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Enhancement of Solubility of Nimesulide in the Presence of Polymer with Milling Technique

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Abstract
Poor aqueous solubility of drugs generally leads to low dissolution rates, poor therapeutic efficiency and low bioavailability. The main aim of this study was to produce physical dispersions of Nimesulide with polymers Eudragit EPO and Mannitol and then subject it for milling, to analyze the role played by different type and concentrations of polymers and the mechanism of impact and attrition milling in enhancing the solubility of the pure drug and its physical dispersions. Using ball milling technique the physical dispersions of Nimesulide with the polymers, prepared in the ratios of 1:1, 1:3, 1:5 were subjected to size reduction for two different time intervals of 30 min and 90 min, individually. Particle size, flow property and solubility of the milled dispersions were assessed and compared with the non milled dispersions and the pure drug. The milled dispersions were fabricated into tablets and the evaluation parameters like weight variation, disintegration time, hardness and dissolution studies were conducted on the prepared tablets. In order to observe the changes in the solid state at powder level and molecular level, the formulations were characterized by Fourier Transform Infra Red Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and X-Ray Diffractometer (XRD). The results obtained show that the physical dispersions prepared by milling with Mannitol helped in increasing the dissolution rate of the drug.

Key words: Eudragit EPO, impact attrition milling, mannitol, physical dispersion

INTRODUCTION

Many drugs are found to have low aqueous solubility which can be attributed to their large particle size, hydrophobic nature or crystallinity of the drug [1, 2]. A number of methods have been developed to increase the solubility of such drugs which include physical modifications for size reduction like micronization, nanosuspensions; modification of the crystal habit by poly and pseudo polymorphs, complexation, use of surfactant and solubilizing excipients, co-crystallization, solvent deposition and so on [3].

Nimesulide, a Non-Steroidal Anti-Inflammatory drug (NSAID) with chemical name N-4-Nitro-2phenoxyphenyl methanesulfonamide is a COX-2 inhibitor used commonly as an analgesic and is found to be sparingly soluble in water (0.01mg/ml) [4, 5].

Milling is a mechanical process used in pharmaceutical industries for size reduction of particles. It uses impact and attrition forces to break larger particles to smaller ones thereby increasing the surface area of the particles [6, 7]. Hence milling can also be used as a method to enhance solubility of the drug. But milling results in re-aggregation of the particles and also recrystallisation [7]. In order to avoid the above problems milling of the drug is performed in the presence of carriers. Milling is often preferred because it is a faster process as compared to many other methods.

The carriers used as solubility enhancers include urea [8], polyvinyl pyrrolidine [9], poly ethylene glycol [10], mannitol [8], hydroxypropylmethyl cellulose, β-cyclodextrin [11] etc. In the present study Mannitol and Eudragit EPO are used as the carriers. Mannitol is obtained from natural sources and helps in increasing the wettability of the drug due to its hydrophilic nature [12]. Eudragit EPO is a synthetic polymer used as a film coating agent and a release modifier. The purpose of this study is to analyze the effect of milling on the physical dispersions of Nimesulide with the carriers, Mannitol and Eudragit EPO and to evaluate its influence in increasing the solubility of the drug.

METHODS AND MATERIALS

Materials

Nimesulide was obtained from Chatan & Chatan, Chennai, India. Eudragit EPO was purchased from Sigma Aldrich, India. Other chemicals obtained were Talc and Micro crystalline cellulose from Sd fine –Chem limited, Mumbai, India, Sodium starch glycolate from LOBA chemicals private limited and Magnesium stearate from Paxmy speciality chemicals. All chemicals and reagents used were of analytical grade.

Ball Mill

The Ball mill was purchased from Khera Pvt. Ltd., New Delhi, India. It is cylindrical in shape with an inner diameter of 33.4 cm and outer diameter of 37 cm. The height of the mill was 17.5 cm. There are three baffles attached inside the cylinder with length and thickness of 17.2 cm and 0.9 cm, respectively.

Methodology

Preparation of solid dispersions

The drug and the polymers were weighed and mixed in three different ratios of 1:1, 1:3 and 1:5 individually and the pure drug of 1g was weighed separately. The prepared physical dispersions and pure drug were further subjected to size reduction with impact and attrition forces by milling using a ball mill. 10 iron balls were placed in the milling vessel along

with the physical mixture and rotated at a speed of 84 rpm for 30 minutes and 90 minutes separately. The pure drug was also milled for the same time intervals as the physical dispersions, which were noted for better comparison studies (Table 1).

Table 1: Composition of Ball Milled Nimesulide Dispersions

Batch Code	Weight of the drug (g)	Polymer weight (g)	Milling time (min)
NM1	1	1	30
NM2	1	3	30
NM3	1	5	30
NM4	1	1	90
NM5	1	3	90
NM6	1	5	90
NEE1	1	1	30
NEE2	1	3	30
NEE3	1	5	30
NEE4	1	1	90
NEE5	1	3	90
NEE6	1	5	90
NP1	1	-	30
NP2	1	-	90

NM- Nemisulide and mannitol,
NEE- Nemisulide Eudragit EPO,
NP- Non-processed

Pre-formulation studies:
Derived properties such as angle of repose, bulk density, tapped density and Carr's index of the ball milled and non-milled powder formulations were evaluated to find out the flow property and the compressibility nature of the mixtures. Angle of repose was performed by funnel method [13] by pouring the powdered samples through a funnel on to a horizontal base to form a conical heap with a distance of 3cm between the base and the funnel. The internal angle between the surface of the heap and the horizontal base gives the angle of repose and hence the height and diameter of the heap was noted. Bulk density was measured as the ratio of mass of powder occupied by a known volume and it depends on the way in which particles are packed [13]. It was calculated by pouring the powder into a measuring cylinder and noting the bulk volume. This was then tapped for 300 times to obtain the tapped volume. The tapped volume was used to calculate the tapped density which is the density indicated after a specified compaction. The formulas given below were used for further calculations.

- Angle of repose= $\tan^{-1}$ (h/r) where, h- height of the heap, r- radius of the heap
- Bulk density =Mass/Bulk Volume
- Tapped density=Mass/Tapped volume
- Carr's index=((bulk volume-tapped volume)/bulk volume)*100

All the above procedures were repeated thrice and the mean and standard deviation was calculated and tabulated.

Preparation of tablets and capsules:
The pure drug and size reduced Nimesulide dispersions prepared with the help of ball mill were made into tablets with fixed average weight and each tablet containing the weight equivalent to 50 mg of the drug, using the tablet press (KI356, Khera instruments Pvt ltd, New Delhi). 1% of Magnesium stearate, 1% of Talc and 1% of Sodium Starch glycolate were used as lubricating, flow aid and disintegrating agent also provides compactness for the drug, respectively.
Powder equivalent to 50 mg of the drug was filled in empty gelatin capsules by manual filling. In order to avoid moisture absorption the tablets and capsules were stored in a desicator with silica gel and calcium carbonate as desicants.

Particle size analysis:
The ball milled dispersions of Nimesulide with Mannitol and Eudragit EPO were subjected to particle size measurements by using a calibrated compound light microscope by the well suited microscopy technique [14]. A small amount of each of the milled powder sample was spread over a glass slide, viewed under a microscope (Khera instruments Pvt ltd) with the help of eye piece micrometer, previously calibrated and the size was measured. Particle size of about 25 particles was noted and the average particle size was calculated using the formula:

$$\text{Average particle size} = \frac{\text{size of the individual particle}}{\text{Total number of particles}}$$

Solubility studies:
To detect and compare the solubility of pure drug with the ball milled Nimesulide dispersions, the solubility studies were carried out. Milled dispersions equivalent to 1 mg of Nimesulide was added to 2 ml of distilled water and was placed in a shaker for 24 hrs at room temperature. This was removed from the shaker and centrifuged at 4500 rpm for 10 min at 4ºC using a cooling centrifuge (C-24, Remi laboratory, India). The supernatant was diluted and the absorbance was analyzed using UV-Vis Spectrophotometer (Sistronic 117, Ahmedabad, India) at 397 nm and concentration was calculated using standard calibration curve [15].

Evaluation of tablets and capsules:
The tablets and capsules prepared using the ball milled physical dispersions of Nimesulide were evaluated for quality control parameters.

Weight variation:
6 tablets/capsules of each formulation were taken and weighed separately using electronic balance (Shimadzu Pvt. Ltd., India). The mean and standard deviation was calculated and tabulated.

Hardness:
Hardness testing was performed to analyze the ability of the tablets to withstand local permanent deformation. Hardness of 3 tablets from each batch of dispersion tablets were measured using Tablet hardness tester Mosanto type (Dolphin, Japan) [16].

Disintegration time:

Disintegration time for the tablets/capsules was analyzed using USP disintegration type 2 apparatus (Lab India, DT 1000). The temperature was maintained at 37°C and 900 ml of distilled water was used as the media [16].

Drug content:

To assess the ball milled Mannitol-Nimesulide and Eudragit EPO-Nimesulide dispersions for uniformity of drug content, assay for the milled samples was performed. 6 tablets/ capsules of each formulation were weighed individually and average mass was calculated; they were further triturated and equivalent weight of the drug was taken and dissolved in 10 ml of methanol. It was bath sonicated for 5 min and then diluted with distilled water. The absorbance was measured using UV-Visible spectrophotometer and the drug content was calculated by using standard calibration curve [9, 16].

***In vitro* dissolution studies**:

Dissolution plays a major role in increasing the bioavailability of a drug. Dissolution studies were performed to analyze the solubility enhancement in aqueous media, for the tablets and capsules containing the milled dispersions of Nimesulide with Mannitol and Eudragit EPO and milled pure drug, using USP dissolution type-1 (paddle) apparatus (DS 8000, Lab India) at 37±5ºC, 50 rpm in 900 ml distilled water. Each formulation containing 50 mg equivalent of the drug was placed into the dissolution medium. At predetermined time intervals of 5, 10, 15, 30, 45 and 60 min, 10 ml of the samples were withdrawn using a syringe and suitably diluted. The dissolution rate was calculated by measuring the absorbance of the samples by UV-Visible spectrophotometer (Systronics 117, Ahmedabad, India) at 397 nm with water as the blank [17].

Fourier Transform Infra-Red Spectroscopy: (FTIR)

FTIR analysis (Perkin- Elmer 200) was performed in order to find out the interaction between the drug and the polymers for ensuring better stability and compatibility of the drug. It was performed using potassium bromide disc technique. The samples were mixed with previously dried and saturated IR grade potassium bromide and placed on KBr press under hydraulic pressure of 150 kg/cm^2. The obtained translucent thin film was scanned over a range of 4000 to 400 cm^{-1} at ambient temperature.

Differential Scanning Calorimetry and Thermogravimetric Analysis: (DSC-TGA)

The thermal characteristics of the samples were analyzed using Differential scanning calorimeter and the weight loss with change in temperature was determined using Thermogravimetric analysis (SDT Q600 V20.9 Build 20), for analyzing the polymorphic changes in the milled dispersions of Mannitol and Eudragit EPO containing the drug Nimesulide. About 4 mg of the sample was placed in aluminium pans and then heated under nitrogen flow of 20 ml/min, at the rate of 10ºC/min within a range of 0º C to 500º C.

X-Ray Diffraction analysis:

The X-ray diffraction techniques are used for the determination of the crystal structure and atomic spacing of materials by constructive interference of monochromatic x-rays on the crystalline samples. The nature of milled powder solid dispersions was studied at room temperature using a X-Ray Diffractometer (Ultimata 3, Rigaku) over a 2θ range of 10º- 80º with a voltage of 40kV and a current of 30 mA and using Cu-Kα as the source.

RESULTS AND DISCUSSION

Preformulation studies:

Angle of repose, Bulk density, Tapped density were performed thrice and the mean with standard deviation was tabulated in table 2. The values show that milled dispersions of Mannitol and Eudragit EPO performed for different time intervals of both 30 and 90 minutes, have a better flow property as compared to the pure drug. The milled dispersions of mannitol with drug, both at 30 and 90 minutes have showed lesser angle of repose resulting in an increase in the flow as compared to pure drug and non-milled dispersions. Angle of repose was found to be around 29° for 90 minutes milled sample for 1:3 ratio. The milled dispersions of Eudragit EPO and the drug showed an increase in flow property as compared to the pure drug with an angle of repose of 24°, 31.6 and 36.5 for the 1:1,1:3 and 1:5 ratios respectively, for the 90 minutes milled dispersions.

Table 2: Preformulation Studies of Milled & Non Milled Physical Dispersions

Batch Code	Angle of repose (º)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)
NP1	29.246±2.016	0.354±0.021	0.5787±.032	38.532±5.832
NP2	26.226±2.545	0.295±0.014	0.5203±0.043	42.96±2.093
NM1	35.035±4.573	0.367±0.013	0.6011±0.009	38.84±1.346
NM2	36.317±6.847	0.424±0.035	0.67±0.027	36.403±8.063
NM3	33.1176±1.481	0.371±0.011	0.737±0.042	49.462±3.041
NM4	31.649±2.276	0.311±0.0116	0.562±0.045	44.7±2.15
NM5	28.238±0.349	0.354±0.005	0.668±0.018	47.47±1.429
NM6	31.166±2.289	0.381±0.010	0.585±0.015	34.949±1.39
NEE1	34.684±1.554	0.309±0.022	0.608±0.096	47.508±1.039
NEE2	37.608±1.083	0.310±0.003	0.504±0.015	42.620±1.039
NEE3	38.098±4.764	0.336±0.022	0.603±0.04	44.06±4.069
NEE4	24.959±0.849	0.3436±0.03	0.514±0.013	34.94±1.4
NEE5	31.647±4.449	0.349±0.022	0.527±0.018	34.15±0.681
NEE6	36.557±2.32	0.345±0.017	0.586±0.015	26.38±1.96
Before Milling				
NM1	40.851±3.031	0.307±0.022	0.536±0.014	42.546±4.393
NM2	45.091±1.687	0.384±0.012	0.638±0.019	39.736±0.95
NM3	44.275±2.981	0.4369±0.006	0.625±0.012	30.084±0.9507
NEE1	34.637±2.137	0.319±0.009	0.454±0.017	29.72±2.16
NEE2	32.283±3.111	0.288±0.003	0.449±0.025	35.518±4.471
NEE3	27.192±4.472	0.298±0.002	0.45±0.006	33.764±1.355
NP	42.500±1.220	0.4292±0.017	0.537±0.261	19.9493±3.624

Particle size analysis:

The average particle size of each formulation was given in table 3. The particle size of pure drug was found to be 16.5 µm, and that of milled drug for 30 and 90 minutes did not show any significant change in the particle size which might be due to agglomeration of the finely divided particles because of adhesion of the particles. Mannitol dispersion showed a reduced particle size whereas Eudragit EPO dispersion showed a slightly larger particle size which might be due to its strong binding nature.

Table 3: Physico-Chemical Evaluation And Particle Size Analysis For Tablets Of Milled Dispersions

Batch Code	Solubility (µg/ml)	Weight Variation (mg)	Hardness (kg/cm2)	Disintegration Time (min)	Particle size (µm)
NM1	46	0.085±0.01	1	2	11
NM2	45.125	0.182±0.02	2	2	17
NM3	51.875	0.285±0.02	1.5	2	15.4
NM4	51.125	0.097±0.018	1	2	14.6
NM5	63.375	0.189±0.011	1	2	6.6
NM6	50.875	0.285±0.016	1	2	14.2
NEE1	62.25	0.087±0.01	1	>60	18.2
NEE2	49.75	0.164±0.02	2.5	>60	17.4
NEE3	56	0.29±0.03	9	>60	16.6
NEE4	56.875	0.114±0.006	1.5	>60	16.6
NEE5	50.75	0.174±0.006	1.5	>60	15.4
NEE6	47	0.29±0.012	6	>60	13.4
NP	48.75	0.0938±0.012	1	>60	16.5
NP1	48.25	0.0946±0.011	1	>60	17.5
NP2	36.75	0.0938±0.012	1	>60	16.5
Solubility of dispersions before milling					
NM1	***NM2***	***NM3***	***NEE1***	***NEE2***	***NEE3***
84.75	97.5	72.5	106.75	65.625	61.375

1,2,3 represent 30 min milled dispersions of different ratios 1:1,1:3,1:5 and 4,5,6 represent 90 min milled solid dispersions of different ratios 1:1,1:3,1:5 of both Mannitol and Eudragit EPO. Also NP – pure drug, NP1 and NP 2 represent 30 min and 90 min milled pure drug.

Solubility studies:

The solubility of ball milled dispersions of Nimesulide with the polymers was shown in table 3. The milled and non-milled pure drug showed a solubility of 48.75µg/ml. Milling of the pure drug did not bring about any significant changes in the solubility. This might be due to re-aggregation of the particles, reduction in the wettability thereby decreasing the solubility.[7] The milled dispersions of the drug with carriers showed a slight increase in solubility. The non-milled dispersions of both mannitol and Eudragit EPO showed better results than Milled dispersions with 106.75 µg/ml for NEE dispersions at 90 min for 1:1 ratio and 97.5 µg/ml for NM dispersions at 90 min for the 1:3 ratio.

Evaluation of tablets and capsules:

The evaluation parameters of the tablets/capsules were tabulated in table 3. The and mean weight and the variation in individual weights were found to be within the pharmacopeial limits for all the formulations containing the milled dispersions. The hardness of the tablets prepared using pure drug was found to be very less. Tablets prepared using milled Eudragit EPO and drug showed a comparatively increase in the hardness which might because of Eudragit EPO being a strong binder. NM tablets showed less hardness which might be because mannitol being a very free flowing powder and requires high amount of binders for the preparation of tablets. Eudragit tablets showed high disintegration time of more than 60 min mainly because of its high binding capacity resulting in high hardness. Milled NM tablets disintegrated within 2 min due to its lesser hardness. The drug content of all milled dispersions was within the limits of 90-110% which reveals that optimum amount of drug is present in all the tablets and capsules.

***In vitro* release studies:**

Tablets of milled drug and mannitol dispersions of 30 minutes and 90 minutes have showed a dissolution rate of only 38% and 52% for the 1:1 ratio, respectively. Dissolution rate for 1:3 ratio was observed to be 81% in 45 min and 100% in 60 min for 30 minutes milled dispersions whereas dissolution rate reached 100% at 45 min for dispersions milled for 90 minutes. But at 1:5 ratio dissolution rate of about 80 % was obtained in 15 min and about 100% in 30 min for tablets of both 30 and 90 minutes milled dispersions. Similarly for NM capsules an increase in dissolution rate was observed for 1:5 ratio between 30 minutes and 90 minutes milled samples. 100% dissolution rate was observed within 15 min for 90 minutes milled dispersions.

Tablets prepared using milled drug with Eudragit EPO dispersion showed very low dissolution rate of only about 10% in 60 min. Capsules of dispersions of 90 minutes milled Eudragit EPO drug dispersion showed a 100% drug release for the 1:1 ratio and decreased for 1:3 and 1:5 ratios at the end of 60 minutes. Similarly 30 minutes milled dispersions at 1:3 ratio showed a good release whereas at other ratios dissolution rate was found to be comparatively low. Eudragit EPO tablets showed a very less release which might be due to the binding capacity of the polymer, resulting in an increase in the hardness of the tablets. The capsules of Eudragit EPO showed a better release at 1:1 ratio compared to 1:3 and 1:5 ratios, because lower concentration showed less binding resulting in more drug release. The lesser release from the capsules may also be attributed to the improper miscibility of Eudragit in aqueous media due to its hydrophobicity (Figure 1-8).

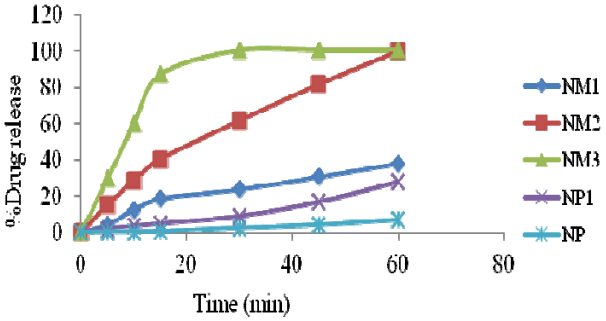

Figure 1: *In-vitro* dissolution studies for tablets of 30 min milled dispersions of NM

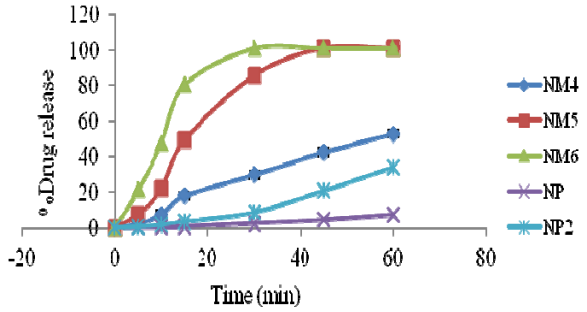

Figure 2 *In-vitro* dissolution studies for tablets of 90 min milled dispersions of NM

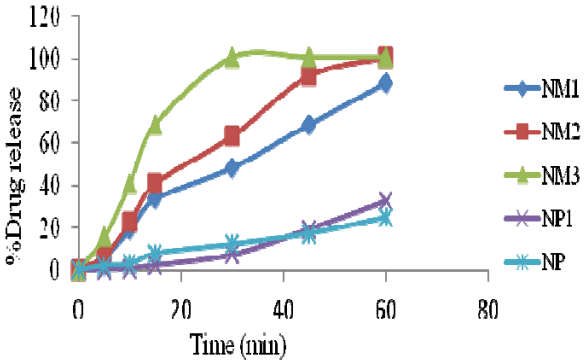

Figure 3 *In-vitro* dissolution studies for capsules of 30 min milled dispersions of NM

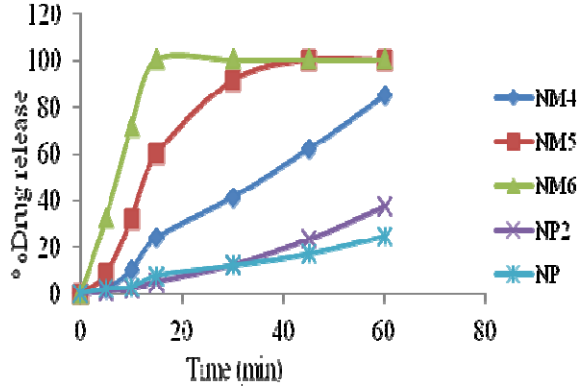

Figure 4 *In-vitro* dissolution studies for capsules of 90 min milled dispersions of NM

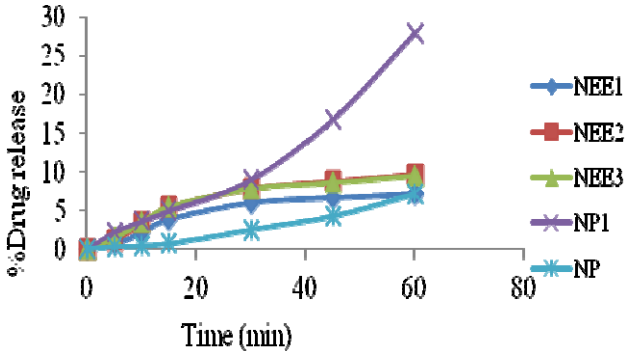

Figure 5 *In-vitro* dissolution studies for Tablets of 30 min milled dispersions of NEE

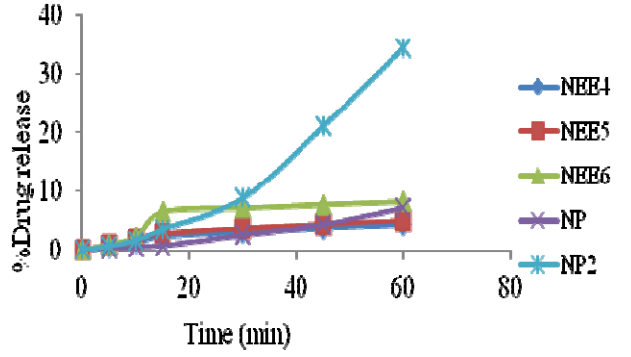

Figure 6 *In-vitro* dissolution studies for Tablets of 90 min milled dispersions of NEE

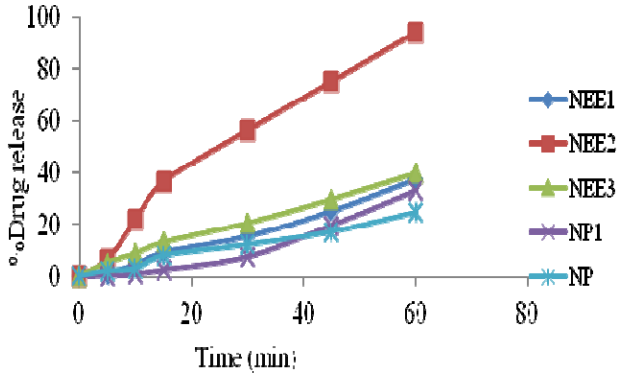

Figure 7 *In-vitro* dissolution studies for Capsules of 30 min milled dispersions of NEE

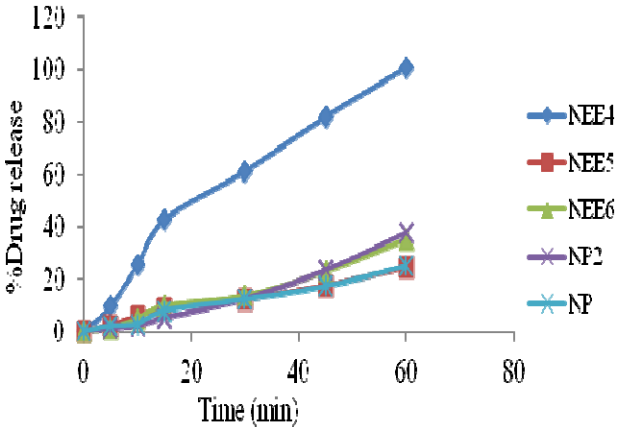

Figure 8 *In-vitro* dissolution studies for capsules of 90 min milled dispersions of NEE

Fourier Transform Infrared Spectroscopy:

The presence of functional groups of pure drug and interactions between pure drug and the polymers was studied using FTIR. The FTIR spectra of the pure drug was shown in (figure 9), characteristic peaks at 3283.24 cm^{-1}showed the presence of alkynes C-H stretch and phenols O-H stretching, at 3090.34 cm^{-1}showed the presence of aromatic ring C-H stretching, at 2847.28 cm^{-1} methyl stretching C-H was observed. Phenyl ring substitution overtones C-H stretching was present at 1905.90 cm^{-1}. Peaks at 1589.54 and 1153.57 cm^{-1} corresponds to the NO_2 asymmetrical stretch and C-N amine stretch [12]. (Figure 10, 11) showed the spectra of milled pure drug, with peaks similar to pure non-milled drug. The shift in the peaks around the range 3600-3200 cm^{-1} showed the bonding between the hydrogen in amide group of Nimesulide with oxygen group of mannitol resulting in a broader peak. Spectra of dispersions of drug with eudragit EPO showed narrow peaks, since the interaction between the drug and the polymer was also less. The sulfonamide group observed at 1153.57 cm^{-1} in pure drug is not observed here which might be because of Eudragit EPO masking the drug since it is a film coating polymer [18].

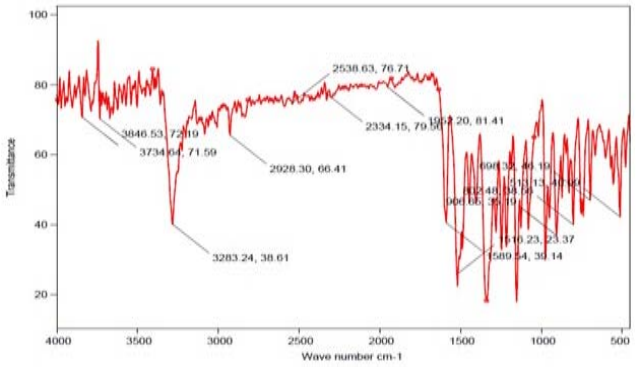

Figure 9: Fourier transform infra red spectra of Nimesulide

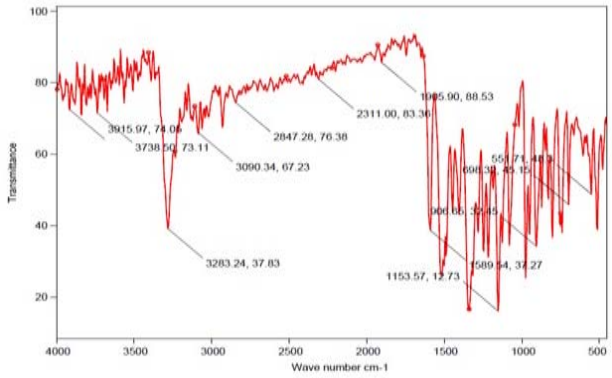

Figure 10: FTIR spectra of 90 min milled Nimesulide

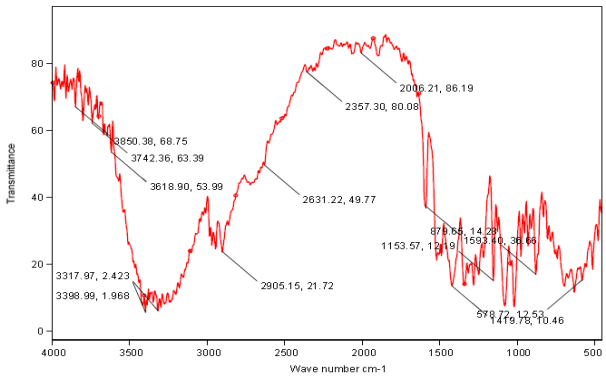

Figure 11 FTIR spectra of milled dispersions of Nimesulide and mannitol

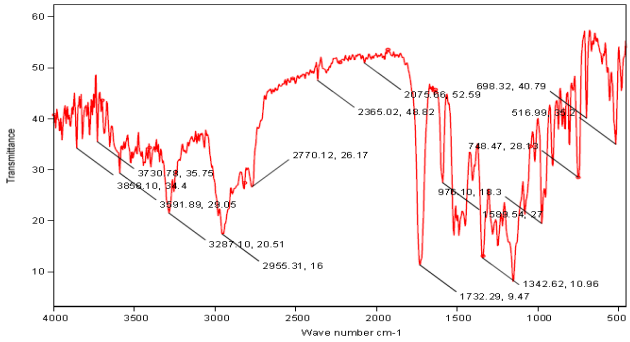

Figure 12 FTIR spectra of milled dispersions of Nimesulide and Eudragit EPO

DSC-TGA:

The DSC studies for the pure drug and the milled physical mixtures of ratios 1:3 were performed to determine polymorphic properties like the percentage crystallinity, glass transition temperature and purity of a substance. The DSC curve of the pure drug showed 2 distinct peaks, an endothermic peak at 150.10°C and an exothermic peak at 335.79°C. The DSC curve of the pure drug milled for 90 minutes was shown in (figure 13-16). A slight shift in the melting point of the pure drug was observed with a single endothermic peak at 148.49°C. Eudragit did not show any significant peaks. Only one exothermic peak at 286.57°C was observed indicating transition in crystallinity of the pure drug due to the presence of Eudragit. The weight loss occurred at a temperature of around 250°C as a multiple decomposition step with a compete decomposition. DSC thermogram of drug with mannitol milled dispersions showed the peak of pure drug at 147.74°C and a peak at 167.51°C corresponding to its melting point. It also showed a peak at 313.19°C which might be due to interaction between the drug and polymer. The TGA curve showed a weight loss of about 25% at 260°C.

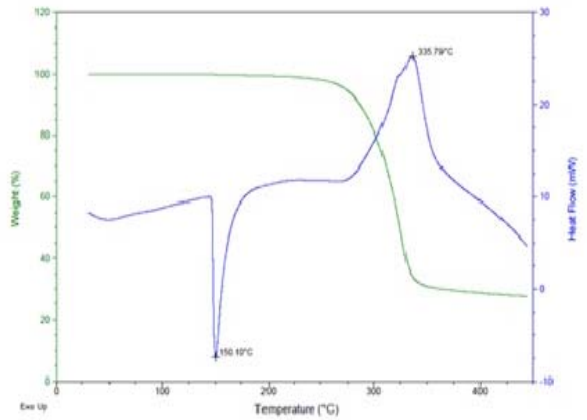

Figure 13: DSC-TGA thermograph of the pure drug Nimesulide

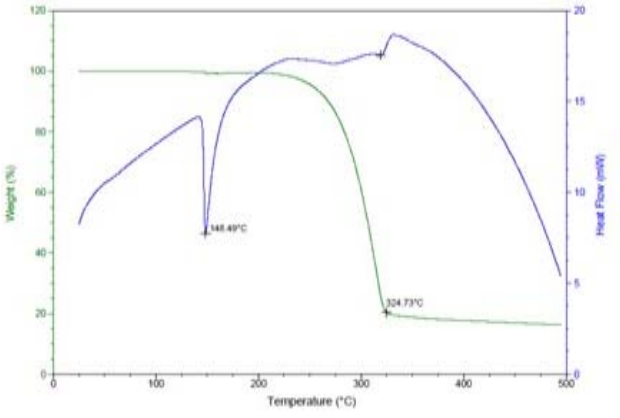

Figure 14: DSC-TGA thermograph of Pure Drug Nimesulide milled for 90 min

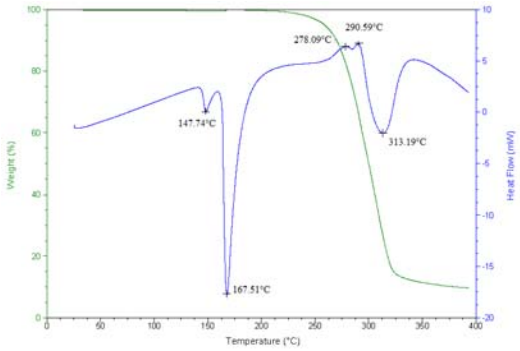

Fig 15 DSC spectra of dispersions of milled drug and mannitol (1:3)

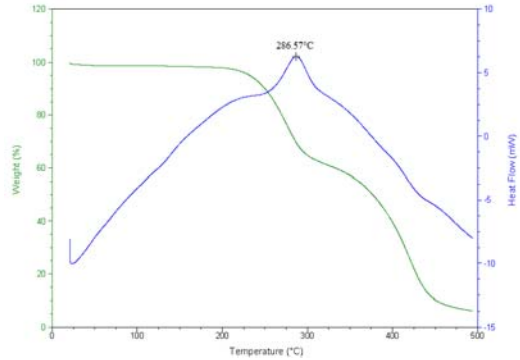

Fig 16 DSC spectra of dispersions of milled drug and Eudragit (1:3)

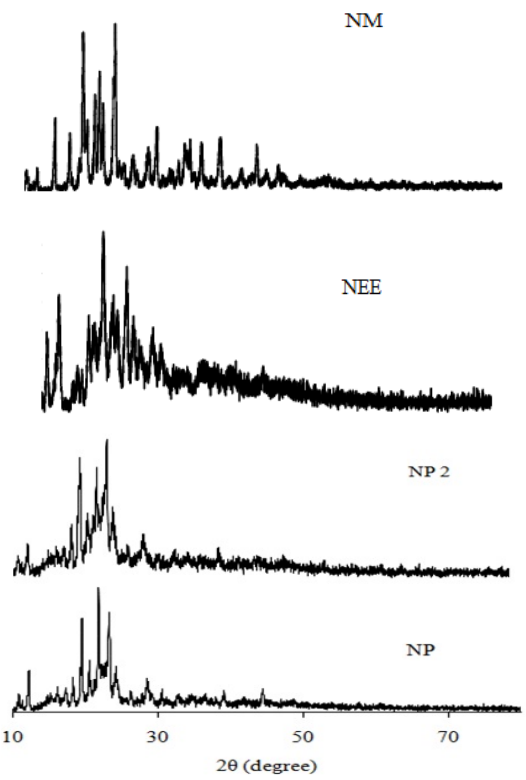

Figure 17: XRD crystallograph of Nimesulide and Eudragit EPO (NEE) , Nimesulide and Mannitol dispersions (NM) , 90 min milled pure drug (NP2) and pure drug (NP).

X-Ray Diffraction analysis:

The peaks for crystallinity of the pure drug and solid dispersions are shown in (figure 17). Characteristic peaks for the pure drug are observed for 2θ value of 19.460°, 19.540°, 21.800° and 23.260°. For 90 minutes milled pure drug the peaks appear with a lower intensity indicating that the reduction in the particle size has helped in bringing the transition from crystalline to semi crystalline form. In the formulations made using mannitol, a number of high intensity peaks were observed at around 23.7°, 23.46°, 19.080°, 21.46°. Though the peaks of the drug appear with lesser intensity presence of the other peaks showed the formulation to be crystalline. But since the intensity of the peaks of drug has reduced, it can be concluded that a change in crystalline nature of the drug has started to occur. Eudragit formulations showed a characteristic peak at 19.62° with an intensity of 660, the intensity of all the other peaks were well below 600 and hence showed that a very good transition in the crystallinity of the drug has occurred due to the presence of Eudragit.

CONCLUSION

The results obtained show that milling in the presence of Mannitol resulted in an increase in the dissolution rate of the drug but milling in the presence of Eudragit EPO did not bring about much changes in the dissolution rate of the drug due to the hydrophobic nature of the polymer. Though mannitol helps in increasing the solubility and dissolution rate of the drug, the tablets made using mannitol dispersion were found to be of lesser hardness, which need further optimization by addition of suitable excipients to ensure its compatibility for commercial purpose.

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