Research Article

Effect of Ball Milling on the Physical Dispersions of Nimesulide for Solubility Enhancement

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ABSTRACT

Bioavailability of many drugs is found to be low due to poor aqueous solubility. The objective of the study was to appraise the effect of milling on the physical dispersions of Nimesulide along with the polymers which helps to enhance the solubility and thereby increases the bioavailability of poorly aqueous soluble drug Nimesulide, using natural and synthetic polymers such as Carrageenen and Polyethylene Glycol (PEG) 4000. Physical dispersions of Nimesulide and the polymers were prepared in the ratios 1:1, 1:3 and 1:5, subjected to size reduction, by Ball Milling technique at two different time intervals 30 and 90 min. The flow properties and solubility of the milled physical dispersions were evaluated and compared with that of non milled physical dispersions and pure drug. Milled physical dispersions were made into tablets and hardness, weight variation, disintegration time, drug content and dissolution were evaluated. The formulations were characterized by Fourier Transform Infra Red Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) and X-Ray Diffractometer (XRD) for its solubility and solid state modification. The results reveal that both the polymers mentioned above help in increasing the solubility of Nimesulide, and ball milling with PEG 4000 has a better effect than milling with carrageenen.

Keywords: Solid dispersions, solubility, milling, polymers.

INTRODUCTION

Nimesulide with chemical name N-4-Nitro-2-phenoxyphenyl methanesulfonamide is a COX-2 inhibitor, Non-Steroidal Anti-Inflammatory drug (NSAID) used as an analgesic and antipyretic agent and is also used for the treatment of osteoarthritis[1,2]. Nimesulide is found to be sparingly soluble in water (0.01mg/ml)[3]. A number of methods have been developed to enhance the solubility of many drugs like Nimesulide. Some of these methods include complexation, modification of the crystal habit, micronization, use of surfactants, nanosuspensions[4] and so on.

Solid dispersion is also one of the techniques used to enhance the dissolution rate and solubility of poorly soluble drugs and has widely been acknowledged. Solid dispersion is termed as the integration of drug or active ingredients into an inert carrier. It reduces the particle size, increases the wettability and converts the substance from its crystalline form to amorphous form thereby increasing the bioavailability of the drug[5]. It can be prepared by chemical methods like solvent evaporation, melting, melt extruder. But these methods have certain disadvantages like drug precipitation, toxicity and degradation of drug and polymer due to heat[6]. Ball milling is a mechanical method used in the preparation of solid dispersions and overcomes the disadvantages of the methods mentioned above. Milling reduces the particle size of the compound by using both impact and attrition forces and hence increases surface area which helps in enhancing the bioavailability. It is a simple process and has the advantage of being faster as compared to many other methods.

Different carriers used as solid dispersions are urea[7], polyvinyl pyrrolidine[8], poly ethylene glycol[9], mannitol[7], hydroxypropylmethyl cellulose, β-cyclodextrin etc. In the present study PEG 4000 and Carrageenen were used as the hydrophilic carriers. PEG produced by polymerization of ethylene oxide helps in improving wettability and also forms solid drug solutions. It has low toxicity and has the advantage of being soluble in many organic solvents[9]. Carrageenens are obtained from a natural source (seaweed) and are highly flexible molecules. They are often used as thickening and stabilizing agents. The purpose of this study was to analyze the effect of milling on the physical dispersions of Nimesulide with polymers PEG 4000 and Carrageenen and to evaluate its influence in increasing the solubility of the drug.

MATERIALS AND METHODS

Materials

Nimesulide was obtained from (Chatan & Chatan, Chennai, India). PEG4000 was purchased from (Qualigens fine Chemicals, Navi Mumbai, India) and Carrageenen from (HIMEDIA Laboratories Pvt ltd, Mumbai, 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.

Methods

Preparation of solid dispersions

Mixture of the drug and the polymers were weighed in three different ratios of 1:1, 1:3 and 1:5 each and pure drug of 1g was weighed separately and mixed gently, the prepared physical dispersions and pure drug were further subjected to size reduction with impact and attrition forces by milling using a ball mill as follows. 10 iron balls were placed in the milling vessel along with the physical mixture and rotated at a speed of 84 rpm for 30 min and 90 minutes respectively. The pure drug was also milled for the same time intervals as the physical dispersions, for better comparison. (Table 1)

Table 1: Composition of ball milled Nimesulide dispersions

Batch Code	Weight of the drug (g)	Polymer weight (g)	Milling time (min)
NPEG1	1	1	30
NPEG2	1	3	30
NPEG3	1	5	30
NPEG4	1	1	90
NPEG5	1	3	90
NPEG6	1	5	90
NC1	1	1	30
NC2	1	3	30
NC3	1	5	30
NC4	1	1	90
NC5	1	3	90
NC6	1	5	90
NP1	1	-	30
NP2	1	-	90

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 of the milled and non milled solid dispersions and pure drug. Angle of repose was performed by funnel method,[10] 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 is the mass of powder occupying a known volume and depends on the way in which particles are packed.[10] 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 bulk density after a specified compaction. The formulas given below were used for further calculation.

- Angle of repose = $\tan^{-1}$ (h/r)

  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

The above procedure was 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 with the help of ball mill were made into tablets with a weight equivalent to 50 mg of the drug using a 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 agents and added for the compactness of the drug. Since the polymer PEG was found to be hygroscopic, in order to reduce its stickiness microcrystalline cellulose was added along with other agents for preparing tablets of Nimesulide and PEG solid dispersions (NPEG).

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 desiccator with silica gel and calcium carbonate as desiccants.

Particle size analysis

The ball milled dispersions of Nimesulide along with PEG and carageenen were subjected to particle size measurements by using a calibrated compound light microscope by well established microscopy technique[11]. 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 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 further removed from the shaker

and centrifuged at 4500 rpm for 10 min at 4°C using a cooling centrifuge (C 24, Remi laboratory, India). The supernatant was diluted and the absorbance was analyzed using UV-Vis Spectrophotometer (Sistronic 117) at 397 nm and concentration was calculated using standard calibration curve [5].

Evaluation of tablets and capsules

The tablets and capsules prepared using the ball milled SD of Nimesulide were evaluated for quality control parameters.

Weight variation

6 tablets 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 analyse the ability of the tablets to withstand local permanent deformation. Hardness of 3 tablets from each dispersion was measured using Tablet hardness tester Mosanto type (Dolphin)[12].

Disintegration time

Disintegration time for the tablets was analysed 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[12].

Drug content

To assess the ball milled PEG, Carrageenen dispersions for uniformity of drug content, assay for milled samples was performed. 6 tablets of each formulation were weighed individually and average mass was calculated; tablets were further triturated and equivalent weight of tablets was taken and dissolved in 10 ml of methanol. It was sonicated for 5 min and further diluted with distilled water. The absorbance was measured using UV-Vis spectrophotometer and the drug content was calculated by using standard calibration curve [8,13].

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 water for the capsules and tablets containing the milled dispersions of Nimesulide PEG and carrageenen and milled and non processed pure drug using USP dissolution type-1 (paddle) apparatus (DS 8000, Lab India) at 37±5°C, 50 rpm in 900 ml distilled water. Each formulation containing 50 mg equivalent of the drug was placed in to the dissolution medium, at predetermined time intervals 10 ml of the samples were withdrawn using a syringe at 5, 10, 15, 30, 45 and 60 min and suitably diluted and dissolution rate was calculated by measuring the absorbance of the samples by UV-Vis spectrophotometer (Systronics 117) at 397 nm with water as the blank[13].

Fourier Transform Infrared Spectroscopy (FTIR)

FTIR analysis (Perkin- Elmer 200) was performed in order to find out the interaction between the drug and the polymers for better stability and compatibility of the drug and the excipients. It was performed using potassium bromate discs technique. The samples were mixed with previously dried and saturated potassium bromate and placed on KBr press under hydraulic pressure of 150 kg/cm^2, the 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 (TGA) (SDT Q600 V20.9 Build 20) for analyzing the polymorphic changes in the milled dispersions of PEG and Carrageenen. About 4 mg of the sample was placed in aluminium pans and then heated under nitrogen flow (20 ml/min). It was performed at the rate of 10 °C/min within a range of 0°C to 500°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-ray and 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 10°- 80° with a voltage of 40kV and a current of 30 mA and 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 NPEG of both 30 and 90 min have a very good flow property. Though NC milled dispersions also showed better flow than pure drug, its flow was less as compared to the NPEG milled dispersions which might be because of the binding nature of carrageenen[14] resulting in a hindrance in flow property.

Particle size analysis

The average particle size of each formulation is given in table 3. The particle size of pure drug was obtained as 16.5 µm and that of milled drug for 30 and 90 min did not show any significant change. This might be because of agglomeration of the finely divided particles resulting in adhesion of the particles. The particle size of milled dispersions decreased with the polymer weight increase and also with increase in time of milling with 1:5 ratio of NPEG at 90 min showing a particle size of only 17.5 µm as compared to 1:1 ratio of 30 min, where a particle size of 51.5 µm was obtained.

Table 2: Preformulation studies for milled and non milled dispersions of drug and polymer

Batch Code	Angle of repose	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
NPEG1	16.602±0.529	0.343±0.012	0.4232±.010	18.675±4.727
NPEG2	17.585±1.573	0.386±0.018	0.5025	23.110±3.631
NPEG3	22.234±1.955	0.399±0.006	0.506±0.004	22.467±3.102
NPEG4	14.629±1.354	0.609±0.019	0.695±0.051	11.802±8.166
NPEG5	21.440±0.933	0.442±0.001	0.523±.006	15.853±9.957
NPEG6	24.566±1.632	0.442±0.024	0.533±0.012	44.9067±3.607
NC1	34.939±3.229	0.360±0.012	0.66	45.382±1.955
NC2	32.263±3.706	0.485±0.0238	0.848±0.034	42.781±2.544
NC3	35.296±2.950	0.50565	0.807±0.016	37.391±1.229
NC4	29.830±0.579	0.359±0.007	0.555±0.022	35.145±2.296
NC5	31.406±1.669	0.485±0.014	0.753±0.012	35.473±2.461
NC6	35.027±0.947	0.473±0.031	0.680±0.003	30.484±4.722
Before Milling				
NPEG1	26.0396±0.747	0.43244±0.087	0.608473±0.074	30.4943±4.378
NPEG2	20.82733±3.782	0.5	0.682547±0.022	26.6667±2.357
NPEG3	16.04936±3.436	0.523397±0.008	0.666880±.0120	21.4697±2.649
NC1	27.65763±2.001	0.342093±0.020	0.536067±0.0137	32.7793±5.119
NC2	29.1399±1.485	0.508547±0.006	0.659503±0.0101	22.8633±1.838
NC3	30.20297±2.942	0.54329±0.024	0.763167±0.018	28.8427±1.689
NP	42.500±1.220	0.4292±0.017	0.537±0.261	19.9493±3.624

Table 3: Evaluation techniques for milled dispersions of tablets of drug and polymers and solubility and particle size analysis of milled and non milled formulations

S. No	Batch Code	Solubility (µg/ml)	Weight Variation (mg)	Hardness (kg-cm)	Disintegration Time (min)	% Drug Content	Particle size (µm)
1	NPEG1	55	0.0944±0.021	2	45	95	51.5
2	NPEG2	65.75	0.196±0.009	2.5	38	98	43.5
3	NPEG3	46	0.321±0.009	3.5	28	103.9	32.5
4	NPEG4	57.5	0.1225±0.009	2	25	100	49.5
5	NPEG5	59.5	0.1898±0.020	2.5	18	110	41.5
6	NPEG6	67.5	0.295±0.023	3.5	12	102.7	17.5
7	NC1	65	0.0904±0.020	1.5	>60	80	24.5
8	NC2	77.75	0.207±0.006	4	>60	80	25.5
9	NC3	63.25	0.342±0.052	5	>60	95.8	31.5
10	NC4	96.25	0.1±0.006	2	>60	94.8	34.5
11	NC5	64	0.2004±0.019	3	>60	106	23.5
12	NC6	106.75	0.2898±0.041	5	>60	99.13	20.5
13	NP	48.75	0.0938±0.012	1	>60	94.8	16.5
14	NP1	48.25	0.0946±0.011	1	>60	109.3	17.5
15	NP2	36.75	0.0938±0.012	1	>60	107.1	16.5

Solubility of PEG-Nimesulide dispersions before milling						
Batch code	NPEG1	NPEG 2	NPEG3	NC1	NC2	NC3
Solubility	40.75	62.5	53.25	49	93.25	70

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 PEG and carrageenen. Also NP – pure drug, NP1 and NP 2 represent 30 min and 90 min milled pure drug.

The larger particle size of NPEG dispersions might be because the drug and the polymer are present together in form of a cluster due to viscous nature of PEG[14]. NC dispersions showed fluctuations in the particle size which might be due to the complex formation between the drug and the polymer. A particle size of 20.5 µm was observed for 90 min milled NC dispersions at 1:5 ratio.

Solubility studies

The solubility of ball milled solid dispersions of Nimesulide and the polymers is shown in table 3. The 90 min milled dispersions of NPEG (1:5) showed better solubility 67.5µg/ml than that of the pure drug which had a solubility of 48.75 µg/ml. Milled Carrageenen dispersions (NC) at 90 min showed a significant increase in solubility, 106.75 µg/ml at 1:5 ratio as compared to pure drug and PEG 4000 SD. Milled and non milled pure drug showed similar solubility values which might be because reaggregation of the particles due to milling resulting in larger size[15].

Evaluation of tablets and capsules

Weight variation

The mean weights of the tablets are tabulated in table 3. The variation in weight was found to be within the pharmacopoeial limits for all the tablets containing milled dispersions.

Hardness test

The tablets made using solid dispersions were found to be of enough hardness. The hardness of milled NPEG tablets was in the range of 2 -4 kg-cm and that of carrageenen was found to be 2-5kg-cm. Good hardness of NC tablets might be because of carrageenen being a good adhesive[14]. The hardness of each formulation is given in table 3.

Disintegration time

The time for disintegration of 90 min milled solid dispersions of PEG was found to be around 20 min which was lesser than the pure drug and that of carrageenen solid dispersions. Carrageenen solid dispersions had a sticky nature and being a viscosity increasing agent[14], the disintegration time was found to be more than 60 min.

Drug content

The drug content of all milled dispersions of NPEG were within 90-110% which reveals that optimum amount of drug is present in all the tablets and capsules.

In vitro release studies

The *in-vitro* dissolution studies were performed in order to observe the enhancement in solubility of the drug with the polymers. The tablets and capsules of the ball milled NPEG dispersions of both 90 and 30 min had a better dissolution than the pure drug. The dissolution profiles of tablets and capsules of NPEG milled dispersions are shown in Figure 1A, C3, 2A and 2C, more than 80% of drug release is observed in 1:3 and 1:5 dispersions of NPEG of both tablets and capsules whereas both milled and non milled pure drug showed a release of only 30%. The 90 min milled formulations of NPEG milled dispersions of 1:5 ratio showed better results than 30 min milled dispersions by dissolving more than 95% of drug within 45 min. The dissolution profiles of NPEG dispersions clearly reveal that as the carrier weight increases the release is more. Similarly more the time of milling more is the drug dissolution[16]. Similarly NC milled dispersions of both 30 and 90 min also showed a better dissolution than the pure drug but lesser than that of NPEG. The dissolution profiles of the dispersions of Carrageenen are shown in figure 1A & D, 2B and 2D. The 1:1 milled dispersions of carrageenen showed better dissolution than the 1:3 and 1:5 milled dispersions which might be due to the complex formation between the drug and carrageenen and high viscous nature of the polymer.

Fourier Transform Infrared Spectroscopy

The FTIR spectra of the pure drug is shown in figure 3A, 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[17]. Figure 3B-D gives the spectra of milled pure drug. Peaks similar to pure non milled drug were observed. The spectra of NPEG showed a broader peak around the wavelength of 3600-3200 cm^{-1} which shows interaction between the drug and the polymer and might be due to the hydrogen bonding of hydrogen atom of NH group of Nimesulide and oxygen group of PEG[18]. The spectra of NC milled dispersions showed even broader peak confirming the complex formation between the drug and polymer.

Differential Scanning Calorimetry and Thermogravimetric Analysis (DSC-TGA)

The DSC curve of the pure drug showed two 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 min is shown in figure 4A. A slight shift in the melting point of the pure drug was observed with a single endothermic peak at 148.49°C. The peak at 335.79°C was also still observed but was less intense. The DSC analysis of the milled dispersions of NPEG showed 2 peaks. There was a shift in the melting point from 148.49° to 57.48° C which corresponds to the melting point of PEG[7] and another shift from 335.79° to 407.98°C. The disappearance of the endothermic peak of the pure drug indicates the loss of Crystallinity of the drug and that the drug has dispersed in PEG. NC milled dispersions also showed 2 peaks an endothermic peak at 147.7° C and an exothermic peak at 255.25° C which indicates that the melting of the solid dispersion occurred at 147.7° C with heat being released at 255.25°C.The weight loss due to

temperature changes are shown in the figure 4B-D. For the pure drug the degradation of the drug starts at around 280° C with a weight loss of 70%. The TGA graph of 90 min milled pure drug shows a similar profile confirming that milling alone has not brought about much change in the drug profile. For NPEG milled dispersions the degradation occurs at 290° C till 400° C and hence weight loss was more as compared to pure drug. The weight loss for NC dispersions was very less and degradation occurred only between 200° C and 300° C. From the data obtained it is clear that milling in the presence of polymer brings about a slight shift in the melting point and influences the crystallinity of the compound.

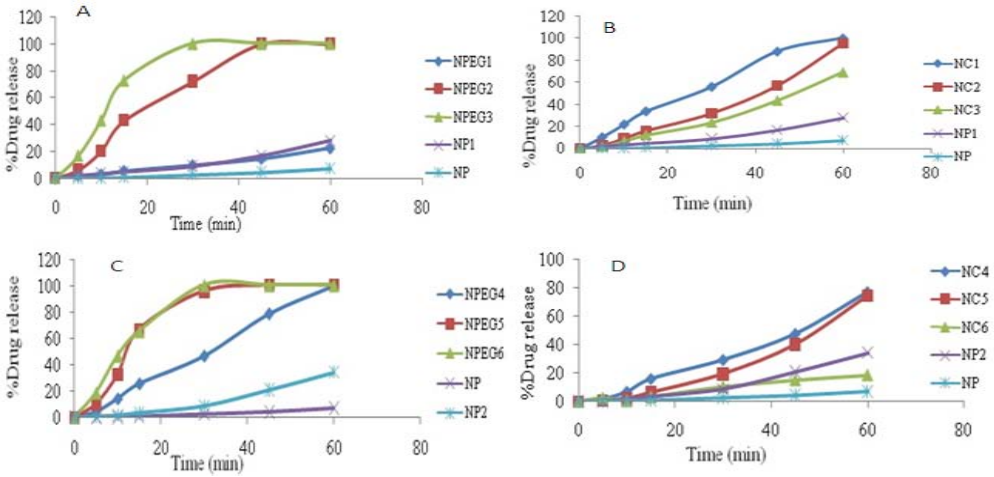

Figure 1: *In-Vitro* dissolution profile of **tablets** of milled dispersions of Nimesulide with A) PEG 4000 milled for 30 min, B) Carrageenen milled for 30 min, C) PEG 4000 milled for 90 min, D) Carrageenen milled for 90 min

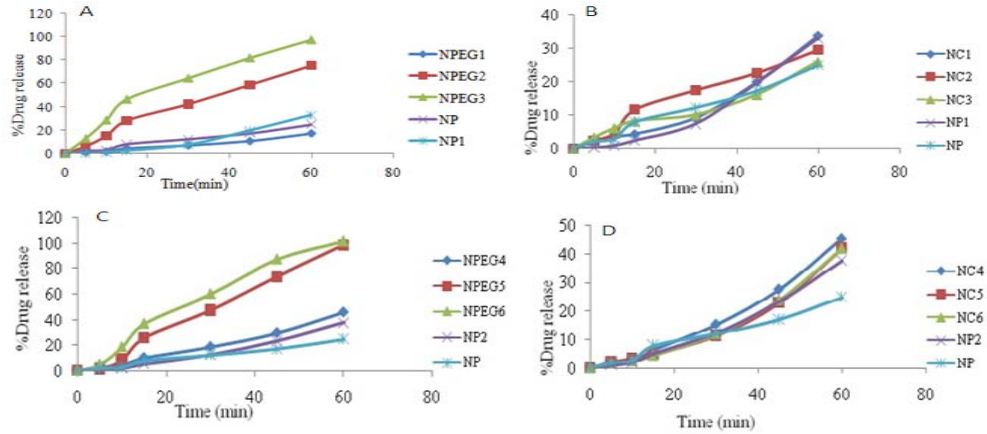

Figure 2: *In-Vitro* dissolution profile of **capsules** of milled dispersions of Nimesulide with A) PEG 4000 milled for 30 min**, B)** Carrageenen milled for 30 min, C), PEG 4000 milled for 90 min D) Carrageenen milled for 90 min.

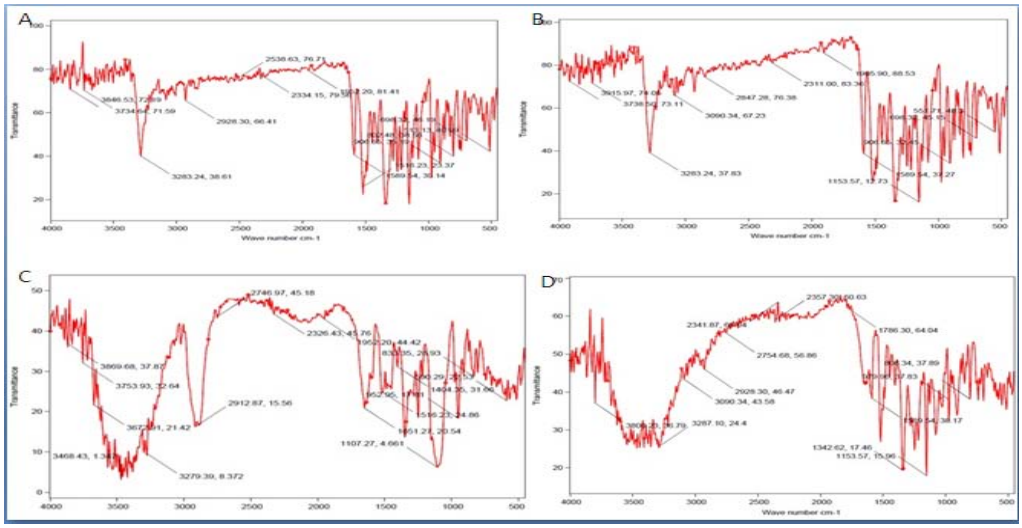

Figure 3: Fourier transform infra red spectra of A) Nimesulide Pure, B) Nimesulide Pure 90 min milled, C) Nimesulide and PEG 4000 (1:3) 90 min milled, D) Nimesulide and carrageenen (1:3) 90 min milled.

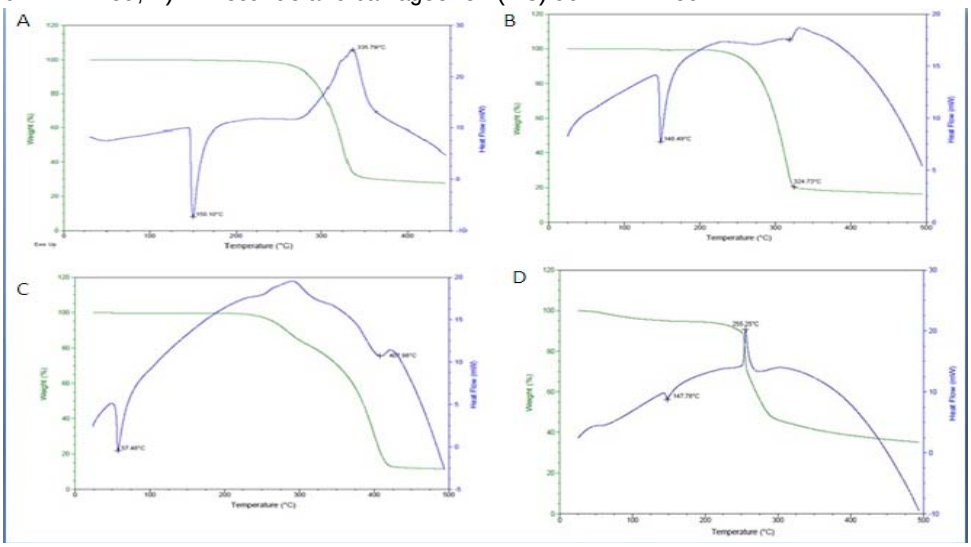

Figure 4: DSC-TGA thermograph of the A) pure drug Nimesulide, B) Pure Drug Nimesulide milled for 90 min, C) Nimesulide and PEG 4000 (1:3) milled for 90 min, D) Nimesulide and Carrageenen(1:3) milled for 90 min.

X-Ray Diffraction analysis

The peaks for crystallinity of the pure drug and solid dispersions are shown in figure 5. Characteristic peaks for the pure drug are observed at a 2 θ value of 19.460°, 19.540°, 21.800° and 23.260°.

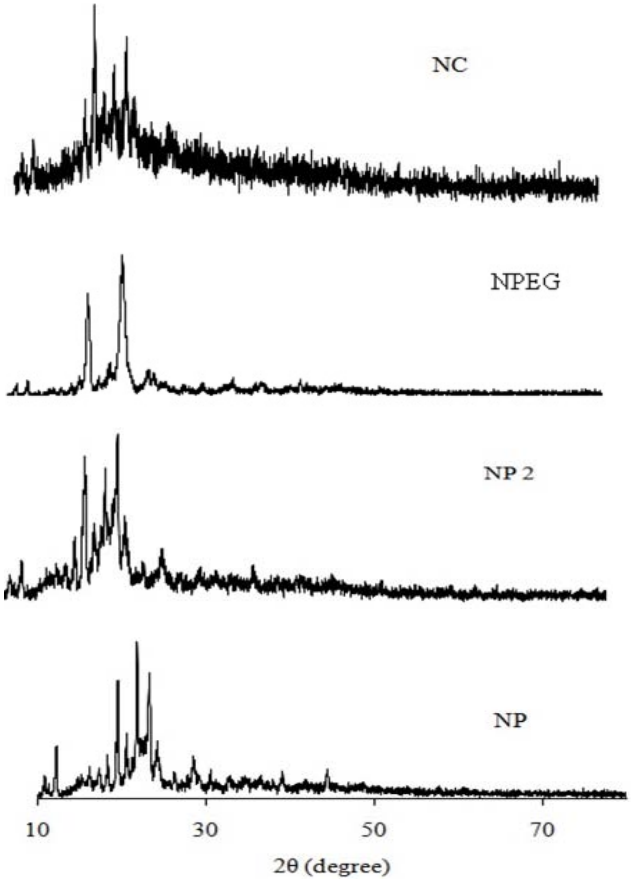

Figure 5: XRD crystallograph of Nimesulide and carrageenen dispersions (NC), Nimesulide and PEG dispersions (NPEG), 90 min milled pure drug (NP2) and pure drug (NP).

For 90 min 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. NPEG milled dispersions show characteristic peaks at 2θ of 23.400° and 19.420° with a high intensity which corresponds to the peaks of pure PEG[9]. The other peaks that were observed in the pure drug are noted as small intensity peaks in the milled dispersions. The milled dispersions of NPEG hence exist in a semi crystalline form since the polymer PEG is itself semi crystalline in nature. The peaks observed in NC milled dispersions have a very less intensity which suggests that there is a transition in the crystallinity to amorphous state due to the presence of polymeric materials in the formulations.

CONCLUSION

From all the data obtained we can conclude that the milled dispersions of the drug with polymers help in increasing the solubility and dissolution rate of Nimesulide. Similarly milling brings about a reduction in particle size thereby increasing the surface area and also helps in conversion of the crystalline compound to semi crystalline or amorphous compound and hence can be used as a method for preparing solid dispersions. Among the 2 polymers used, PEG 4000 shows better improvement in dissolution than carrageenen as there were not much interactions between PEG and Nimesulide where as carrageenen formed a complex with Nimesulide which resulted in decrease in dissolution rate.

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