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EFFECT OF PHYSICAL MODIFICATION ON DISSOLUTION OF NABUMETONE: A BCS CLASS II DRUG

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ABSTRACT: Objective: Physically modified forms of BCS class II drug Nabumetone (NBT) was studied for dissolution in water and pharmacopoeial dissolution media (2% w/v sodium lauryl sulfate in water). Characterization was to identify the suitability of physical processing like heating, cooling, grinding, and milling operations anticipated during commercial manufacturing of dosage forms. **Materials and Methods:** NBT was subjected to melting followed by quench cooling, grinding, and ball milling to alter the physical characteristics. These were subjected to dissolution studies and compared the values with the raw material. Characterization was done with DSC, FTIR, and PXRD. **Results:** The quench cooled form of NBT exhibited low dissolution in water compared to NBT raw material and size reduced samples. In water, the cumulative percentage release (CPR) of NBT after 120 min was found to be 4.64 ± 0.04 , 4.62 ± 0.09 , 4.50 ± 0.07 and 4.06 ± 0.04 for NBT raw material, ground NBT, ball-milled NBT and quench cooled NBT respectively. The CPR of NBT after 120 min in 2% SLS was 86.10 ± 1.46 , 92.58 ± 1.63 , 90.76 ± 2.17 and 84.52 ± 1.09 for NBT raw material, ground NBT, ball-milled NBT and quenched cooled NBT samples respectively, indicating enhanced dissolution in Pharmacopoeial dissolution media. Upon characterization, a change in crystallinity pattern was noticed during physical processing, while other parameters remain unaltered. **Conclusion:** Physical processing can alter the crystallinity and dissolution of NBT. The low dissolution may probably due to the hydrophobic aggregates formed during processing. The crystalline rearrangement upon quench cooling might have resulted in the low water solubility compared to other forms.

INTRODUCTION: Solubility, dissolution, and GI permeability were identified as the fundamental factors that govern the rate and extent of absorption and bioavailability of drugs¹. So these key factors were considered during dosage form design^{2,3}.

It was reported that almost 70% of the newly developed drug candidates had poor solubility in water^{4,5}. To address this, a scientific framework, the Biopharmaceutical Classification System (BCS) has introduced for classifying drug substances based on their aqueous solubility and gastrointestinal permeability^{6,7}.

In BCS, drug substances are classified as Class I (High solubility, High permeability), Class II (Low solubility, High permeability), Class III (High solubility, Low permeability) and Class IV (Low solubility, Low permeability).

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The classification was introduced by Amidon *et al.*, (1995)¹. A drug substance is considered as highly soluble if the highest dose is soluble in 250 mL or less aqueous media. The values were considered over a pH range of 1-7.5 at a temperature of 37°C^{1, 8}. NBT is a BCS class II non-steroidal anti-inflammatory drug (NSAID) used in the treatment of osteoarthritis (OA) and rheumatoid arthritis (RA)^{9, 10, 11, 12}. To improve the aqueous solubility of NBT, many methods were evaluated like nanoparticles^{13, 14}, nano-emulsions^{15, 16}, solid dispersions^{17, 18, 19}, spherical agglomeration²⁰ and inclusion complex formation²¹. Size reduction is considered as one of the methods to improve the solubility and dissolution of poorly soluble drugs^{22, 23}. In this study, NBT and its physically modified forms were prepared and evaluated to understand the possible differences in characteristics upon mechanical processing like milling, melting, and/or sudden cooling.

MATERIALS AND METHODS: Nabumetone USP was procured from Divis Laboratories Pvt. Ltd., Hyderabad. Sodium lauryl sulfate used to prepare dissolution media was from Nice Chemicals, Cochin, Kerala. Water used was double distilled water.

Preparation of Physically Modified Forms of NBT:

Quench Cooled Sample: 5 gm of NBT was placed in a Borosil® beaker and heated on a water bath maintained at 90°C with occasional stirring until it melts, and glass transparency was noted. The molten material was poured onto an ice cold stainless steel surface maintained at about 0 °C. It was allowed to solidify. The resultant mass was desiccated for 12 h to remove water completely. The dry mass was scraped, pulverized, and passed through sieve #60. The powder was kept in an amber-colored airtight glass bottle till taken for further studies.

Ground Sample: 5 gm of NBT was placed in a clean, dry glass mortar and pulverized using a pestle for about 30 min. The grinding was continued till the physical appearance of material has changed completely from a crystalline to a fine sticky powder. The powder was passed through sieve #60 and kept in amber-colored airtight glass bottle till taken for further studies.

Ball Milled Sample: 2 gm of NBT was loaded into the stainless steel jar of a planetary micro mill (Fritsch GmbH, Germany) with stainless steel balls (5mm diameter and 500 mg weight). The ball to powder weight ratio (BPR) was maintained at 15:1 with a rotational speed of 300 rpm. Milling was done for 3 h, with a pause period of 10 min for every 30 min to avoid excessive heating of the material. The operation was carried out under normal atmospheric condition and repeated to get a sufficient quantity of powder (about 5 gm). The powder was passed through sieve #60 and kept in amber-colored airtight glass bottle till taken for further studies.

Evaluation Criteria:

Dissolution Studies: Dissolution testing was done on the samples after filling in transparent hard gelatin capsule shells (Natural Capsules, India) using USP dissolution testing apparatus, Type II paddle (HMG, India) in 900 mL double distilled water with a rotation speed of 50 rpm. 2 mL aliquots of the sample were withdrawn at 15 min intervals up to 120 min and replaced with the same volume of the blank sample prepared only with empty transparent hard gelatin capsules. The samples were filtered through a nylon membrane filter (0.22 µm). The filtrate was analyzed for NBT concentration by UV spectrophotometric method. Dissolution testing was repeated in a similar fashion using 2% w/v SLS solution as the dissolution media.

Fourier Transform IR Spectroscopy (FTIR):

FTIR spectra of samples were obtained using Thermo Nicolet, Avatar 370 instrument with a spectral range of 4000-400 cm⁻¹. A small quantity of each sample was triturated with KBr (1% w/w of drug content) and placed into the sample holder for analysis. The resolution was 2 cm⁻¹ and scan speed was 32 scans/sec.

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) thermograms of the samples were obtained using a DSC instrument (Mettler Toledo DSC 822e). The heating rate employed was 10 °C/min in the range of 25 °C (Room Temperature) to 300 °C in a nitrogen atmosphere (flow rate 20 mL/min). Thermograms were recorded using TA60-WS software (Shimadzu).

Powder X-Ray Diffraction (PXRD): PXRD of samples (100 mg each screened using sieve #80) were recorded to determine the crystallinity changes and/or polymorphic transformations by using an X-ray diffractometer (Bruker AXS D8 Advance, Configuration: Vertical, Theta/2 Theta geometry; Rheinstetten, Germany), X-ray source was Cu, wavelength 1.5406 Å, Detector: Si (Li) PSD. The diffractograms were recorded at a scanning speed of 2°/min, and a chart speed of 2°/2 cm per 2 Theta and the angular range fixed was from 3° to 70°.

Scanning Electron Microscopy (SEM): The morphology of raw material and milled sample were examined by SEM (JEOL Model - JSM 6390LV) to find out the particle size reduction and morphology. The operating conditions were an accelerating voltage of 15-20kV, with a working distance of 4 to 6mm at a spot size of 45-55. Size of a few particles in the field was measured using the software based on magnification.

RESULTS AND DISCUSSION:

Dissolution Studies:

Dissolution in Water: Dissolution was carried out in double distilled water using dissolution test apparatus USP type II at 50 rpm, and the sampling

was done at 15 min intervals up to 120 min. The results were tabulated. The drug release profile shows that the cooled quench form of NBT was having low dissolution in water compared to NBT raw material and milled samples. The maximum cumulative % release of NBT after 120 min was found to be 4.64 ± 0.04 , 4.62 ± 0.09 , 4.50 ± 0.07 and 4.06 ± 0.04 for NBT raw material, ground NBT, ball-milled NBT and quench cooled NBT respectively. These data indicate that NBT is highly insoluble in water even after particle size reduction.

Dissolution in 2% w/v Sodium Lauryl Sulphate Solution (2% SLS):

Dissolution was carried out in 2% w/v SLS using dissolution test apparatus USP type II at 50 rpm, and the sampling was done at 15 min intervals up to 120 min. The results were tabulated. NBT exhibited a favourable uplift in the dissolution when the medium was changed from water to 2% SLS. The cumulative % release of NBT after 120 min in 2% SLS was found to be 86.10 ± 1.46 , 92.58 ± 1.63 , 90.76 ± 2.17 and 84.52 ± 1.09 for NBT raw material, ground NBT, ball-milled NBT and quench cooled NBT samples respectively. The ground sample of NBT had better dissolution compared to other forms, and low dissolution was exhibited by the quench cooled sample.

TABLE 1: DISSOLUTION OF SAMPLES IN WATER

Time interval (min)	Raw material	Quench cooled NBT	Ground NBT	Ball-milled NBT
	Cumulative Percentage Released \pm SD (n=3)			
15	0.54 \pm 0.09	0.33 \pm 0.10	0.75 \pm 0.16	0.46 \pm 0.09
30	1.28 \pm 0.09	0.63 \pm 0.13	1.52 \pm 0.15	0.94 \pm 0.15
45	2.00 \pm 0.07	1.38 \pm 0.18	2.30 \pm 0.14	1.72 \pm 0.20
60	2.91 \pm 0.10	1.78 \pm 0.13	3.24 \pm 0.13	2.74 \pm 0.16
75	3.62 \pm 0.13	2.49 \pm 0.13	3.94 \pm 0.13	3.41 \pm 0.18
90	4.07 \pm 0.13	3.40 \pm 0.10	4.16 \pm 0.14	3.95 \pm 0.11
105	4.48 \pm 0.09	3.94 \pm 0.10	4.42 \pm 0.09	4.22 \pm 0.11
120	4.64 \pm 0.04	4.06 \pm 0.04	4.62 \pm 0.09	4.50 \pm 0.07

TABLE 2: DISSOLUTION OF SAMPLES IN 2% W/V SLS

Time interval (min)	Raw material	Quench cooled NBT	Ground NBT	Ball-milled NBT
	Cumulative Percentage Released \pm SD (n=3)			
15	40.61 \pm 2.19	32.37 \pm 2.54	43.59 \pm 1.99	32.61 \pm 5.02
30	56.24 \pm 1.98	46.40 \pm 1.99	58.28 \pm 1.98	49.03 \pm 3.82
45	61.46 \pm 2.52	56.27 \pm 2.34	63.26 \pm 1.80	58.07 \pm 3.50
60	72.35 \pm 3.06	62.29 \pm 2.34	75.11 \pm 2.36	69.23 \pm 3.61
75	81.01 \pm 2.56	69.13 \pm 2.17	86.16 \pm 2.34	78.25 \pm 3.40
90	83.68 \pm 2.53	75.74 \pm 2.55	88.49 \pm 2.52	83.55 \pm 3.35
105	85.37 \pm 1.82	81.27 \pm 2.16	91.13 \pm 2.20	86.92 \pm 2.80
120	86.10 \pm 1.46	84.52 \pm 1.09	92.58 \pm 1.63	90.76 \pm 2.17

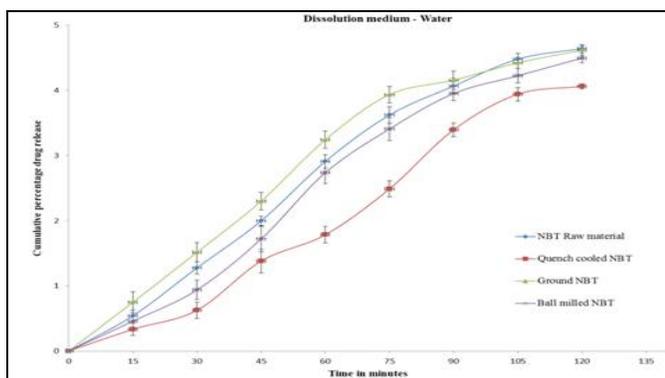


FIG. 1: DISSOLUTION PROFILE OF NBT AND ITS PHYSICALLY MODIFIED FORMS IN WATER

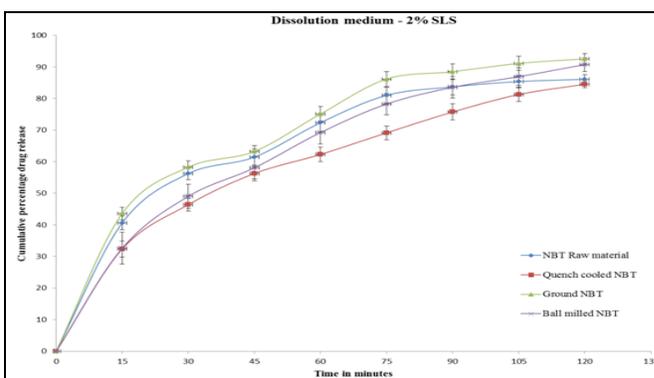


FIG. 2: DISSOLUTION PROFILE OF NBT AND ITS PHYSICALLY MODIFIED FORMS IN 2% SLS

FTIR Spectra: FTIR spectra of NBT and its physically modified forms were recorded and given below.

TABLE 3: CHARACTERISTIC FTIR SPECTRAL VALUES IN PHYSICALLY MODIFIED SAMPLES OF NBT

S. no.	Reference values ²⁴ (cm ⁻¹)	Raw material (cm ⁻¹)	Quench cooled NBT (cm ⁻¹)	Ground NBT (cm ⁻¹)	Ball milled NBT (cm ⁻¹)
1	3053	3054	3055	3053	3052
2	2955	2949	2949	2949	2951
3	1705	1704	1704	1703	1704
4	1607	1603	1602	1603	1605
5	1361	1354	1353	1356	1357
6	1263	1262	1262	1262	1263
7	1227	1224	1224	1225	1226
8	1156	1159	1159	1159	1161
9	1027	1024	1024	1024	1025
10	846	845	845	845	845
11	815	810	810	811	812

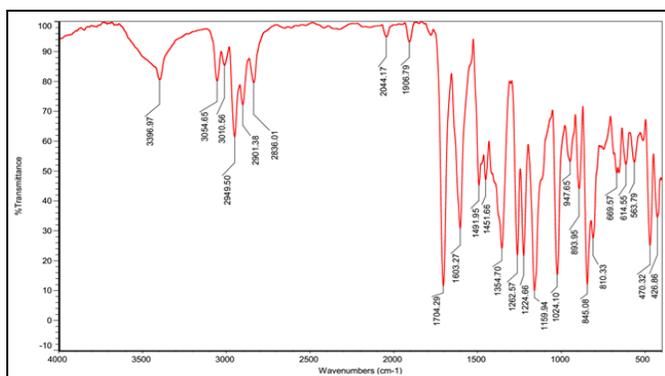


FIG. 3: FTIR SPECTRUM OF NBT RAW MATERIAL

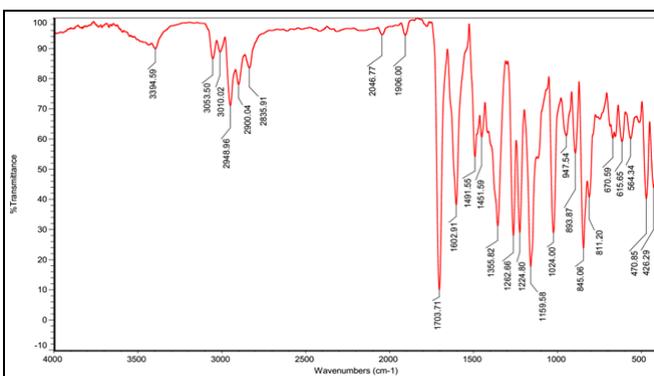


FIG. 5: FTIR SPECTRUM OF NBT GROUND SAMPLE

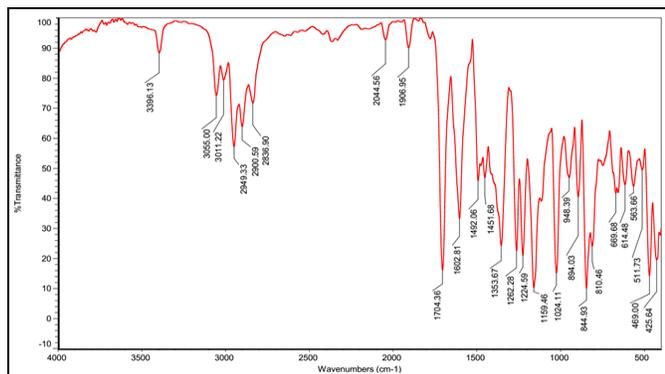


FIG. 4: FTIR SPECTRUM OF NBT QUENCH COOLED SAMPLE

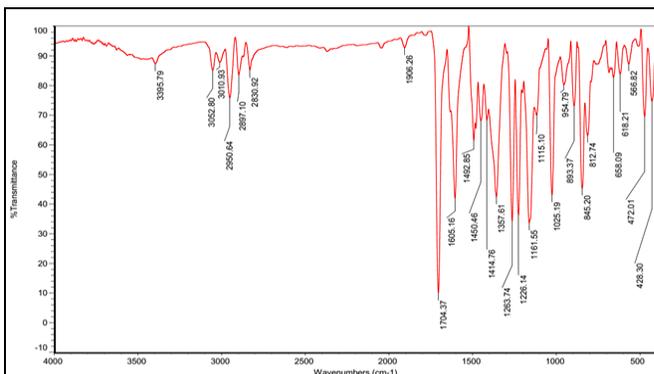


FIG. 6: FTIR SPECTRUM OF NBT BALL-MILLED SAMPLE

The FTIR spectra show all characteristic values attributed for NBT²⁴ in the fingerprint region, corresponding to the various atomic bonds. The physically modified forms do not show any significant difference in the spectrum compared to pure NBT sample indicating the stability of NBT even after subjecting to process like size reduction, applying shear stress, melting and cooling. The slight difference compared to reference values

could be due to the difference in instrumental set up.

Differential Scanning Calorimetry: NBT, along with the physically modified forms were subjected to DSC, to study the thermodynamic patterns. The peaks did not show significant differences indicating the stability of the material.

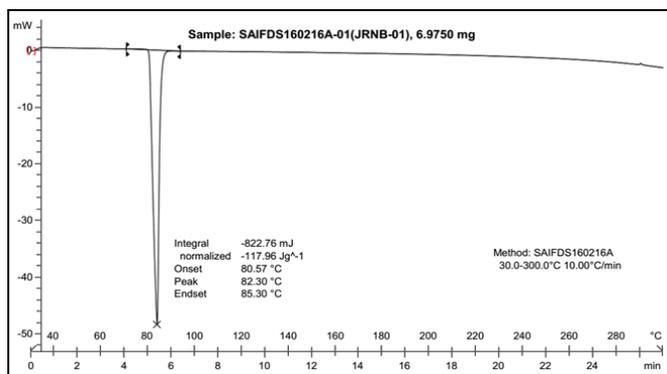


FIG. 7: DSC THERMOGRAM OF NBT RAW MATERIAL

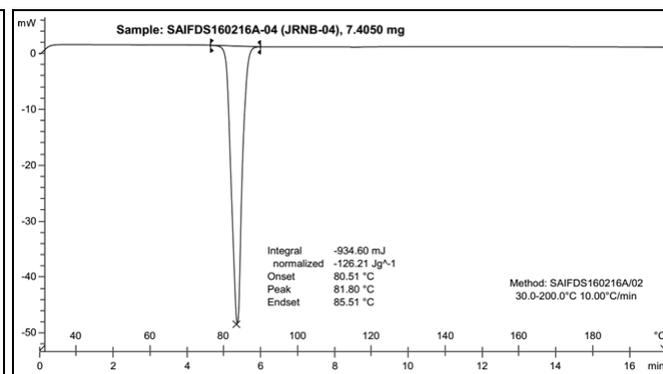


FIG. 9: DSC THERMOGRAM OF NBT GROUND SAMPLE

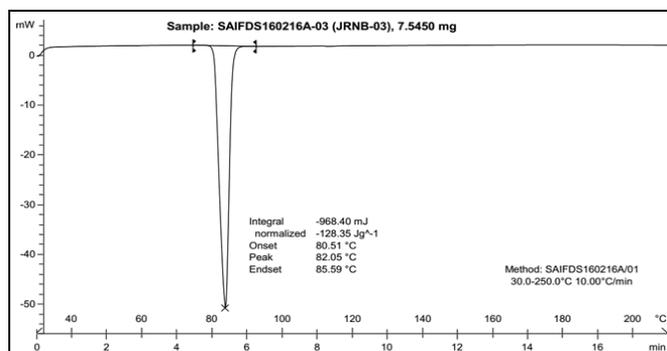


FIG. 8: DSC THERMOGRAM OF NBT QUENCH COOLED SAMPLE

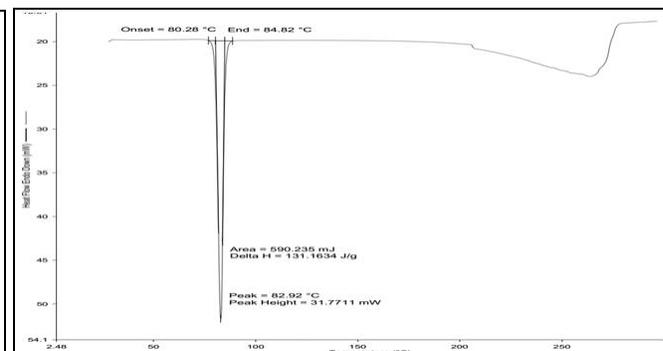


FIG. 10: DSC THERMOGRAM OF NBT BALL-MILLED SAMPLE

The peaks for NBT from the DSC thermograms were 82.30 °C, 82.05 °C, 81.80 °C and 82.92 °C for raw material, quench cooled sample, ground sample, and ball-milled sample respectively, indicating the chemical integrity of the material during physical processing with no significant change in the melting point.

Powder X-ray Diffractogram: Powder crystal X-ray crystallography was carried out on NBT and its physically modified forms to study the crystallinity of the materials.

The intensity of peaks were different in physically modified forms compared to NBT raw material. The quench cooled sample exhibited a sharp peak, and the pattern was different from other diffractograms, suggesting a possible difference in

the crystalline pattern of physically modified forms. This may be the reason for the difference in dissolution exhibited by each during dissolution studies.

Scanning Electron Microscopy: SEM of raw material was compared with the milled sample to understand the particle size reduction and surface morphology. It was found that the particle size was reduced considerably after processing.

The micron-sized particles of raw material were reduced to submicron level after milling. Increase in surface area as a result of size reduction can enhance dissolution, whereas formation of hydrophobic aggregates during milling may retard the same.

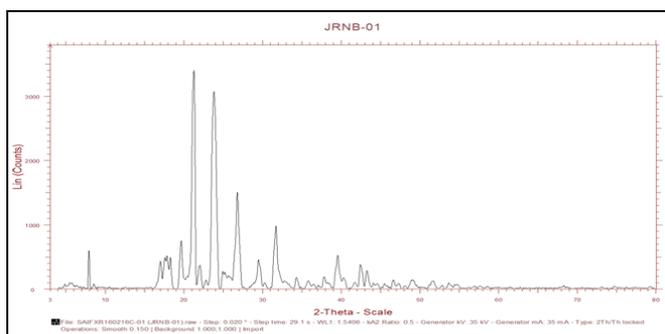


FIG. 11: X-RAY DIFFRACTOGRAM OF NBT RAW MATERIAL

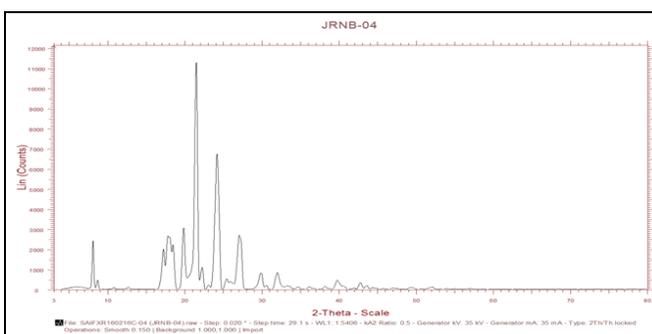


FIG. 13: X-RAY DIFFRACTOGRAM OF NBT GROUND SAMPLE

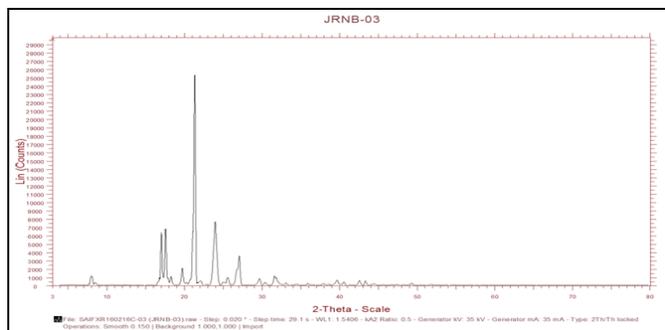


FIG. 12: X-RAY DIFFRACTOGRAM OF NBT QUENCH COOLED SAMPLE

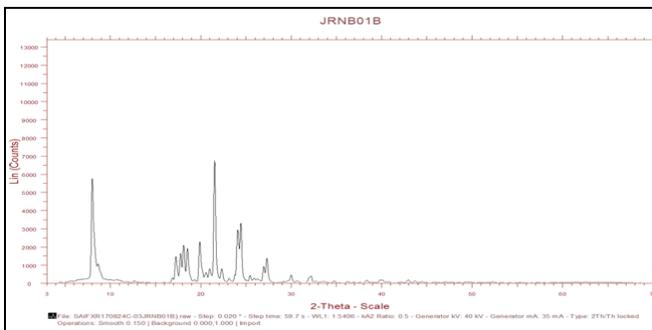


FIG. 14: X-RAY DIFFRACTOGRAM OF NBT BALL-MILLED SAMPLE

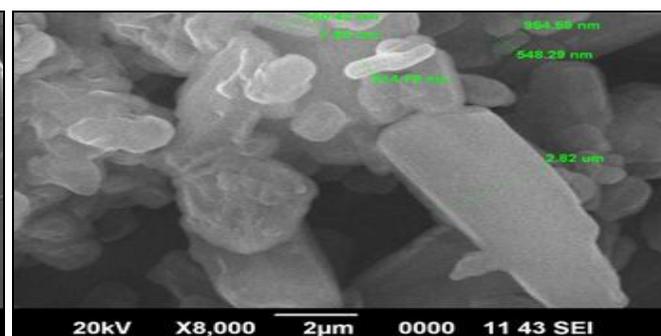
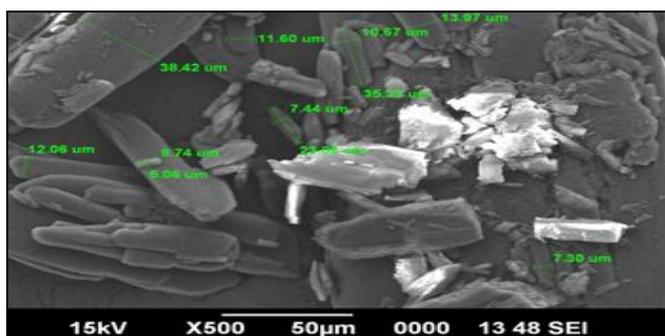


FIG. 15: SEM IMAGES OF RM (LEFT) AND MILLED SAMPLE (RIGHT)

CONCLUSION: A difference in the dissolution pattern was observed among various physically modified forms of NBT. The low solubility of ball-milled NBT in comparison with the ground sample, may probably due to the hydrophobic aggregates formed during the high energy milling process. The raw material was free-flowing without any aggregates and dispersed uniformly in the medium during dissolution study.

FTIR proved that the chemical integrity of the material was not lost during the process. This indicates the stability of the material and its suitability in dosage form manufacturing where it needs to undergo processes like size reduction, heating, and cooling. The DSC thermograms were by the melting range of NBT indicating the stability of the material. PXRD pattern shows the difference

among raw material and other physically modified forms. Physical processing can alter the crystallinity pattern and dissolution of NBT.

The change in the crystalline pattern of NBT during quench cooling might have projected in the low water solubility compared to other forms. The cumulative percentage drug release in 2% SLS at 45 min was found to be 61.46 ± 2.52 for NBT raw material, 56.27 ± 2.34 for quench cooled NBT, 63.26 ± 1.80 for ground NBT and 58.07 ± 3.50 for ball-milled NBT. Out of these results, none were satisfying the limits set by pharmacopeia for Nabumetone tablets USP²⁵ dissolution parameter. Therefore, formulation ingredients and the process have to be properly designed to meet the dissolution criteria while formulating NBT into a tablet dosage form.

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CONFLICTS OF INTEREST: None

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