. 3: Scanning electron micrograph of PEG 4000

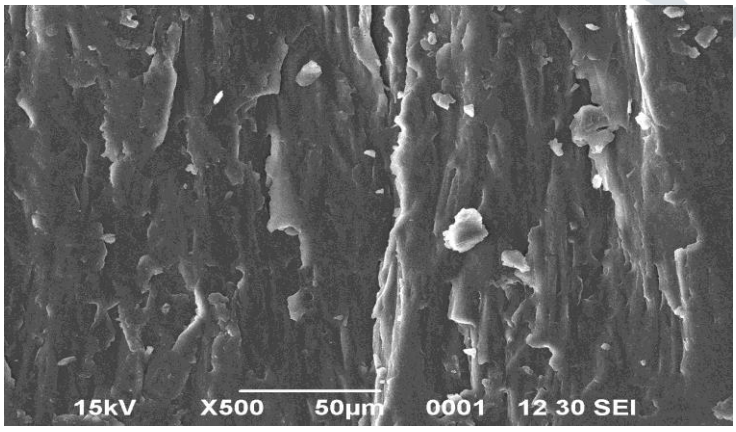


Fig. 4:Scanning electron micrograph of Sodium citrate

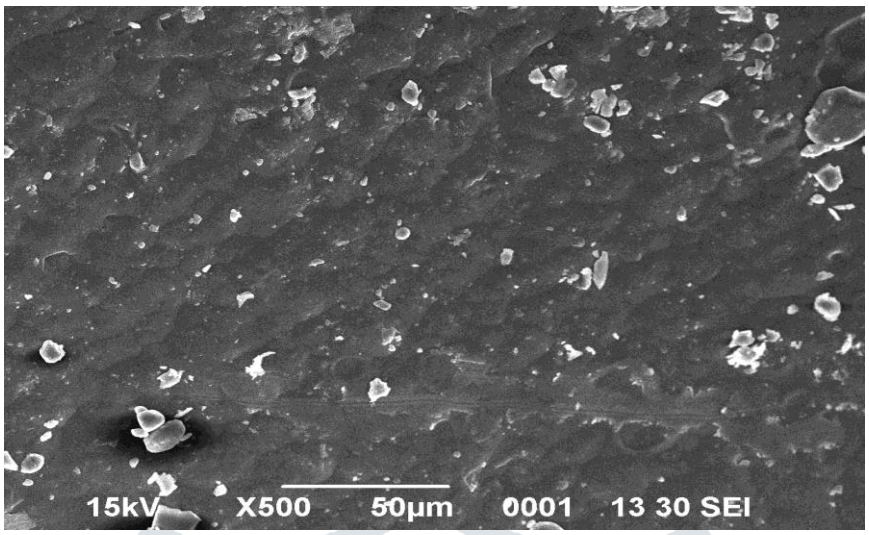


Fig. 5: Scanning electron micrograph of mixed hydrotropic solid dispersion (1: 10 Norfloxacin: CNP blend)

Surface micrographs of mixed hydrotropic solid dispersion of Norfloxacin and pure Norfloxacine were determined using scanning electron microscopic technique. The scanning electron micrograph of pure Norfloxacin showed large crystalline forms of drug agglomerates with ordered shape and size in Fig.1. Scanning electron micrograph of solid dispersion prepared using interaction of Norfloxacinn and hydrotropic agents at micro level. The particle size of combined matrix showed marked decrease in size. The surface characteristics of solid dispersion showed rough disordered and intact structures, which subsequently help to dissolve Norfloxacin when comes in contact with aqueous fluid.

In vitro dissolution study

Table 7: Cumulative % drug release of pure Norfloxacin, physical mixture and mixed hydrotropic solid dispersions of Norfloxacin from simulated gastric fluid (pH 1.2)

Time in min.	Cumulative % drug release from pure drug, physical mixture and solid dispersions of Norfloxacin in simulated gastric fluid (pH 1.2)				
	Norfloxacin	PM	NF1	NF2	NF3
0	0	0	0	0	0
10	8±1.2	14±1.5	26.3±1.6	23±2.6	25±2.5
20	13.4±0.8	25.1±1.3	42.1±2.2	46.7±1.5	49.1±2.6
30	21.3±1.8	40.6±1.8	49.6±2.8	52.1±2.9	56.2±1.5
40	27.2±0.9	51.2±0.9	66.2±1.9	68.1±1.8	73.5±1.7
50	31±1.6	60.3±1.9	79.4±0.9	82.8±1.5	86.4±0.9
60	33.2±0.5	69±2.5	84.7±0.9	87.6±1.4	91.7±1.2
70	39.5±1.5	74.3±0.9	89.8±0.5	91.2±1.1	95.4±1.2
80	42.4±0.8	80.3±1.3	93.8±0.5	97.7±1.2	99.2±1.1

(Mean ± SD, n=3)

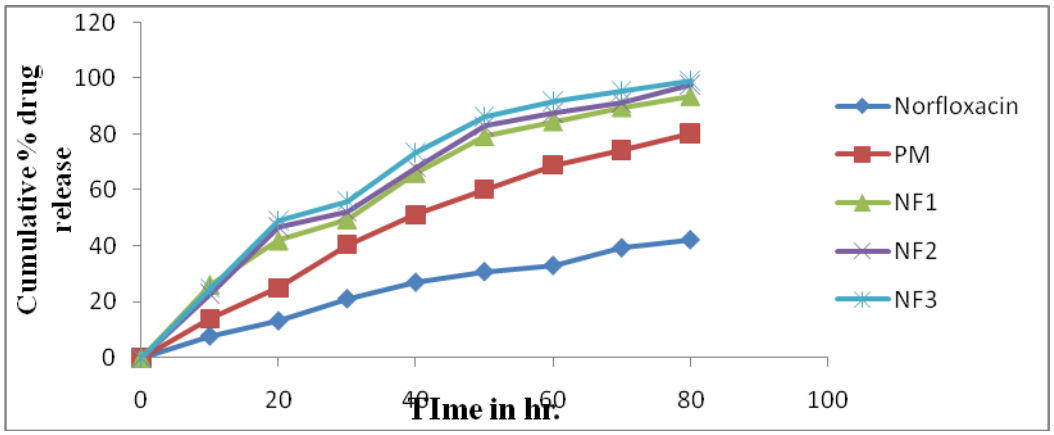


Figure 6: Cumulative % drug release of pure Norfloxacin, physical mixture and mixed hydrotropic solid dispersions of Norfloxacin from simulated gastric fluid (pH 1.2)

Table 8- Cumulative % drug release of pure Norfloxacin, physical mixture and mixed hydrotropic solid dispersions of Norfloxacin from simulated intestinal fluid (pH 6.8)

Time (min)	Cumulative % drug release from physical mixture and solid dispersions of Norfloxacin in SIF (pH 6.8)				
	Norfloxacin	PM	NF1	NF2	NF3
0	0	0	0	0	0
10	9.7±1.2	16.1±1.6	22.5±1.1	24.6±0.2	23.2±1.1
20	16.2±0.4	27.6±0.6	36.3±0.2	37.2±1.2	41.4±0.5
30	25.2±1.2	42.7±1.2	59.4±0.6	62.5±1.5	66.2±1.3
40	29.1±1.7	54.5±0.8	69.8±1.2	73.4±0.1	78.5±0.2
50	36.4±0.5	64.2±1.1	82.1±0.6	85.4±1.2	86.9±1.3
60	41.6±1.2	71.7±1.8	88.3±1.2	89.3±0.2	92.1±1.4
70	42.8±0.7	76.1±0.6	91.6±1.2	93.2±1.6	97.2±1.1
80	44.8±1.2	79.1±1.2	95.9±1.1	98.4±0.6	99.3±0.6

(Mean ± SD, n=3)

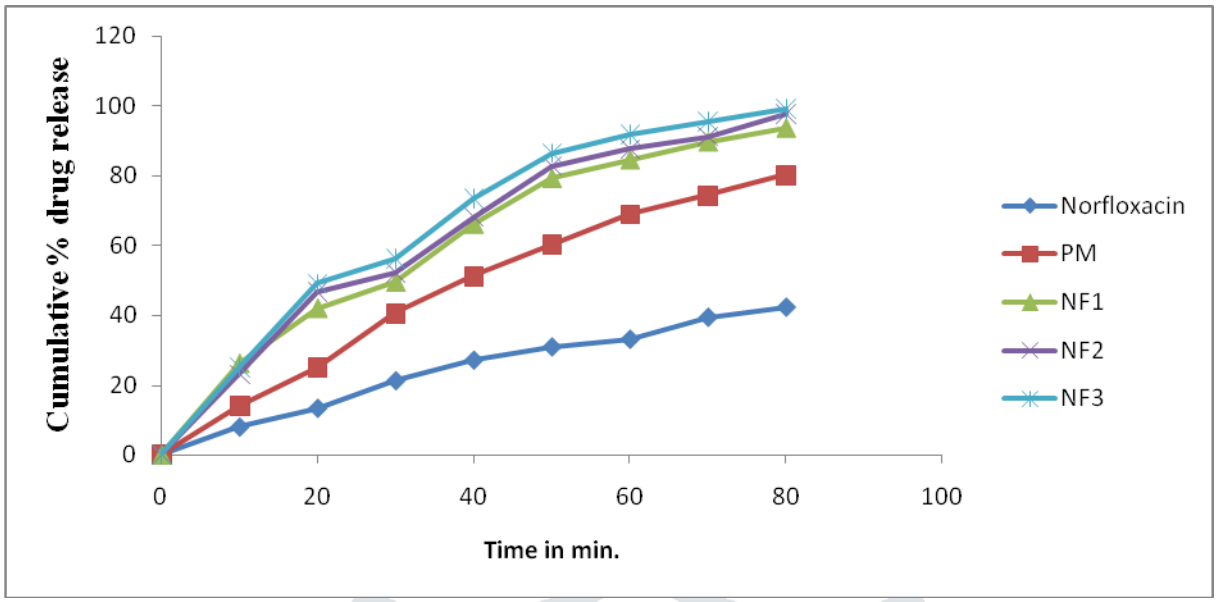
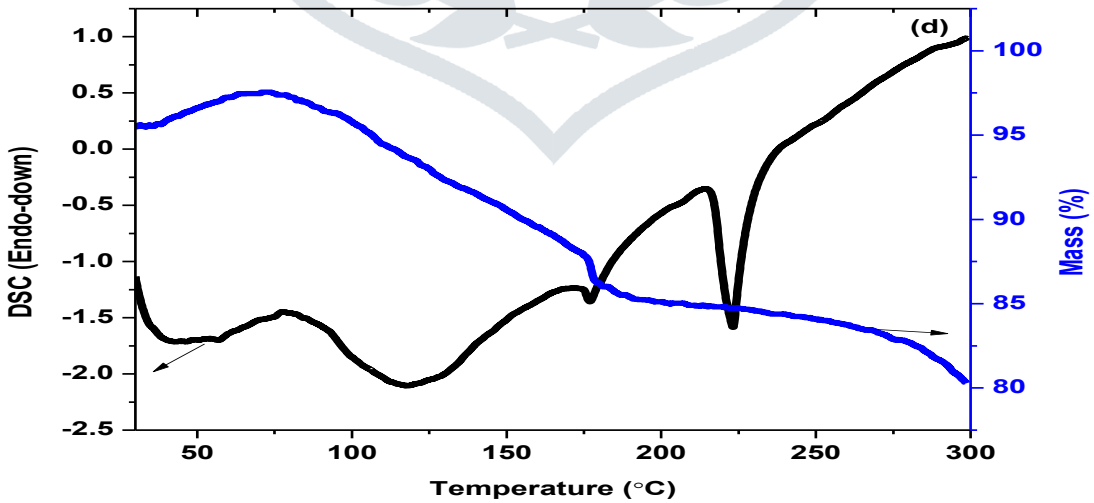


Figure 7: Cumulative % drug release of pure Norfloxacin, physical mixture and mixed hydrotropic solid dispersions of Norfloxacin from simulated intestinal fluid (pH 6.8)

From tables (Table 7 and Table 8) and figures (Fig.6 andFig.7), drug release rate was found to be in following order: Mixed hydrotropic solid dispersions of Norfloxacin > physical mixture > pure Norfloxacin

Highest drug release rate from mixed hydrotropic solid dispersion might be due to decrease in particle size of combined matrix of Norfloxacin and hydrotropic agents. In comparison to pure Norfloxacin, the dissolution rate of physical mixtures was slightly increased probably because the hydrotropic agents can wet the surface of Norfloxacin particles and acts to solubilize them. It was also observed that on increasing the concentration of solubilizing agent dissolution behavior was improved. The quick onset of action and better extent of absorption is expected after oral administration of these mixed hydrotropic solid dispersions due high initial rate of drug release from hydrotropic solid dispersion as compared to initial rate of drug release from bulk drug Norfloxacin alone.

Differential Scanning Calorimetry



. 8: Differential Scanning Calorimetry graph of Norfloxacine

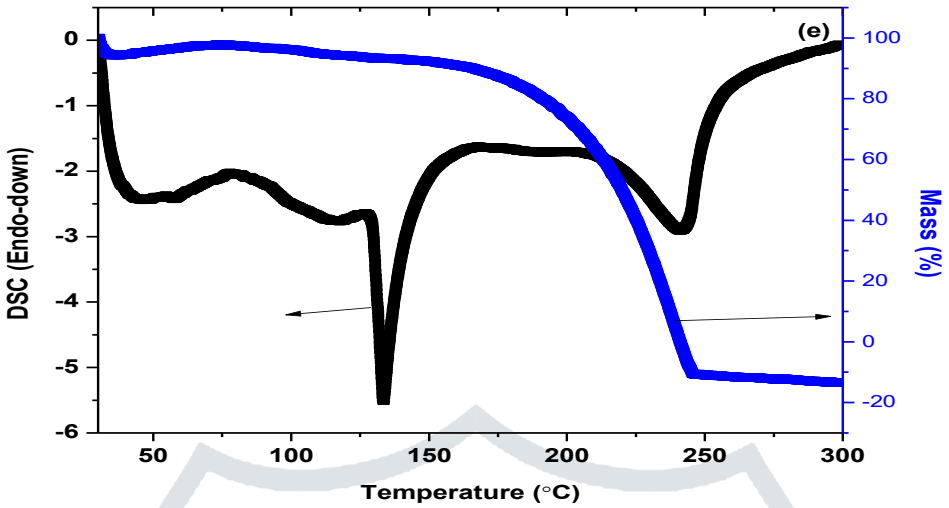


Fig. 9: Differential Scanning Calorimetry graph of Niacinamide

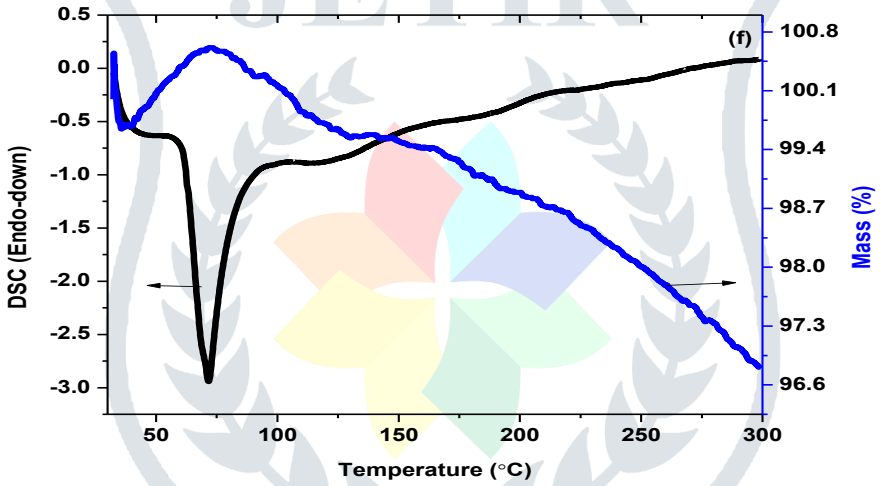


Fig. 10 : Differential Scanning Calorimetry graph of PEG 4000

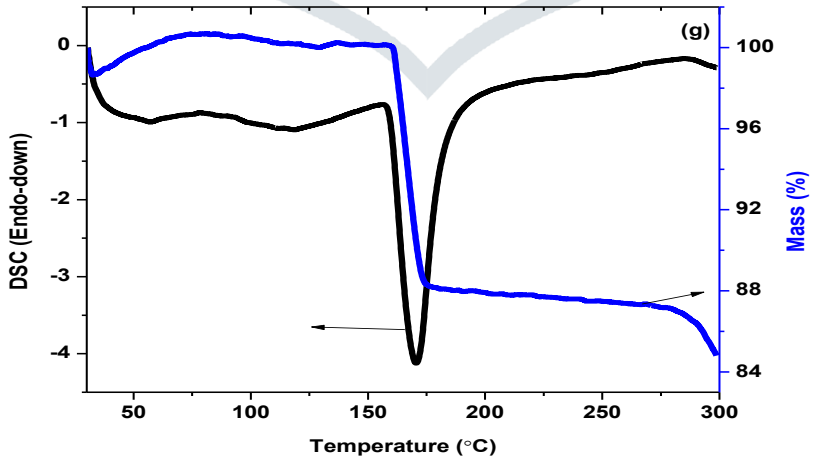


Fig. 11: Differential Scanning Calorimetry graph of sodium citrate

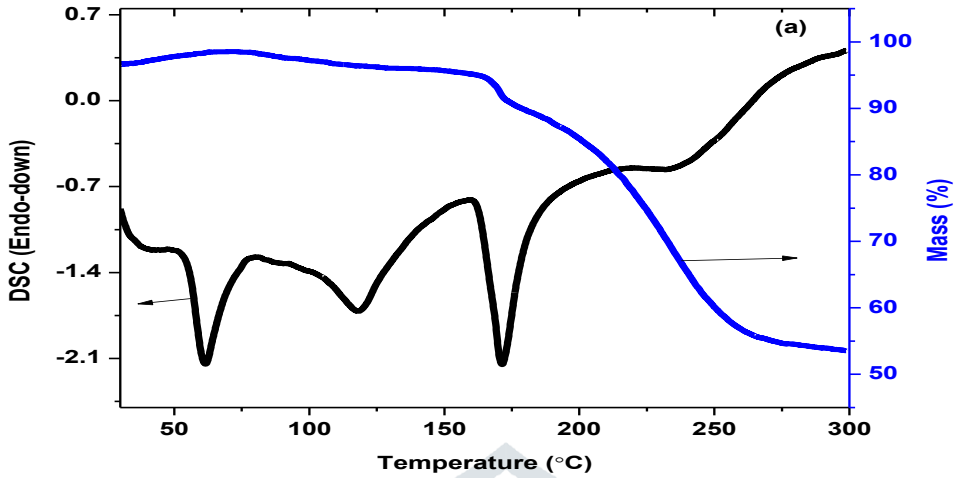


Fig. 12: Differential Scanning Calorimetry graph of solid dispersion (1: 10 Norfloxacin: CNP blend)

The Differential Scanning Calorimetry for Norfloxacin showed a sharp melting peak at 221ºC which corresponds to its melting point. This is indicative of the crystalline nature of the drug. The Differential Scanning Calorimetry curve for niacinamide showed a peak at 135ºC, PEG 4000 shows a peak on 79ºC, sodium citrate shows a peak on 300º C which corresponds to their melting points. The Differential Scanning Calorimetry curve for the solid dispersion of 1: 10 Norfloxacin: CNP showed a peak at 174 ºC but did not show any peak at 221ºC. The disappearance of the endothermic peak at 221ºC indicates that the drug is dispersed in the mixture of hydrotropic solvents. Thus the Differential Scanning Calorimetry studies indicate the formation of solid dispersions for Norfloxacin with CNP in the ratio of 1:10**.**

X-ray diffraction analysis

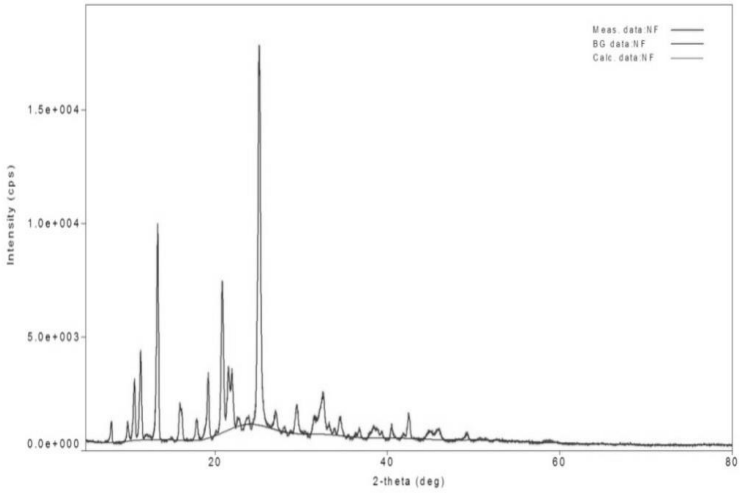


Fig. 13: X.R.D. spectra of pure Norfloxacin

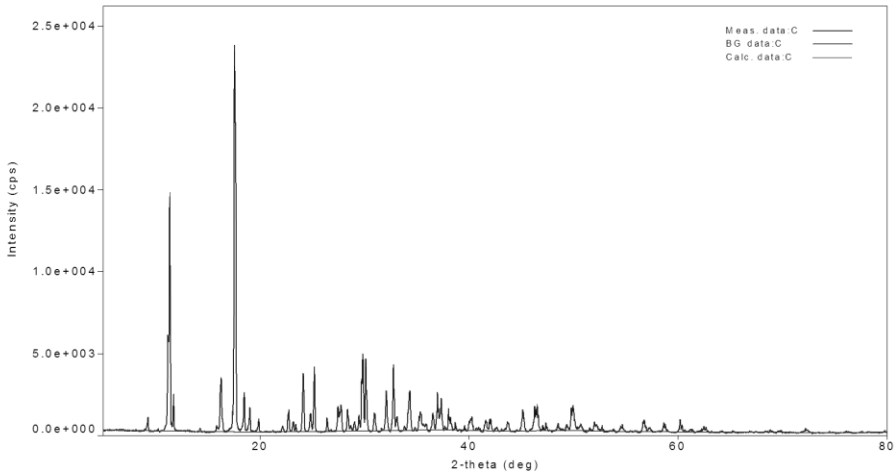


Fig. 14: X.R.D. spectra of sodium citrate

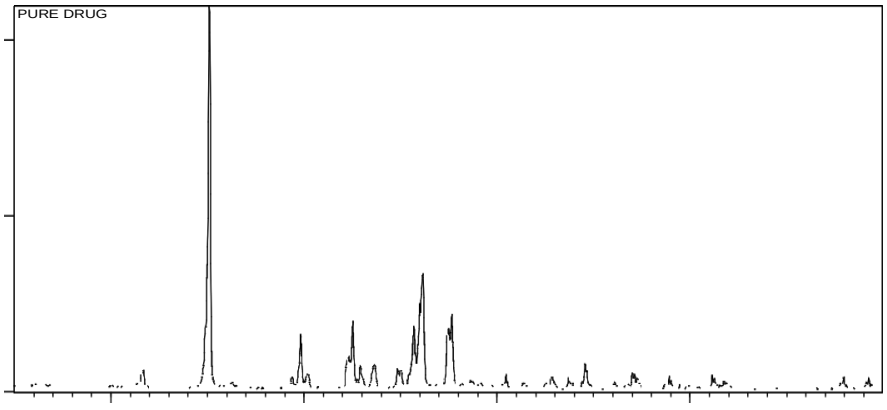


Fig. 15: X.R.D. spectra of niacinamide

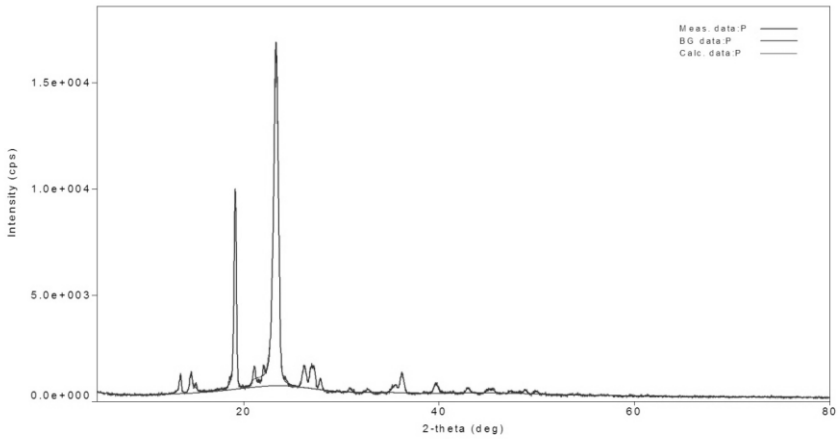


Fig. 16: X.R.D. spectra of PEG 4000

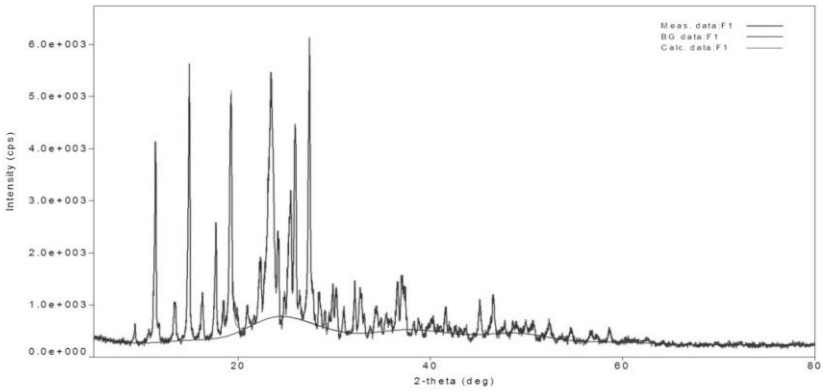


Fig. 17: X.R.D. spectra of solid dispersion (1: 10 Norfloxacin: CNP blend)

The X.R.D. pattern of Norfloxacin showed intense and sharp peaks that prove crystalline nature of Norfloxacin. Also X.R.D. patterns of solid dispersion gave sharp and intense peaks and are thus easily comparable with that of Norfloxacin.

STABILITY STUDIES

Table 5.27: Chemical stability data of Norfloxacin hydrotropic solid dispersions and physical mixture (n=3)

Condition	Time (months)	Percent residual drug in formulations (mean ± S.D.)		
		NF1	NF2	NF3
Room temperature	1	99.63 ± 0.868	99.76 ± 2.307	99.69 ± 1.330
Room temperature	3	99.36 ± 0.720	99.26 ± 1.131	99.21 ± 1.992

Room temperature	6	99.13 ± 0.568	99.16 ± 1.107	99.19 ± 1.330
40°C/75% RH	1	98.56 ± 0.720	98.76 ± 1.131	98.51 ± 0.992
40°C/75% RH	3	98.51 ± 0.868	98.51 ± 2.307	98.39 ± 1.330
40°C/75% RH	6	98.36 ± 0.720	98.26 ± 1.131	98.21 ± 0.992
55°C	1	98.33 ± 0.868	98.76 ± 2.307	98.69 ± 1.330
55°C	3	97.36 ± 0.720	97.26 ± 1.131	97.21 ± 0.992
55°C	6	97.12 ± 0.720	97.16 ± 1.131	97.11 ± 0.992

The residual drug content after storage for 6 months at room temperature in all formulations was above 98% (much above 90.00%), showing very good chemical stabilities at room temperature. The residual drug contents after storage for 6 months at 40°C/75% RH in all formulations was above 96%, showing good chemical stabilities at moderate temperature. The residual drug content in all formulations was found to be above 97.00% after storage for 6 months at 55°C, proving good chemical stabilities at a higher temperature.

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REFERENCES:

1. Pillay V, Fassih R. Unconventional dissolution methodologies. Journal of Pharmaceutical Sciences. 1999; 88(9):843-851.
2. CuratoloW. Physical chemical properties of oral drug candidates in the discovery and exploratory development settings. Pharmaceutical Science & Technology Today. 1998; 1(9):387-393.
3. Patel DV, Gordon EM. Applications of small-molecule combinatorial chemistry to drug discovery. Drug Discovery Today. 1996;1(4):134-144.
4. Lipinski CA, Lipinski F, Domin BW, Feene PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advanced Drug Delivery. 2001; 46(1-3):3-26.
5. Thummar, J.M., Parmar, H., Prajapati, N., Pradhan, P., Upadhayay, U., A review on hydrotropy: a novel concept for solubility enhancement. IJPRD. 2012; 4(5):103-110.
6. Konno H, Taylor LS. Influence of different polymers on the crystallization tendency of molecularly dispersed amorphous felodipine. J Pharm Sci 2006; 95:2692-2705.
7. Tong W-Q (Tony). Practical aspects of solubility determination in pharmaceutical preformulation. In: Augustijns P, Brewster ME, editors. Solvent systems and their selection in pharmaceutics and biopharmaceutics. New York; Springer, 2007:137–149.
8. Akiladevi, D., Shanmugapandiyan, P., Jebasingh, D. and Basak, S. (2011). Preparation and evaluation of paracetamol by solid dispersion technique. *Int J Pharm Pharm Sci, 3*, 88-191.
9. Swamy NGN and Abbas Z. Preparation and In Vitro Characterization of Mucoadhesive Polyvinyl Alcohol Microspheres Containing Amlodipine Besylate for Nasal Administration. Indian J. Pharm. Educ. Res. 2012; 46: 52-58.

10. Swamy NGN and Abbas Z. Mucoadhesive microspheres containing Amlodipine Besylate for nasal administration; improvised preparation and *In vitro* characterization. Indian Drugs. 2011; 48:30-39
11. Masareddy RS, Bolmal UB, Patil BR, Shah V. Metformin HCl loaded sodium alginate floating microspheres prepared by ionotropic gelation technique: Formulation, evaluation and optimization. Indian J. Novel Drug delivery. 2011; 2:125-133.
12. Yunxia B, Sunada H, Yonezawa Y, Danjo K. "Evaluation of rapidly disintegrating tablets prepared by Direct compression method", Dev ind pharm, 25(5), 1999:571-681.
13. Widjaja E, Kanaujia P, Lau G, et al. Detection of trace crystallinity in an amorphous system using Raman microscopy and geometric analysis. Eur J PharmSci 2011; 42:45e54.
14. Chowdary KPR and Srinivasa Rao Y. Preparation and evaluation of mucoadhesive microcapsules of Indomethacin. Saudi Pharmaceutical journal. 2003b; 11: 97-103.
15. Osama AA, David SJ, Andrews GP. Understanding the performance of melt-extruded poly (ethylene oxide)-bicalutamide solid dispersions: Characterization of microstructural properties using thermal, spectroscopic and drug release methods. J Pharm Sci 2012; 101:200-213.
16. Forster A, Hempenstall J, Tucker I, et al. Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis. Int J Pharm 2001; 226:147-61.
17. Hirasawa, N., Ishise, S. Miyata, H. and Danjo, K. (2003). An attempt to stabilize nilvadipine solid dispersion by the use of ternary systems. *Drug. Dev. Ind. Pharm.*, *29*(9), 997-1004.
18. Singh, S. (2006) In; Pharmaceutical Product Development, Jain, N.K., (1st Edition), New Delhi: CBS Publishers and Distributors.
19. Pugh, J. (2002). In; Phramaceutics: The Science of Dosage Form Design, Aulton, M.E., (2nd Edition), Edinburgh: Churchill Livingstone.