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Review Article

EFFECT OF IMPACT AND ATTRITION MILLING ON NIMESULIDE FOR SOLUBILITY ENHANCEMENT

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ABSTRACT

This study has investigated the effect of milling in increasing the solubility of a poorly soluble drug Nimesulide. Nimesulide was subjected to ball milling in the presence of a natural polymer, β-Cyclodextrin and a synthetic polymer, Poly ethylene glycol (PEG) 6000. The physical dispersions of the drug with each polymer were taken in three different ratios of 1:1, 1:3, 1:5 respectively and milled at time intervals of 30 min and 90 min individually. Before and after milling the physical dispersions and the pure drug were subjected to various evaluation parameters like solubility, particle size analysis and flow property. The milled physical dispersions showed a better flow property and solubility (153µg/ml) than the non-milled dispersions. The milled physical dispersions were developed into tablet and capsule dosage form and evaluated for thickness, diameter, hardness (2-4Kg/cm^2), weight variation (109-321 mg), disintegration time (8-20 min), drug content (95-101%) and dissolution rates. Modifications in the solid state were observed by various characterization techniques with the help of Fourier Transform Infra Red Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC) shows changes in melting point, and X-Ray Diffractometry (XRD) reveals reduction in crystalinity. The data obtained showed an increase in the dissolution rates of the ball milled dispersions with increase in time of milling and at higher concentration of the polymers (above 90% at 1:5 ratio).

Keywords: PEG, Cyclodextrin, BCS, NSAID, COX-2 inhibitor

INTRODUCTION

Solubility is very important for a drug because a drug in order to permeate through gastrointestinal barrier should dissolve in the gastrointestinal fluid. Dissolution becomes a rate limiting step in such cases and hence rate of dissolution has to be increased to increase the bioavailability [1]. Drugs belonging to BCS class II have a low dissolution rate and a number of Non-Steroidal Anti-Inflammatory drug (NSAID) come under this class [2]. Nimesulide, a COX-2 inhibitor with chemical name N-4-Nitro-2phenoxyphenyl methanesulfonamide is one such drug which is sparingly soluble in water (0.01mg/ml) [3,4].

Many methods have been performed to increase the solubility of such poorly aqueous soluble drugs some of which includes inclusion complexation, modification of the crystal habit, micronization, use of surfactants, nanoformulations etc. [5]. Solid dispersion is also one of the techniques widely used for solubility enhancement which involves the incorporation of the poorly soluble drug into an inert soluble carrier [6,7]. Methods like solvent evaporation, melting, melt extrusion are used for preparing solid dispersions. Precipitation, toxicity and degradation of drug and polymer due to heat are some of the disadvantages observed due to the above mentioned methods [8].

Milling is a method which is commonly used for reducing the particle size. Size reduction modifies the surface properties like surface area and porosity [9]. Particle size is very important for drug delivery and bioavailability and has been proved to aid in increasing the dissolution rates of poorly soluble drugs like progesterone and oxfendazole [10,11]. Hence milling has gained a lot of importance in the recent years for size reduction. Ball milling works based on attrition and impact forces and results in high amounts of mechanical energy and brings about structural changes thereby increasing the surface area and stability and facilitating compression of tablets. Ball milling is a simple and faster process but results in reaggregation and recrystallization of the drugs [11]. In order to avoid this problem, the drug is milled in the presence of polymers which help in increasing the wettability of the drug and prevents reaggregation, re-crystallization. Commonly used polymers for enhancing the solubility are urea [12], polyvinyl pyrrolidine[13], poly ethylene glycol [14], mannitol [13], hydroxypropylmethyl cellulose.

In the present study Poly ethylene glycol 6000 and β-Cyclodextrin are used as the polymers. Poly ethylene glycol 6000 helps in improving wettability, has low toxicity and has the advantage of being soluble in many organic solvents [14]. Cyclodextrins are mostly poorly aqueous soluble but still help in enhancing solubility of a drug by forming complexes with the drug [15].The main aim of the study was to analyze the effect of milling on the physical dispersions of the Nimesulide and the polymers Poly ethylene glycol 6000 and β-Cyclodextrin.

METHODS AND MATERIALS

Materials

Nimesulide was obtained from (Chatan & Chatan, Chennai, India). PEG 6000 was purchased from (Qualigens fine Chemicals, Navi Mumbai, India) and β-Cyclodextrin from (Sd fine-chem 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 throughout the study were of analytical grade.

Ball Mill

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

Methods

Preparation of solid dispersions

The physical mixture of the drug and the polymers were prepared in three different ratios of 1:1, 1:3 and 1:5 for each polymer individually. The pure drug of 1g was weighed separately and sieved uniformly. The prepared physical dispersions and the 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. The process was carried for two different time durations such as 30 and 90 min and the mixtures were collected separately, for comparing the effect of ball milling time efficiency. The pure drug was also milled for the same time intervals as the physical dispersions table 1.

Table 1: Composition of Ball Milled Nimesulide Dispersions

Batch Code	Weight of the drug (g)	Polymer weight (g)	Milling time (min)
NPEG4	1	1	30
NPEG5	1	3	30
NPEG6	1	5	30
NPEG7	1	1	90
NPEG8	1	3	90
NPEG9	1	5	90
NBCD1	1	1	30
NBCD2	1	3	30
NBCD3	1	5	30
NBCD4	1	1	90
NBCD5	1	3	90
NBCD6	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 their flow property and compatibility for compression into tablets. Angle of repose was performed by funnel method [16] by pouring the powdered samples through a funnel onto 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 the mass of powder occupied by its volume and depends on the way in which particles were packed [16]. It was calculated by pouring the weighed quantity of powder into a measuring cylinder and noting the bulk volume. This was then tapped for 300 times to obtain the constant tapped volume which was used to calculate the tapped density, i.e., the density after a specified compaction. The formulas given below were used for further calculation.

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

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 the ball milled Nimesulide physical dispersions were made into tablets with a 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 agents respectively. SSG also aided for the compactness of the bulk for effective compression. 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 with PEG 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 with PEG and β-Cyclodextrin were subjected to particle size measurements by using a calibrated compound light microscope by well established microscopy technique [17]. 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 particle size of about 25 particles was measured 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 the enhancement of solubility of the ball milled Nimesulide dispersions compared to the pure drug, 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 4º 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 [6].

Evaluation of tablets and capsules

The tablets and capsules prepared using the ball milled SD of Nimesulide was 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 average weight and the deviations from standard limits (as per monograph) were checked. 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 was measured using Tablet hardness tester Mosanto type (Dolphin) [18].

Disintegration time

Disintegration time for the tablets 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 [18].

Drug content

To assess the ball milled PEG, β-Cyclodextrin dispersion tablets for uniformity of drug content, assay for powdered tablets was performed. 6 tablets of each formulation were weighed individually and average mass was calculated; tablets were further triturated and equivalent weight of tablets average weight was taken and dissolved in 10 ml of methanol. It was sonicated for 5 min, filtered and further diluted with distilled water. The absorbance of the solution was measured using UV-Vis spectrophotometer and the drug content was calculated by using standard calibration curve [13,19].

***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 capsules and tablets containing the milled dispersions of Nimesulide PEG and β-Cyclodextrin and milled non-processed pure drug using USP dissolution type-1 (paddle) apparatus (DS 8000, Lab India) at 37±5ºC, 50 rpm in 900 ml distilled water. Each sample containing 50 mg equivalent of the drug was placed into the dissolution medium, and 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-Vis spectrophotometer (Systronics 117) at 397 nm with water as the blank [19].

Fourier Transform Infrared Spectroscopy: (FTIR)

FTIR analysis (Perkin-Elmer 200) was performed using potassium bromide disc technique, in order to find out the interaction between the drug and the polymers for better stability and compatibility of

the materials used. The samples were mixed with previously dried and saturated potassium bromide and placed on KBr press under hydraulic pressure of 150 kg/cm^2, and the translucent thin film obtained 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 thermo gravimetric analysis (SDT Q600 V20.9 Build 20), especially for analyzing the polymorphic changes in the milled dispersions of PEG and β Cyclodextrin. About 4 mg of the sample was placed in the aluminium pans and then heated under nitrogen flow (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 were used for the determination of the crystal structure and atomic spacing of materials by constructive interference of monochromatic x-ray on 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 º- 80º with a voltage of 40kV and a current of 30 mA and using Cu-Kα as the source.

RESULTS AND DISCUSSION

Angle of repose, Bulk density, and Tapped density were performed thrice and the mean with standard deviation was tabulated in table 2. The non-milled physical dispersions of PEG 6000 with drug show an increase in the flow property in comparison to the pure drug. At 1:5 ratio, the angle of repose of 29.24° was obtained for the non-milled dispersions. The milled dispersions showed a good flow property with 13.83° angle of repose for 1:1 ratio milling done for 90 min, as compared to the other 2 ratios of 1:3, 1:5 ratios which showed angle of repose of 21.44° and 24.56° respectively, for the 90 min milled dispersions. Though the 30 min milled dispersions showed a good flow property it was found to be less as compared to the 90 min milled dispersions. The non-milled dispersions of β-Cyclodextrin with drug, did not show a significant increase in the flow, the angle of repose being 39.8° for 1:5 ratio. The milled dispersions comparitively showed better results especially the 90 min milled samples with an angle of repose of 24° for 1:1 ratio.

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
NPEG4	19.988±0.152	0.366±0.004	0.522	29.919±0.729
NPEG5	16.856±1.014	0.417±0.020	0.618	32.455±3.264
NPEG6	27.442±1.24	0.449±0.010	0.669±0.017	32.74±3.376
NPEG7	13.836±0.738	0.434±0.005	0.494±0.006	14.163±0.745
NPEG8	22.44±2.889	0.409±0.002	0.576±0.004	28.998±0.152
NPEG9	22.146±0.791	0.433±0.02	0.577±0.017	28.99±0.152
NBCD1	34.916±3.874	0.351±0.014	0.592±0.009	38.847±1.346
NBCD2	34.974±3.38	0.413±0.009	0.849±0.082	36.403±8.0634
NBCD3	40.264±1.493	0.457±0.03	0.737±0.009	48.46±3.041
NBCD4	24.803±3.143	0.380±0.01	0.585±0.015	48.46±3.041
NBCD5	25.366±0.733	0.454±0.005	0.69±0.012	34.15±0.681
NBCD6	30.309±0.462	0.464	0.631±0.017	26.38±1.96
Before Milling				
NPEG4	34.758±1.593	0.215±0.008	0.394±0.164	37.5
NPEG5	27.831±4.213	0.566±0.015	0.732±0.026	29.30±1.036
NPEG6	29.23	0.5423±0.009	0.733±0.025	25.589±2.381
NBCD1	39.468±.557	0.336±0.047	0.476	29.40±9.998
NBCD2	37.3068±3.946	0.422±0.008	0.857±0.017	50.662±2.005
NBCD3	39.821±4.34	0.409±0.013	0.672±0.013	39.047±1.73
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^2)	Disintegration Time (min)	Particle size (µm)
1	NPEG4	65.625	0.102±0.01	2	20	26.2
2	NPEG5	47.5	0.193±0.02	2	15	13.8
3	NPEG6	47.25	0.196±0.02	2.5	12	15
4	NPEG7	40.375	0.127±0.003	2	17	12.6
5	NPEG8	52.75	0.222±0.015	2.5	13	21.4
6	NPEG9	50.875	0.328±0.005	4	8	17.8
7	NBCD1	62.25	0.09±0.005	2.5	2	15.4
8	NBCD2	56.25	0.197±0.01	2.5	2	12.2
9	NBCD3	153.125	0.29±0.012	2	2	18.2
10	NBCD4	102	0.105±0.012	2	4	15.4
11	NBCD5	84.375	0.222±0.331	3.5	14	17.8
12	NBCD6	149.25	0.321±0.017	3.5	20	11.8
13	NP	48.75	0.0938±0.012	1	>60	16.5
14	NP1	48.25	0.0946±0.011	1	>60	17.5
15	NP2	36.75	0.0938±0.012	1	>60	16.5
Solubility of physical dispersions before milling						
Batch code	NPEG4	NPEG 5	NPEG6	NBCD1	NBCD2	NBCD3
Solubility	75.25	74	69.875	97.75	107	104.125

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 dispersions of different ratios 1:1,1:3,1:5 of both PEG and cyclodextrin. Also NP – pure drug, NP1 and NP 2 represent 30 min and 90 min milled pure drug.

The average particle size of each formulation was given in table 3. The particle size of pure drug was obtained as 16.5 µm. The particle size of the milled dispersions of polymers with drug showed larger particle size due to the polymer size and nature. PEG 6000 being waxy [20] in nature have formed clumps which resulted in larger particle size whereas cyclodextrin showed reduced particle size. The results also proved that all the dispersions showed a reduced particle size when milled for 90 min. Hence milling for a longer time period reduces the particle size to a significant extent.

The solubility of ball milled dispersions of Nimesulide with 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 its solubility. This might be due to reaggregation of the particles, reducing the wettability thereby not increasing the solubility. [11] Milled dispersions of polymers with drug showed an increase in solubility, chiefly with the value of 153 µg/ml observed for the β-Cyclodextrin dispersion.

The mean weight of the tablets was tabulated in table 3. The variation in individual weight was found to be within the pharmacopieal limits for all the tablets prepared with the milled dispersions. The hardness of each formulation is given in table 3.

The hardness of NPEG tablets were found to be between 2-5 Kg/cm^2 and the tablets of milled β-Cyclodextrin with drug dispersions showed the hardness between 2-4 Kg/cm^2. NPEG 6000 and NBCD at all ratios disintegrated within 20 min. The disintegration time of each formulation was given in table 3. The drug content of all milled dispersions of NPEG was within the limits of 90-110% which reveals that optimum amount of drug is present in all the tablets and capsules.

Dissolution rate of tablets containing milled (30 min milling time) dispersions of drug with PEG 6000 were found to be around 48 % for 1:1 ratio and 100% for other two ratios 1:3 and 1:5. Dissolution rate of tablets of 90 min milled physical mixtures increased with 1:3 and 1:5 ratios showing 100% release within 45 and 30 min respectively. The capsules of the dispersions of drug with PEG 6000 milled for both 30 and 90 min showed similar results with 1:3 and 1:5 ratios showing 100% release in 60 min and 1:1 ratio showing a release around 45%. The dissolution profile of milled β-Cyclodextrin dispersions was similar to milled PEG dispersions, that is with increase in the polymer weight an increase in dissolution rate was observed. But the 90 min milled samples showed a lesser dissolution rate compared to 30 min at 1:5 ratio this might be due to a complex formation between finely ground particles of drug and cyclodextrin.[21](Fig. 1,2).

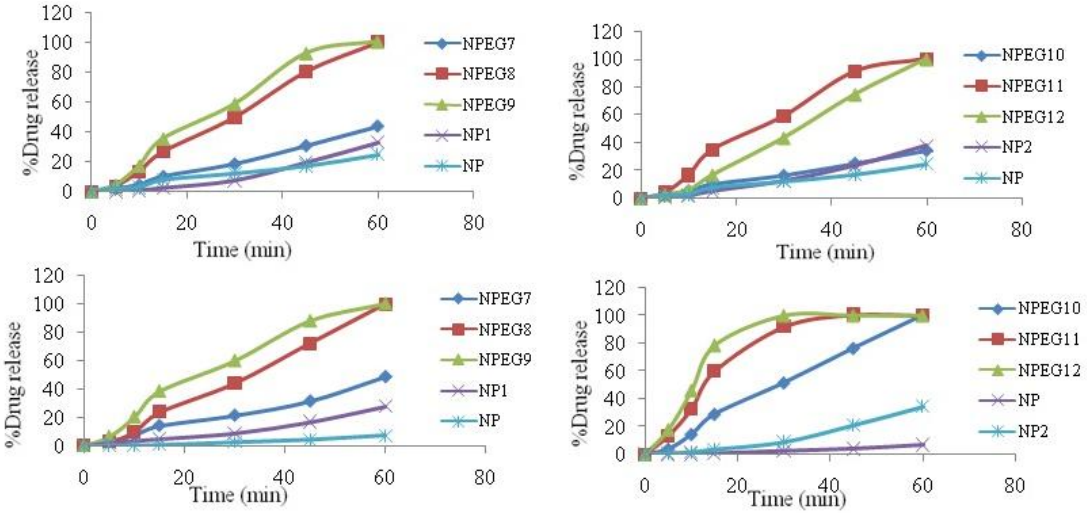

Fig. 1: *In-vitro* dissolution studies for milled dispersions of NPEG 6000. a-Tablets of 30 min milled dispersions NPEG 6000, b- Tablets of 90 min milled dispersions of NPEG 6000, c- capsules of 30 min milled dispersions of NPEG 6000, d-capsules of 90 min milled dispersions of NPEG 6000.

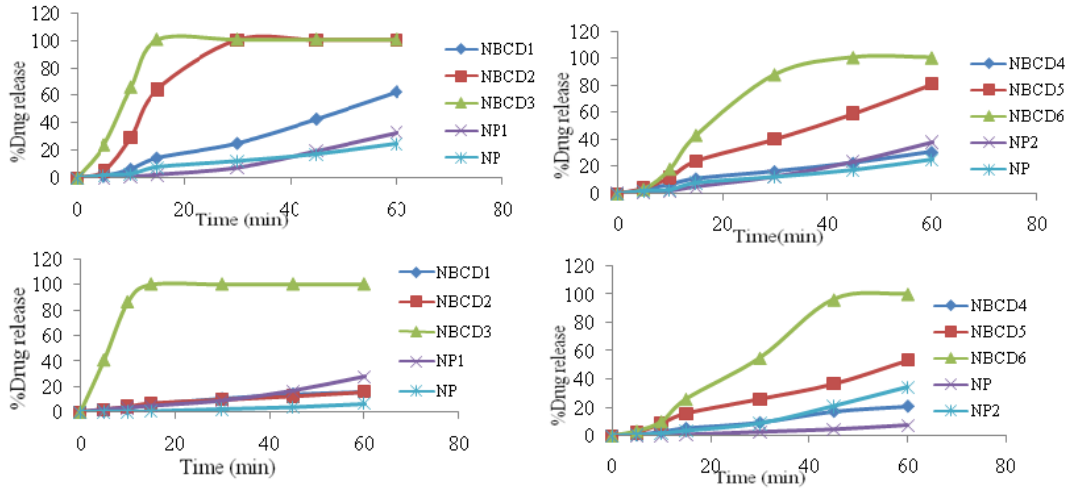

Fig. 2: *In-vitro* dissolution studies for milled dispersions of NBCD. a Tablets of 30 min milled dispersions NBCD, b- Tablets of 90 min milled dispersions of NBCD, c- *C*apsules of 30 min milled dispersions of NBCD, d- *C*apsules of 90 min milled dispersions of NBCD.

For the pure drug, the characteristic peaks at 3283.24 cm^{-1} showed the presence of amides N-H stretch, at 3090.34 cm^{-1} showed the presence of aromatic ring C-H medium stretching, at 2847.28 cm^{-1} C-H methyl stretching. Phenyl ring substitution overtones C-H stretching was present at 1905.90 cm^{-1}. Peaks at 1589.54 cm^{-1} corresponds to the NO_2 asymmetrical stretch and 1153.57 cm^{-1} corresponds to sulfonamide group of Nimesulide [22]. The FTIR spectra of pure milled drug showed peaks similar to the pure drug with very minute shifts in peaks indicating that milling does not affect the functionality of the pure drug [1].In case of dispersions, no shift in the peak at 3283.24 was observed but newer peaks at 3615.04 cm^{-1} and 3773.22 cm^{-1} were found indicating a mild interaction between the drug and the polymer between the hydrogen of amide group of the polymer and oxygen group of the drug [23]. Also a shift in the sulfonamide group from 1153.57 to 1107 cm^{-1} was observed which might be due to the stabilizing effect of hydrogen group of PEG 6000 with oxygen atom of the sulfonamide group. Similarly in presence of β-Cyclodextrin an interaction between the hydrogen atom of Nimesulide with oxygen group of polymer was observed resulting in a complex formation between the drug and the polymer. The peak corresponding to the sulfonamide was not observed due to complete encapsulation of the drug inside the polymer cyclodextrin ring resulting in a complex formation (Fig. 3).

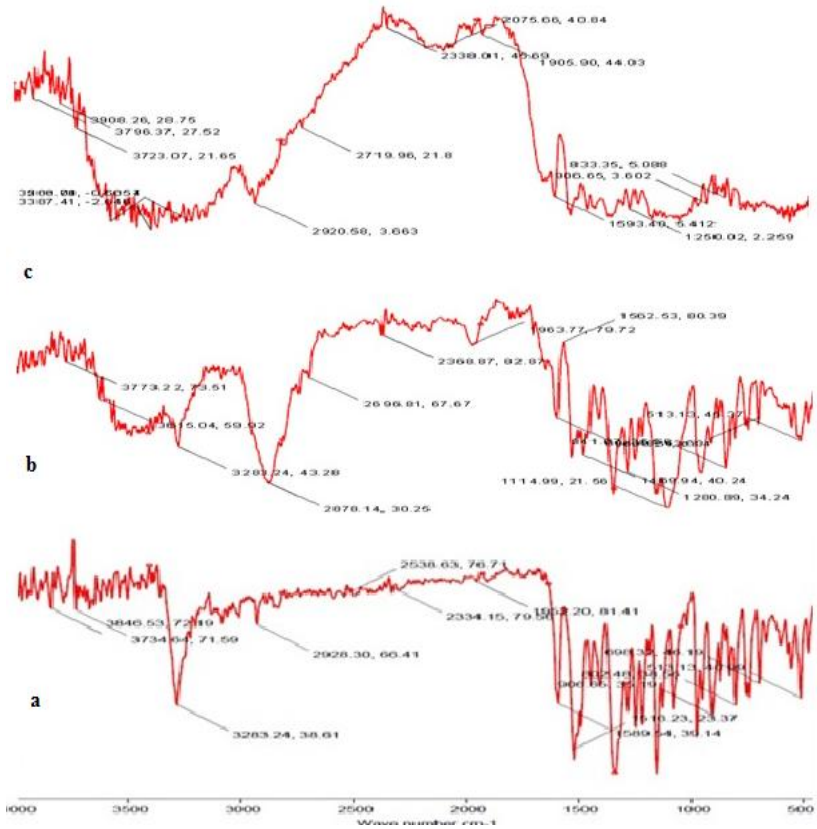

Fig. 3: Fourier transform infra red spectra of Nimesulide and polymers. a-Nimesulide, b -Dispersions of Nimesulide and PEG 6000 (Milled), c- Dispersions of Nimesulide and β-Cyclodextrin (Milled).

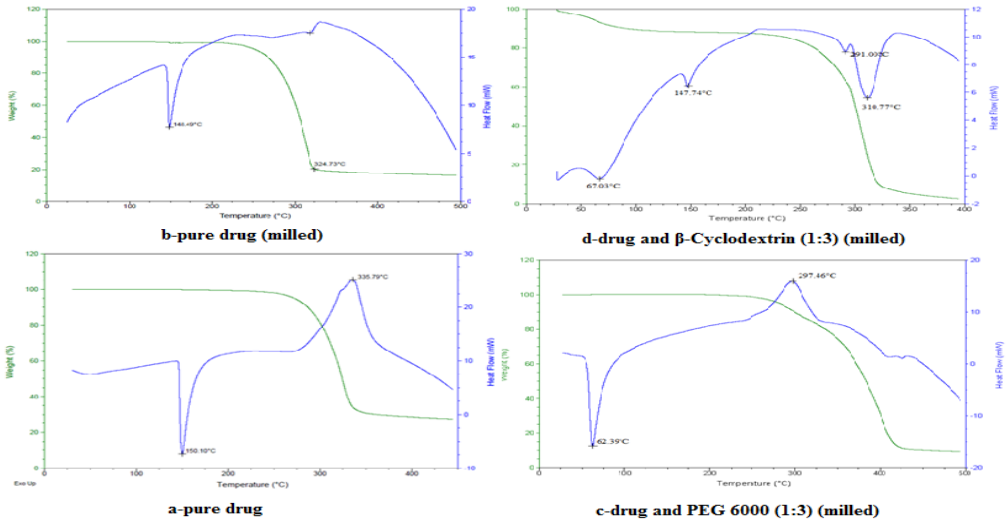

Fig. 4: Differential Scanning Calorimetric spectra of pure drug and milled dispersions

The thermal analysis of pure drug showed 2 peaks, one sharp endothermic peak at 150.10° C corresponding to the melting point of the drug and a second, exothermic peak at 335.79° C. Drastic weight loss occurred at 280° C with a loss of 70% which proved that the drug is of strong crystalline nature. The pure milled drug showed a sharp endothermic peak at 148.49° C representing a small shift in the melting point of the pure drug on milling, and the exothermic peak observed in the pure drug was obtained as a very small intensity peak which indicated that milling has reduced the crystallinity of the drug. Dispersions using PEG 6000 showed an endothermic peak at 62.39° C corresponding to the melting point of the pure PEG and an exothermic peak at 297.46° C. The absence of peak of the pure drug indicated the loss of crystallinity and also revealed that the drug has dissolved completely in the liquid phase of PEG [14]. The thermogram of the dispersion of drug with β-Cyclodextrin showed 4 peaks one corresponding to its melting point at 310.77° C and two peaks of drug at 147.74° C and 291.00° C with a slight shift and very less intensity compared to pure, indicating mild interaction between drug and polymer and finally the peak at 67 .03° C corresponding to β-Cyclodextrin. The weight loss of about 80% was observed at 260° C and this might be due to the complex formation and complete entrapment of the drug within the polymer (Fig. 4)

Characterstic peaks for the pure drug were observed at 19.460°, 19.540°, 21.800° and 23.260° for 2θ values. 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. Both the milled NPEGs showed peaks of high intensity at 23.4 °and 19.420° which corresponds to the peak of pure PEG. The other peaks observed in the sample were with very low intensity in the dispersions, indicating that the transition from crystalline form has started. The dispersions of NPEG hence exist in a semi crystalline form since the polymer PEG is itself semi crystalline in nature. Characteristic peak with an intensity of 593 occurred at 19.62°. In cyclodextrin dispersion, the peaks observed for the drug occurred with intensity less than 500 showing that the presence of the polymer cyclodextrin has brought about a change in the crystallinity of the formulation (Fig. 5).

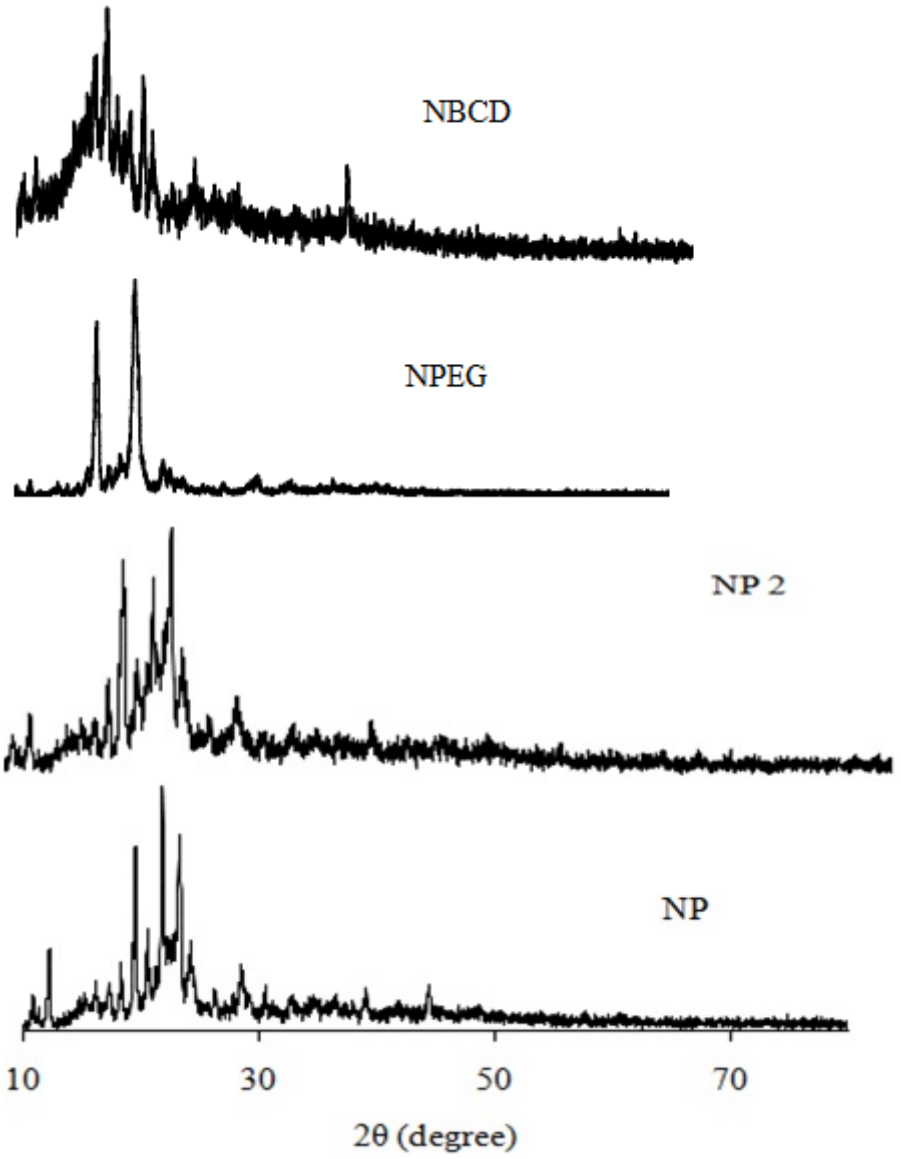

Fig. 5: X-Ray crystallograph of Nimesulide and β-Cyclodextrin dispersions (NBCD), Nimesulide and PEG dispersions (NPEG), 90 min milled pure drug (NP2) and pure drug (NP).

CONCLUSION

From the data obtained we could conclude that milling in the presence of the polymers polyethylene glycol and β-cyclodextrin helped in increasing the flow property, solubility and dissolution rate of the drug. Moreover with increase in the time of milling, increase in dissolution rate was observed which implies that a reduction in the particle size has increased the surface area thereby increasing the solubility. Among the two polymers used polyethylene glycol serves as a better enhancer of solubility because of its hydrophilic nature.

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