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ENHANCEMENT SOLUBILITY AND DISSOLUTION RATE OF IBUPROFEN BY NANOBIOCOMPOSITES USING MICROWAVE INDUCED DIFFUSION (MIND) METHOD

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ABSTRACT

Solubility is one of the important factors to achieve required concentration of drug in systemic circulation for pharmacological action. At present only 8% of new drug candidates have both high solubility and permeability. More than 1/3 of the drugs listed in the U.S. Pharmacopoeia fall into the poorly water-soluble or water-insoluble categories. Hence there is need of enhancement of solubility and dissolution of such type of drug. In this study, we increase the solubility and dissolution of practically insoluble drug Ibuprofen by converting into Nanobiocomposite using microwave-induced diffusion (MIND), which ultimately leads to enhanced bioavailability. In this study, we use biodegradable polymer rather than non-biodegradable polymer. The addition of biodegradable polymer into nanofiller production of novel class of materials called Nanobiocomposite. We have used the Microwave induced synthesis method which is a promising and novel synthesis method for the polymer nanobiocomposite. Nanobiocomposite formed by using natural polymer such as Acacia and Ghatti Gum with the help of microwave-induced diffusion (MIND). On the basis of their wetting and surfactant properties polymers were selected. Solubility study and dissolution study was carried out to check the enhanced properties of Nanobiocomposite. Formulated Nanobiocomposite were characterized by Fourier Transform Infrared Spectroscopy (FT-IR), Differential Scanning Calorimetry (DSC), X-ray Diffraction Study (XRD), Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), Particle size distribution. Finally it was found that, the concentration of polymer into the composite enhances the solubility and dissolution of Ibuprofen. The optimized ratio of

drug to polymer for all composite was found to be 1:2. In this work we use novel method for the preparation of nanobiocomposite by microwave irradiation. It was found to be fast, convenient, mild, energy-efficient, higher yields, high purity products, short residence time and environment friendly to produce nanobiocomposite in one step. Hence, this study demonstrates the use of microwave assisted Nanobiocomposite to enhance solubility and dissolution of drug.

KEYWORDS: Nanobiocomposite, Ibuprofen, Microwave–induced synthesis method, Natural polymer.

INTRODUCTION

At present, solubility of drug is most tough aspects in the formulation development. Hence more knowledge regarding dissolution and absorption of low aqueous soluble drug is very important to formulate more soluble and bio available drug.[1] Drug effectiveness can be severely limited by poor aqueous solubility and most of the drugs also show side effects due to their poor solubility. By increasing solubility we increase efficiency and reduce side effects of certain drugs.[2] Drugs having poor water solubility are associated with the slow drug absorption and finally inadequate or different bioavailability. Today about 40 % of the new drugs are poorly water soluble. [3] The poorly aqueous solubility of drug in the gastrointestinal fluid often causes inadequate bioavailability. The drug having poor aqueous solubility require high dose to reach therapeutic plasma concentration. For oral administration of any type of drug it must be in an aqueous form at the site of action.[4] According to Biopharmaceutics Classification System (BCS) drugs are classified into four categories on the basis of their solubility and permeability. BCS class II of drug exhibit high permeability and low solubility.[5] Most of the NSAIDs are belonging to the BCS Class II. They are highly permeable through biological membrane but having poor aqueous solubility. Rate of drug absorption and bioavailability of such poorly soluble drugs are controlled by rate of dissolution in gastrointestinal fluids. [6] This problem can be solved by the various solubility enhancement techniques to enhance solubility and dissolution ultimately bioavailability.[7]

Oral route is the most common way of drug delivery system for drug administration. The majority of sold pharmaceutical products (drugs) in the US and Europe market are given orally.[8] A key objective in development of oral dosage forms is a good understanding of the *in vivo* and *in vitro* performance of the dosage form important for poorly soluble drugs and controlled release dosage forms.[9] The surface area increases due to the reduction in particle

size and therefore increase in dissolution. The Nano size means the particle having size between 100 nm to 1000 nm.[7] Nanobiocomposite posses increased saturation solubility and therefore shows increased dissolution velocity as well as increased mucoadhesion.[10] Advancement in the other drug delivery system dominate oral drug delivery system to increase clinical efficiency and patients compliance. From pharmaceutical point of view a numerous type of polymer are used to control drug release from pharmaceutical dosage form. The use of natural polymer rather than synthetic polymer is more in the drug delivery system. Natural polymers are mainly used because they are readily available, inexpensive, capable of chemical modification and potentially compatible and degradable.[11] Due to the development of polymer nanobiocomposite, these are rapidly used by the pharmaceutical industry. Polymer nanocomposites are the polymer that has been reinforced with small quantities of Nano size particles having high aspect ratio.[12]

In this study we use novel technique called microwave irradiation which is green and cost effective instrument for the production of molecular dispersion. Microwaves are electromagnetic waves containing electric and magnetic field component. Microwave irradiation has more application in the chemistry. Microwave synthesis is generally fast, simple and efficient in energy.[14] The microwave irradiation are used in the various fields such as molecular sieve preparation, preparation of inorganic complexes, radiopharmaceuticals and oxide, organic reaction, plasma chemistry, analytical chemistry and catalysis.[13] Now a days it is mostly used in the preparation of solid dispersion, coating of tablets, drying of granules and in the semisolid formulation.[15] The microwave heating is based on the mechanism of conversion of electromagnetic radiation into heat energy. Microwave heating produce rapid and homogeneous heating to reaction mixture.[16] Microwave irradiation is electromagnetic radiation are located in between the infrared and radiofrequency in the range of 0.3-300 GHz with wavelength 1 cm to 1 m.[7]

The natural polymer acacia are used in the formation of nanobiocomposite which are obtained from stem and branches of *acacia sengal tree*.[17] Gum Ghatti is naturally occurring, water soluble, complex polysaccharides obtained from the bark of *Anogeissus latifolia*. The carriers are selected on the basis of their good surfactant and wetting property which help in the increasing the solubility and dissolution.[18]

Ibuprofen is a non-selective cyclooxygenase (COX) inhibitor, inhibiting both COX-1 and COX-2 forms, its antipyretic, analgesic, and anti-inflammatory activities are achieved

principally through COX-2 inhibition .With most analgesics, including ibuprofen, the initial rise in plasma concentration following oral administration is a main factor in determining the time to onset of pain relief . It is 80% absorbed after oral administration. The time for peak plasma concentration (t^{max}) for ibuprofen is approximately 2 h and it has a short plasma half-life of 2 h. Several reports have shown a variation in the absorption rate and potential bioequivalence problems associated with ibuprofen solid dosage forms. Similar to other NSAIDs, ibuprofenhas potentially serious gastrointestinal (GI) side effects. Theseside effects may be ameliorated when ibuprofen is combined with aphospholipid. The adverse reactions, variable absorption, and short plasma half-life have led this drug to be considered as a good candidate for formulation with phospholipids.[23]

MATERIALS

Ibuprofen drug was gift sample from Flemingo Pharmaceuticals (Nanded, Maharashtra, India). Acacia and Ghatti gum were kindly supplied by the Premcem Gums Pvt Ltd (Mumbai, Maharashtra, India).The microcrystalline cellulose, sodium starch glycolate, Talc and magnesium stearate all of these are purchased from the S.D. Fine chemicals (Mumbai, Maharashtra, India). The materials which are received are directly used without further purification. The chemicals like Hydrochloric acid and Sodium dihydrogen phosphate were used of analytical grade.

Fourier Transform Infrared Spectrophotometric Analysis

Infrared study was carried out to check drug excipients compatibility. Infrared spectrum of Ibuprofen was determined on Fourier Transform Infrared spectrophotometer (Shimadzu DR-8031) using KBr dispersion method

Solubility Study

The solubility study was carried out by shake flask method. An excess amount of pure Ibuprofen drug added into distilled water in separate flask. Then this sample were shaken 24 hrs at 37^{o}C temperature in a shaker .Then sample was placed undisturbed for 12 hrs for equilibrium. The supernatant liquid ware collected and filtered through 0.45µ membrane filter and analyzed by UV visible spectrophotometer (UV-1800; Shimadzu, Tokyo, Japan) at 222 nm respectively.[19]

Swelling Index

SI of gums was calculated to check the swelling power of gums. Accurately weighed 10 g of acacia gum and Ghatti gum were transferred to 100 ml measuring cylinder. The initial volume occupied by gum was noted. Distilled water was added in the cylinder Upto 100 ml the open end of cylinder was sealed with an aluminum foil and kept aside for 24 hrs. After 24 hrs volume of swelled gum was noted. The swelling index of gum was calculated by the following formula

$$SI = H_f - H_i / H_i \times 100 \quad \ldots\ldots\ldots\ldots\ldots\ldots (1)$$

Where, S = Swelling index of gum.

H_i = Initial height of powder.

H_f = Final height of powder after 24 hrs.[20]

Viscosity determination Viscosity of gum was calculated by taking 1 gm of each Acacia and Ghatti gum and dipped in 100 ml distilled water (1 % w/v). The viscosity of resultant dispersion was measured by viscometer at 100 rpm.[21]

Foaming Index

The foaming index of gum was calculated to check the surfactant properties of the gum. Surfactant property of gums can be determined by foaming index. Accurately weighed 1 g of drug and transferred it in 250 ml measuring cylinder. 100 ml distilled water was added in measuring cylinder to make dispersion. Resultant dispersion was vigorously shaken for 2 minutes. The foaming index of gum calculated by the following equation,

$$\text{Foaming index} = H_f - H_i \quad \ldots\ldots\ldots\ldots\ldots (2)$$

Where, H_f is the height of solution of gum after shaking and H_i is the height of solution of gum before shaking.[22]

Preparation of Solid Systems

Physical Mixtures

Physical mixture of individual drug Ibuprofen (IBU) and individual polymer (Acacia gum and Ghatti gum) were prepared by mixing them in different ratio (drug: polymer) from 1:1 to1:2 w/w using a mortar and pestle. Ratio optimization was carried out using a solubility determination method. The physical mixture of drug with polymer was denoted with $IBUAC_P$,[1,2] $IBUGG_P$ [1,2,7]

Microwave Induced Fusion Method for Nanobiocomposite

The Nanobiocomposite prepared by fixed amount of drug Ibuprofen and carrier (Acacia and Ghatti gum) was in the w/w proportion of 1:1 to 1:2 by keeping mixture constant. By homogeneous mixing of drug and carrier in mortar and pestle the physical mixture was prepared. Homogenous slurry was prepared by adding 5 ml of water in each gram of drug carrier physical mixture. A fixed amount of slurry (6g) was placed in a glass beaker and irradiated with microwave radiations at power 640 W (power grill 20 black, ONIDA, Mumbai, Maharashtra, India) with continuous stirring. Only one beaker at a point in time was placed inside the microwave oven in an accurate place. Nanobiocomposite were grounded in mortar and pestle then passed through 100 mesh sieve to get uniform particle size of 80-250 µm.[7]

Drug Content Analysis

To calculate the amount of drug incorporated into the Nanobiocomposite by dissolving Nanobiocomposite mixture in the anhydrous ethanol. Then the drug content analyzed by UV-Visible spectrophotometerically at wavelength of 222 nm (UV-1800; Shimadzu, Tokyo, Japan) against the ethanol as a blank The value at which the absorbance of the polymers is negligible Calibration curve was obtained by plotting the absorbance of the standard drug solutions against the standard the concentration. the percent drug content was compared to the calculated value. The experimental value was the average of three replicates.[23]

Solubility Study

The solubility study was carried out by shake flask method. An excess amount of pure drug Ibuprofen, physical mixtures and the Nanobiocomposite were determined in distilled water at $37^{O}C \pm 0.5\ ^{O}C$. For each preparation, an equivalent of 30mg of drug added to 10mLof the water in a glass vial with a screw-cap. Then this vials allowed equilibrating at $37 \pm 0.2^{O}C$with shaking on a glass shaker orbital for 24 h. A as 1ml aliquot was taken from each vial and filtered through 0.45µm Millipore filter. The supernatant liquid ware collected and filtered through 0.45µ membrane filter and analyzed by UV visible spectrophotometer at of 222 nm(UV-1800; Shimadzu, Tokyo, Japan).[19]

Powder Dissolution Test *In-vitro* dissolution test was performed according to USP XXIV apparatus 2 (paddle) methods. Phosphate buffer 900 ml of pH 7.2 was used as dissolution media. Powder containing 200 mg of Ibuprofen (IBU) was added in dissolution media maintaining temperature at $37 \pm 0.5\ ^{o}C$ and rotation speed of paddle at 50 rpm. 5 ml of sample

were withdrawn at 5, 10, 15, 30, 45 and 60 minute by replacing 5 ml buffer solution in dissolution media. Then samples were suitably diluted and filtered through 0.5 µ membrane filter and analyzed spectrophotometric ally at wavelength of 222 nm. Correction factor was considered during each sampling and during calculating % cumulative drug release (CDR).[24]

Characterization of Nanobiocomposite

Fourier-Transform Infrared Spectroscopy (FT-IR)

FT-IR spectra of pure drug Ibuprofen, pure polymers (Acacia and Ghatti gum) and Nanobiocomposite of drug with individual polymers (Acacia and Ghatti gum) i.e. ($IBUAC_{NBC}$, $IBUGG_{NBC}$) was carried out to check compatibility of drug with polymer. Nanobiocomposite of drug with each polymer ($IBUAC_{NBC}$ and $IBUGG_{NBC}$ were mixed with potassium bromide (KBr) of IR grade in the ratio of 1:100. The pellets were then scanned using FT-IR Spectrophotometer (Shimadzu DR-8031). The wavelength ranged from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. The FT-IR spectra of mixture were compared with that of the FT-IR Spectra of pure drug and polymer for change if any in the principles peaks of spectra of pure drug and polymers.[25]

Differential Scanning Calorimetry (DSC)

DSC studies of pure drug Ibuprofen, pure polymer (Acacia and Ghatti gum) and Nanobiocomposite of drug with individual polymer (Acacia and Ghatti gum) i.e. ($IBUAC_{NBC}$, $IBUGG_{NBC}$) performed to access what changes had actually made when Nanobiocomposite were formed and what phenomenon these increase solubility of drugs. DSC thermo gram was obtained using DSC (Mettler Toledo DSC 822e, Greifensee, Switzerland) equipped with Star swe computer program) at heating rate of 10^{o}C/min from temperature 40^{o}- 340^{o}C.[25]

X-ray Diffraction Studies (XRD)

XRD study of drug Ibuprofen, pure polymers (Acacia and Ghatti gum), and Nanobiocomposite of drug Ibuprofen with individual polymers (Acacia and Ghatti gum) i.e. ($IBUAC_{NBC}$, $IBUGG_{NBC}$) were carried out to access the changes in the crystallanity made when drug was mixed with polymers. XRD patterns were recorded using (Miniflex II, Rigaku) and Cu-kα radiation (I=1.5418).The powder sample were scanned in angle ranged from 1^0 to 80^0 of 2θ, steps were of 2^0/mm of 2θ and the counting time was 1s/step the currernt used was 30 mA and the voltage was 40 Kv.[7]

Scanning Electron Microscopy (SEM)

The surface morphology of Ibuprofen Nanobiocomposite (IBUACNBC, IBUGGNBC) was observed by scanning electron microscopy. The samples were mounted directly onto the SEM sample holder using double sided sticking tape and images were recorded at the required magnification at acceleration voltage 20 kV and examined using a scanning electron microscope of (JSM 5400LV; Jeol Tokyo, japan). The mean particle size, standard deviation, and 95% confidence interval were calculated by a written program which randomly selected 100 particles of the SEM images. The sample were coated with gold iron before imaging due to prevents charge-up of sample .Coating for 5-6min.[26]

Transmission Electron Microscopy (TEM)

The optimized ratio of ibuprofen Nanobiocomposites showing the best results in the solubility and dissolution studies was subjected to Transmission electron microscope (TEM) study was performed to confirm size and shape of drug crystal dispersed in the polymer. The sample for TEM (PHILIPS CM200,) was mounted on a carbon-coated copper grid made up of disc type with thinned central area of size 3 mm. Transmission electron microscope at operating voltages 20-200kv with a resolution of $2.4A^{0}$.[7]

Particle size analysis

Particle size analyzer of the Ibuprofen Nanobiocomposite were determined using a Malvern Zetasizer Nano ZS (Malvern Instruments, UK) each sample was suitably diluted with water (up to 2ml) to avoid multi scattering phenomena and placed in a disposable sizing cuvette, The size analysis of a sample consisted of three measurements, and the results were expressed as mean size ±SD.[27]

Preparation of Immediate Release Tablet

Nanobiocomposite of Ibuprofen with Acacia was selected for the formulation of immediate release tablet. Drug to carrier ratio was selected 1:2. Ingredient and composition of tablets used is shown in table. All ingredients are sieve through # 60 sieve. Direct compression method is used to prepare tablet using 12 mm punch (Karnavati Engineering Ltd, Gujrat).

Table 1: Composition of immediate release tablet Ibuprofen NBC′s.

Formulation batches					
Sr. No.	**Ingredient**	**F1**	**F2**	**F3**	**F4**
1	$IBUAC_{NBC}$ powder	600 mg	600 mg	600 mg	600 mg
2	Microcrystalline cellulose	25 mg	20 mg	25 mg	20 mg
3	Sodium starch glycolate	15 mg	15mg	20 mg	20 mg
4	Magnesium stearate	3.5 mg	3.5 mg	3.5 mg	3.5 mg
5	Talc	6.5 mg	6.5 mg	6.5 mg	6.5 mg

$IBUAC_{NBC}$ (Ibuprofen acacia nanobiocomposite)

Evaluation of Immediate Release Tablet

Precompression Evaluation

Precompression evaluation of immediate release tablet include angle of repose, Carr's index (compressibility), Hausner's ratio of tablet mixture were performed as according to USP 30 (2007).

Post compression Evaluation

Post compression evaluation include following test Hardness, weight variation, friability, disintegration time, drug content evaluation were performed by following USP 30 (2007).

***In vitro* dissolution test of Nanobiocomposite powder**

In vitro dissolution test was performed according to USP XXIV apparatus 2 (paddle) methods. Phosphate buffer 900 ml of pH 7.2 for Ibuprofen was used as dissolution media. Powder containing 200mg of Ibuprofen was added in dissolution media maintaining temperature at 37± 0.5 ^{o}C and rotation speed of paddle at 50 rpm. 5 ml of sample were withdrawn at 5, 10, 15, 30, 45 and 60 minute by replacing 5 ml buffer solution in dissolution media. Samples were filtered through 0.5 µ membrane filter and analyzed spectrophotometrically at wavelength of 222 nm.(US Pharmacopoeia) Correction factor was considered during each sampling and during calculating % cumulative drug release (CDR). Instead of Solubility studies dissolution studies of drug along with gums give more specific information about the solubility of drug. Solubility studies are not always a reliable means to access the solubility-enhancing properties of any substance; dissolution efficiency (DE) is suitable variable for evaluation of in-vitro dissolution data.DE_{45} values were calculated from dissolution data and these were used to evaluated the dissolution rate of drug from nanobiocomposite.

In-vivo evaluation

In-vivo study was performed according to a protocol submitted and approved by the Institutional Animal Ethical Committee of Nanded Pharmacy College, Nanded, MS, India. Anti-inflammatory activity of F_2tablet was evaluated by carrageenan induced rat paw edema study as described by 0.1 mL of 1% (w/v) carrageenan suspension in 0.9% (w/v) sterile saline was injected into the plantar tissue of the left hind paw of albino wistar rats. Rats were divided in to three groups each containing eight rats. Animals of respective groups (n=8) were administered orally with vehicle (tween 80, 3 mL of 1% solution), indomethacin 10 mg/kg b. w., p. o. and 100 mg/kg b. w., p. o. of F_2tablet before 1 h prior to the carrageenan induced paw edema. The right paw served as a reference to non-inflamed paw for comparison. The paw volume of all the groups was measured using Plethysmograph for next 24 h after carrageenan injection. The percentage inhibition of edema volume by F_2 tablet and indomethacin drug treated groups were compared with control group. The percentage inhibition of edema volume was calculated using the formula:

$$\text{Percentage inhibition} = (1-Vt/Vc) \times 100$$

Where Vt and Vc are the relative changes in the edema of the F_2tablet and control respectively.

Stability study

Stability study of bionanocomposite -containing optimized tablets was performed as according to international conference on hormonisation (ICH) guidelines at 40^0C temperature and 75% relative humidity for three months. Tablets were filled in cap vials packed in aluminium strips and kept in stability chamber for three months (CHM 10S; REMI Instruments Ltd, Thane, India). Sample were removed and analyzed for disintegration time, % drug content and *in-vitro* drug release at 0, 30, 60 and 90 days.

Physical Characterization of Polymer

Table 2: Physical Characterization of Polymer.

Material	% Swelling*	Viscosity*	Foaming index*
Acacia	71.92 ± 2.21	4.161 ± 0.25	18 ± 0.92
Ghatti gum	75.31 ± 1.01	5.67 ± 0.11	16 ± 0.65

*Data are means +/- SD, n=3

From the results, it is concluded that, swelling properties and viscosity of Acacia and Ghatti gum are low. Due to the less viscosity of acacia and Ghatti gum, they are used to increase the

solubility and dissolution of drug. Acacia having low viscosity and high foaming index than the Ghatti gum. Hence acacia gum is more suitable than Ghatti gum for increasing solubility and dissolution rate of drug material.

Drug Content Analysis

Uniform dispersion of Ibuprofen drug in the nanobiocomposite can be determined by drug content analysis. It was found that 95-99 % Ibuprofen drug was incorporated in the nanobiocomposite showing uniform dispersion of drug in the nanobiocomposite of Ibuprofen.

Table 3: Drug content analysis.

Nanobiocomposite	$IBUAC_{NBC}$	$IBUGG_{NBC}$
Amount of drug incorporated	99%	95.00%

$IBUAC_{NBC}$ (Ibuprofen acacia nanobiocomposite), $IBUGG_{NBC}$ (Ibuprofen ghatti gum nanobiocomposite).

Solubility Studies

Solubility studies were performed in order to analyze enhancing properties of bionanocomposites. Calibration curve of ibuprofen in pH 7.2 phosphate buffer

A standard solution of 100 µg/mL was prepared by dissolving 10 mg of IBN in 100 mL of pH 7.2 Phosphate buffer. From the stock solution aliquots of 0.4-2 mL were withdrawn and were diluted with phosphate buffer of pH 7.2 upto 10 mL. The resultant dilutions were analyzed by UV spectrophotometer (1700 Shimadzu, Japan) at 221 nm against blank buffer and absorbances were taken. Graph of absorbance versus concentration was plotted. From the R^2 value it can be concluded that drug show linearity in the concentration range of 4-20 µg/mL.

Table 4: Calibration curve of ibuprofen in ph 7.2 phosphate buffer.

Sr. No.	Concentration (µg/ml)	Absorbance
1.	00	00
2.	4	0.249
3.	8	0.453
4.	12	0.646
5.	16	0.888
6.	20	1.084

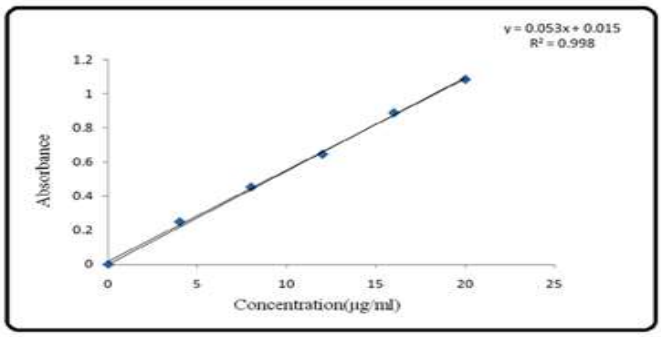

Figure 1: Standard Calibration Curve of Ibuprofen in phosphate buffer pH 7.2.

Table 5: Solubility studies of Ibuprofen.

Medium	Solubility (µg/ml)
Distilled water	29.94
0.1N HCl	58.54
Phosphate buffer ph 7.2	1049.05

Table 6: Solubility studies of physical mixture and BNCs of IBU (µg/ml).

Ratio (Drug: polymer)	$IBUAC_{PM}$	$IBUAC_{NBC}$	$IBUGG_{PM}$	$IBUGG_{NBC}$
1:1	272	818.86	306	384.90
1:2	306	1316.98	336	715.094

Table 7: Comparative solubility study of Ibuprofen and $IBUAC_{NBC}$ and $IBUGG_{NBC}$.

Ratio of drug to polymer	Solubility of $IBUAC_{NBC}$ (µg/ml)	Enhancement of Solubility compared to pure drug (Folds)	Solubility of $IBUGG_{NBC}$ (µg/ml)	Enhancement of Solubility compared to pure drug(Folds)
1:1	818.86	27.35	384.90	12.82
1:2	1316.98	43.95	715.094	23.88

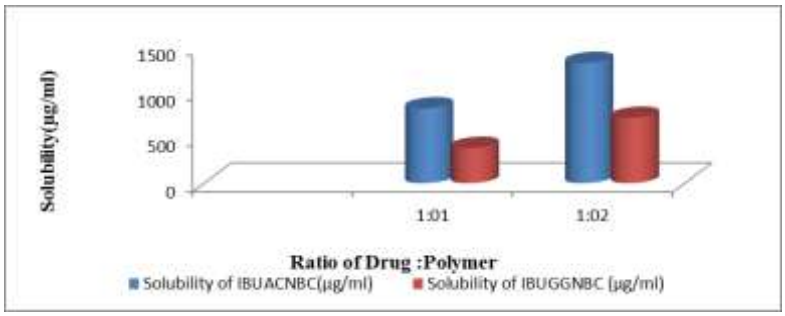

Figure 2: Comparative solubility study of ibuprofen and $IBUAC_{NBC}$ and $IBUGG_{NBC}$.

Solubility Studies give the basis for selection of best ratio that is to be forwarded for formulation. Pure drug Ibuprofen and physical mixture of Ibuprofen individual drug with individual polymer in various ratio as well as bionanocomposites of individual drug with

individual polymer in various ratio were analyzed for solubility determination. The results of the same were shown in table to solubility studies reveals that AC,GG are having very good solubility enhancing property as they have good surfactant property and reduction of crystal size of the drug to nanoscale in the form of Nanobiocomposites enhances the solubility. Solubility studies of physical mixtures and Nanobiocomposites clearly indicate that as the ratio of drug to polymer increases solubility also increases. It was also found that after certain ratio i.e.1:2 for Ibuprofen NBC i.e. $IBUAC_{NBC}$ AND $IBUGG_{NBC}$ Nanobiocomposites. $IBUAC_{NBC}$ solubility remains constant hence 1:2 ratio was optimized. This optimized ratio was then confirmed with powder dissolution and further preceded formulation development, dissolution studies.

Table 8: Dissolution test parameters for powder dissolution of BNC's.

BNC's (Drug)	Dissolution Media (900mL)	Paddle Speed (rpm)	Bath Temperature (^{0}C)	UV Analysis (Wavelength) (nm)	Sampling Interval (min)
IBN	pH 7.2 buffer	50	37.0±0.5	221	5,10,15,30,45, 60

Powder Dissolution Test

From the dissolution profiles of NBC's (figure) it was evident a remarkable improvement of the dissolution rates of drug BNC's than the pure drugs.

Table 9: Power dissolution study of pure IBU,$IBUAC_{NBC}$,$IBUGG_{NBC}$.

Sr. No.	Time (min)	Pure IBU	$IBUAC_{NBC}$	$IBUGG_{NBC}$
1.	5	10.10	9.25	0.594
2.	10	21.91	17.58	2.80
3.	15	28.59	33.99	16.73
4.	30	47.02	53.13	40.52
5.	45	59.46	76.96	53.21
6.	60	78.72	94.87	85.71

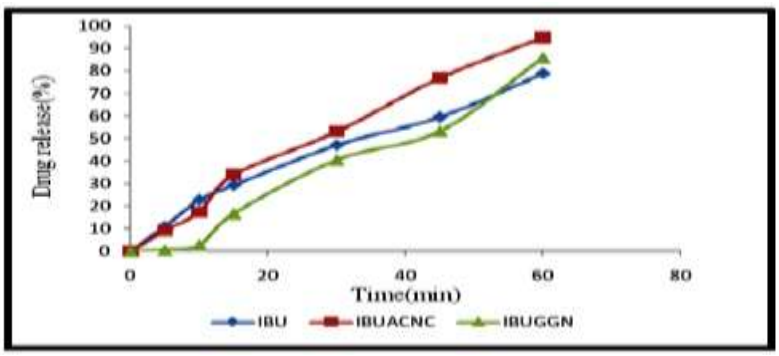

Figure 3: Powder dissolution study of pure IBU, $IBUAC_{NBC}$,$IBUGG_{NBC}$.

$IBUAC_{NBC}$

Powder released 94.87%of drug in solution compared to pure drug which released only 78.72%. $IBUGG_{NBC}$ powder released 85.71%.from $IBUAC_{NBC}$ and $IBUGG_{NBC}$,the dissolution rate of drug is more in $IBUAC_{NBC}$ than $IBUGG_{NBC}$. It can be concluded that dissolution rate has been enhanced with nanobiocomposite.

Drug content analysis

Uniform dispersion of drug in the nanobiocomposite can be determined by drug content analysis. It was found that 95-99 % drug was incorporated in the nanobiocomposite showing uniform dispersion of drug in the nanobiocomposite.

Table 10: Drug content analysis.

Nanobiocomposite	$IBUAC_{NBC}$	$IBUGG_{NBC}$
Amount of drug incorporated	99%	95.00%

$IBUAC_{NBC}$ (Ibuprofen acacia nanobiocomposite), $IBUGG_{NBC}$ (Ibuprofen ghatti gum nanobiocomposite).

***In-vitro* Dissolution study of Ibuprofen tablets**

Table 11: Comparative Dissolution Profile of Ibuprofen tablets.

Time (Min)	Cumulative % drug release				
	F1	F2	F3	F4	Marketed
0	0	0	0	0	0
5	23.24	13.75	18.54	16.98	14.56
10	27.86	18.03	27.95	35.42	26.47
15	44.11	31.01	55.49	47.60	40.08
30	63.72	43.44	71.34	74.82	62.48
45	78.19	71.19	82.55	79.92	71.35
60	94.32	88.4	94.95	92.06	81.05

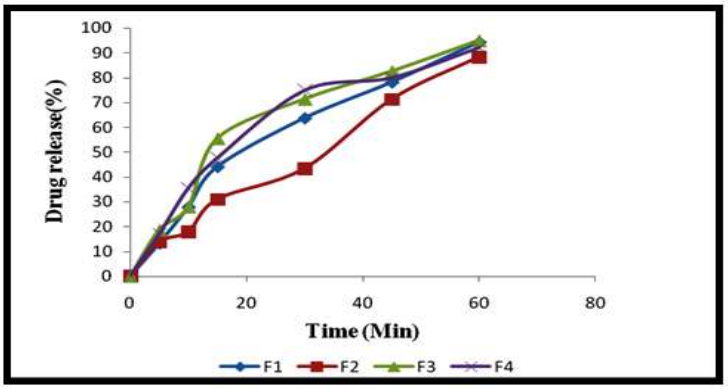

Figure 4*: In-vitro* Dissolution study of Ibuprofen tablets.

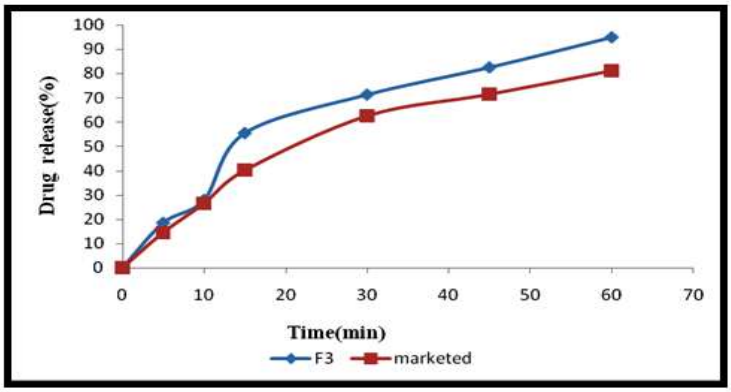

Figure 5: *In-vitro* dissolution study of optimized IBU formulation and marketed formulation.

The dissolution of ibuprofen Nanobiocomposite tablet formulation exhibited improved dissolution behavior than tablets prepared by pure ibuprofen i.e. Marketed formulation of ibuprofen. Here formulation F_3 shows higher drug release (94.95 % in 60 Min) than marketed formulation (81.05 % in 60 Min).

Characterization of Nanobiocomposite formulation

From results obtained by solubility and dissolution studies, the NBC that showed better results were selected for further characterization

FT-IR Studies

The FT-IR studies are done to check what changes are done drug with polymer. FT-IR studies of drug (IBU), polymers (AC and GG) and BNC of individual drugs with individual polymer (IBUAC and IBUGG) were done. FT-IR spectra of pure polymer, pure ibuprofen and Nanobiocomposite are shown in following fig.

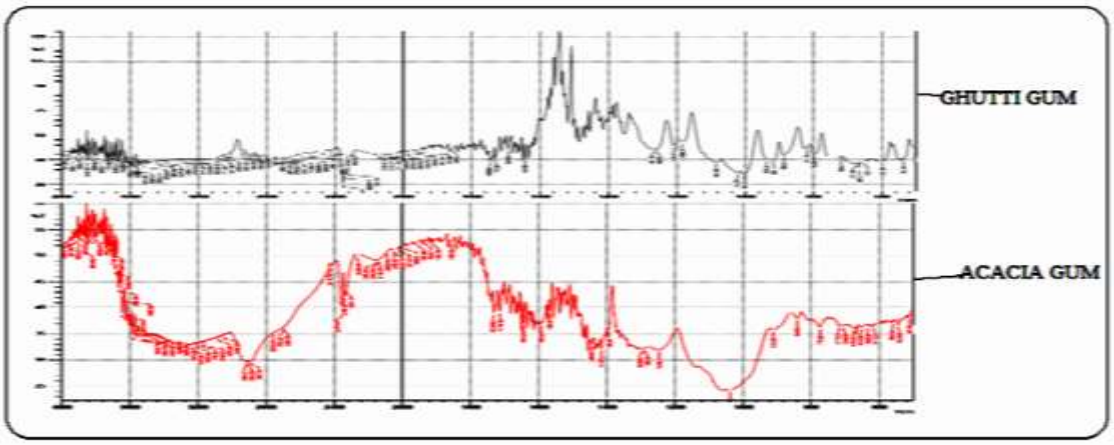

Figure 6: FTIR spectra of pure AC and pure GG.

Table 12: Principle peaks of pure AC and pure GG.

Functional group	Standard IR ranges (cm^{-1})	Acacia Gum	Ghutti Gum
Stretching of O-H bond	3500-3200	3381.21	3417.86
Stretching of C-H bond	3000-2850	2916.37	2945.30
Stretching of C=O bond of Carboxylate group	1760-1690	1714.72.	1732
Stretching of C-O ether and alcoholic group	1320-1000	1068	1085,1025
Stretching of carbonyl group	1670-1820	1732.08	1745.58

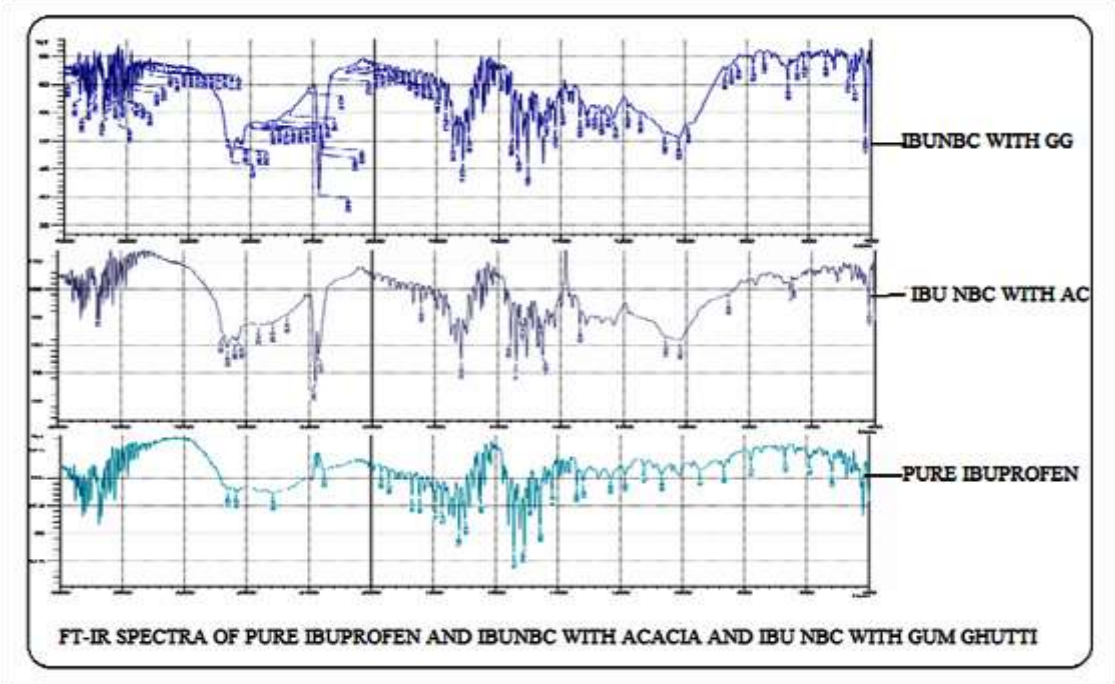

Figure 7: FT-IR studies of pure Ibuprofen, Ibuprofen and Acacia Nanobiocomposite ($IBUAC_{NBC}$) and Ibuprofen and Ghatti Gum Nanobiocomposite ($IBUGG_{NBC}$).

Pure Ibuprofen shows principle peak at O-H stretching (Carboxylic acid group at 2922.16), C=O.

Stretching (1716.65), and C=C bonding (1647.21). These entire principle peak shown in the pure drug are unchanged in the FT-IR spectra of $IBUAC_{NBC}$ and $IBUGG_{NBC}$. It indicates that there is no chemical reaction between drug and polymer. After microwave irradiation Ibuprofen form physical composite with the polymer.

Differential Scanning Calorimetry (DSC) Studies

DSC thermo grams of pure drugs (IBU), polymers (AC and GG) and NBC of individual drug with individual polymer are shown in the following figure.

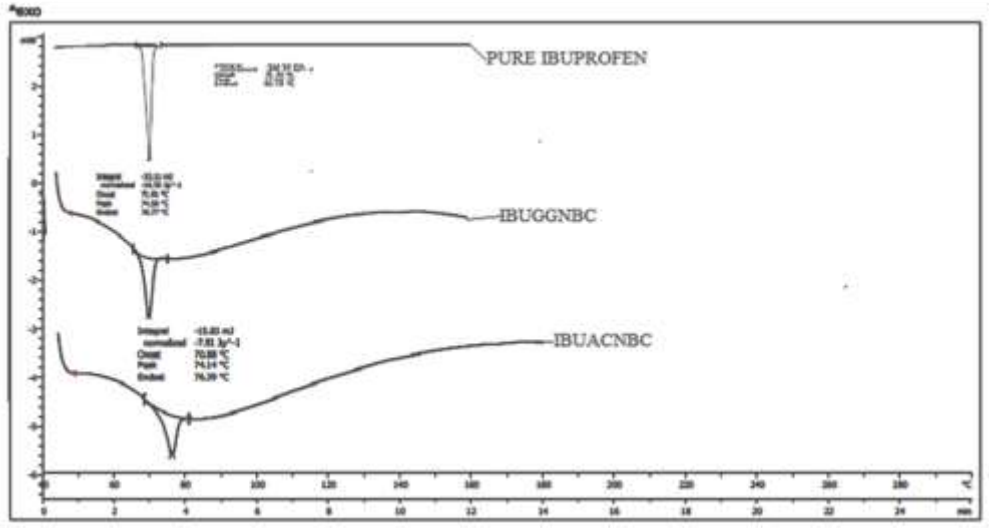

Figure 8: DSC studies of pure Ibuprofen,Ibuprofen and Acacia Nanobiocomposites ($IBUAC_{NBC}$) and Ibuprofen and Ghatti Gum Nanobiocomposite ($IBUGG_{NBC}$).

DSC of pure Ibuprofen shows sharp endothermic peak at 77.60 ^{o}C that means indicating melting of Ibuprofen drug at that temperature. DSC of $IBUAC_{NBC}$ and $IBUGG_{NBC}$ shows 74.14 ^{o}C and 74.56 ^{o}C endothermic peak as that of pure drug but with reduced intensity this may be due to decrease in the crystalline size of drug. Small shift in the melting point indicate reduction of drug to nanocrystalline form. Broadening of peak indicate that most of the drug converts into nanocrystalline form. It also concludes that there is no chemical interaction between drug and polymer. Due to the physical interaction drug is bound to the polymer. These studies show that as the reduced crystallinity and its melting point also reduces.

X-ray Diffraction Studies (XRD)

XRD was performed to check the physical state of drug and its nanobiocomposite. XRD pattern of pure drug (IBU), pure polymer (AC and GG) and its nanobiocomposite are shown in the following. With intense peak at 2θ- 19.7, 20.45, 20.82, 22.57, 22.71, 22.82 indicate crystalline nature of ibuprofen. While XRD pattern of $IBUAC_{NBC}$ and $IBUGG_{NBC}$ show reduced peak intensity due to decreased crystallanity. Reduced peak intensity of nanobiocomposite may be due to reduction in size of drug to Nano level. X-Ray Diffraction Study:

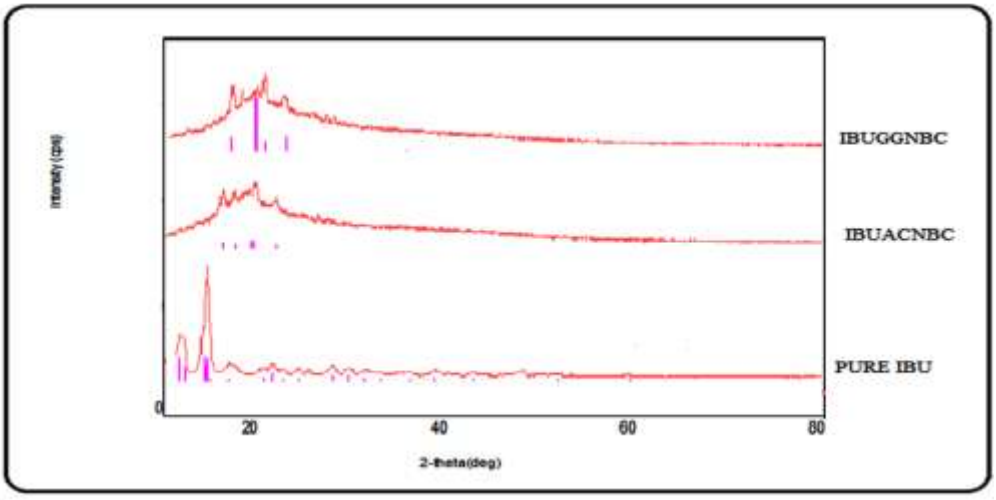

Figure 9: X-ray diffraction studies of pure Ibuprofen, Ibuprofen and Acacia Nanobiocomposite ($IBUAC_{NBC}$) and Ibuprofen and Ghatti Gum Nanobiocomposite ($IBUGG_{NBC}$).

XRD was performed to check the physical state of drug and its nanobiocomposite. XRD pattern of pure drug (ACE), pure polymer (AC and GG) and its nanobiocomposite are shown in the following. With intense peak at 2θ-22.55, 22.78, 25.10, 26.58, 27.03, 32.72 indicate crystalline nature of Aceclofenac. While XRD pattern of $ACEAC_{NBC}$ and $ACEGG_{NBC}$ show reduced peak intensity due to decreased crystallanity. Reduced peak intensity of nanobiocomposite may be due to reduction in size of drug to Nano level.

Scanning Electron Microscopy (SEM)

The SEM studies are done to check surface morphology of the drug particles. The SEM of polymer (AC and GG) is shown in the following figure 8.32. The morphological characteristic of drug and processed drug, polymer & polymer complex is shown in following Fig 8.32.

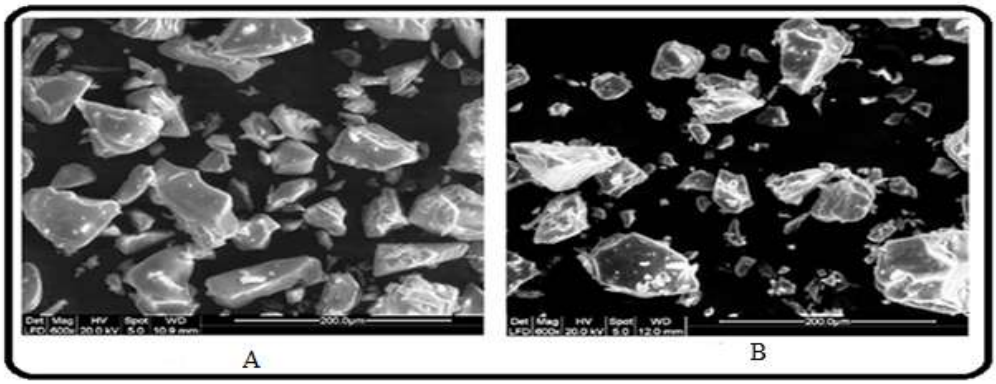

Figure 10: SEM images of A) Acacia Gum and B) Ghutti Gum.

In case of Acacia Gum it was seen that they were large particle with irregular shape and size, while in case of Ghutti Gum it was seen that they were of larger diamond shape and smaller needle like shape irregular shape and size.

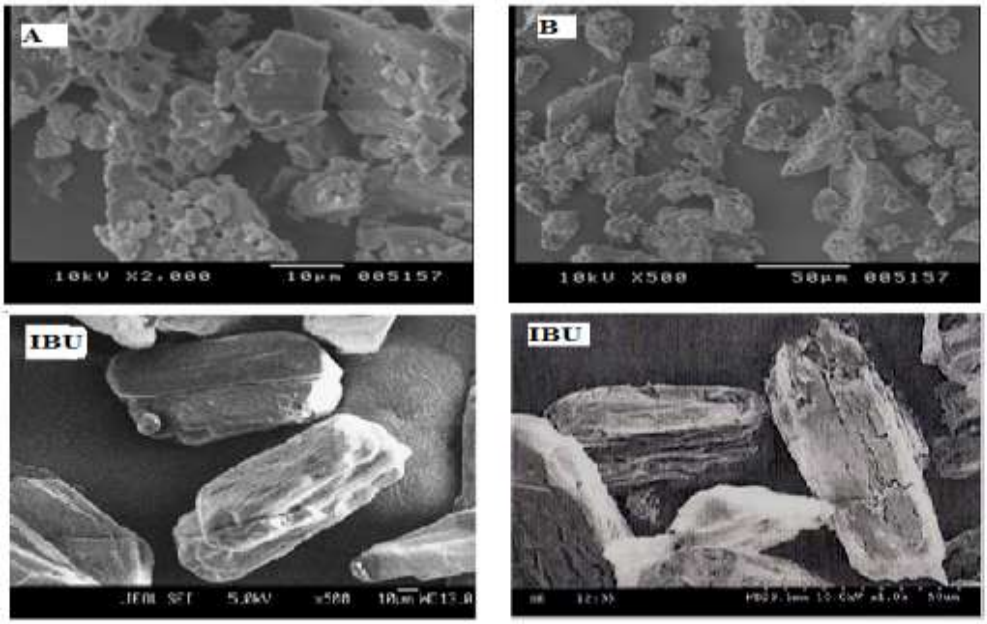

Figure 11: SEM images of pure Ibuprofen and IBUAC$_{NBC}$ [A] 50µm, [B] 10µm.

SEM images of Ibuprofen and Ibuprofen Nanobiocomposite

SEM images show the size of the particles is in approximate 50-500 nm. In case of IBN it was seen that they were small particle with regular shape and size with needle shape while in case of IBUAC$_{NBC}$ it was seen that they were of larger irregular shape and size. It was observed that crystal shape of IBN was completely changed in IBUAC$_{NBC}$ indicating embedded nanocomposite crystals in the Acacia matrix.

Transmission electron microscope (TEM)

TEM image of IBUAC$_{NBC}$ is shown in figure. TEM image was taken to check dispersion of drug nanocrystals in the acacia gum. From image it can be concluded that Drug crystals are plate shape embedded in the acacia gum.TEM micrograph of IBUAC$_{NBC}$ at 100 nm and 50 nm. Many lone ibuprofen seen dispersed in the matrix indicating an absence of any aggregation.

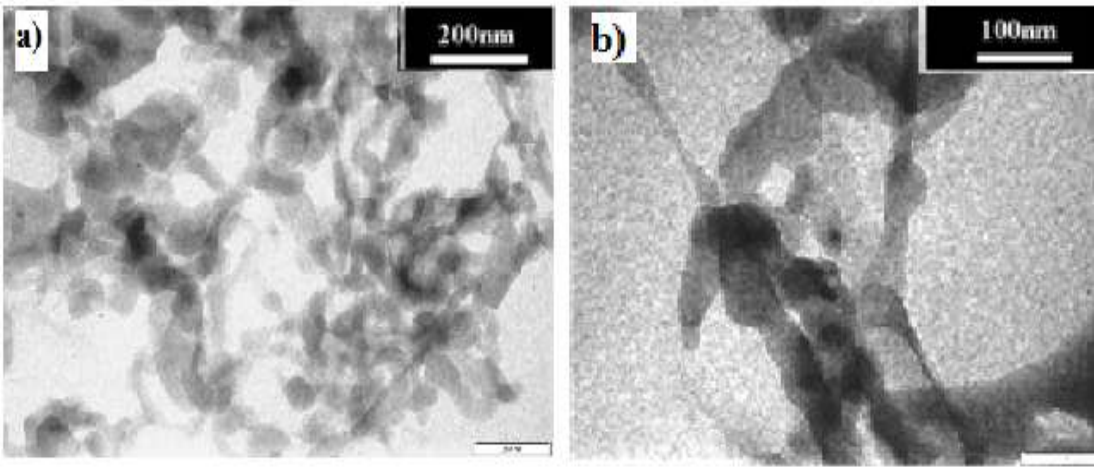

Figure 12: Transmission electron microscope of pure drug Ibuprofen (a) 200 nm (b) 100 nm and IBUAC$_{NBC}$ [A] 200nm [B] 100nm.

Particle size Distribution of Ibuprofen

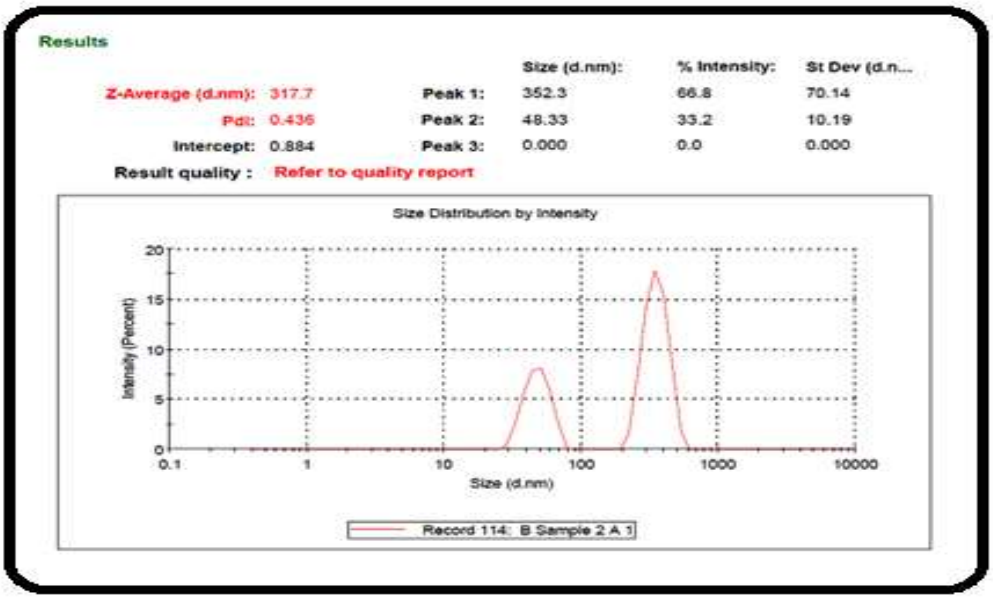

Figure 13: Particle size distribution of IBUAC$_{NBC}$.

The report shows single peak having particle diameter 352.3 nm & 48.33 nm with 66.8 & 33.2 % intensity and the Z- Average diameter is 317.7 nm.

Evaluation of Immediate Release Tablet

Pre Compression Evaluation

The angle of repose, Carr's index and Hausner's ratio of all formulation was measured.Results of Precompression evaluations of formulation mixtures are shown in the following table. From results of Precompression study, it can be concluded that, prepared

formulation mixture has excellent flow properties, good compressibility and Hausner's ratio. Mixture can be easily compressible into tablet and does not show any type of flow problem.

Table 13: Precompression evaluation of $IBUAC_{NBC}$ formulations.

Formulation	Angle of repose	Carr's index	Hausner's ratio
F1	27.90±1.84	18.80±0.50	1.2100±0.01
F2	28.60±2.60	17.85±0.57	1.2212±0.01
F3	28.50±1.50	18.21±0.73	1.2308±000
F4	29.90±1.60	18.74±0.50	1.2308±0.01

Post Compression Evaluation

The formed formulation was subjected to various tests for post compression evaluations such as hardness, friability, content uniformity of prepared tablets, disintegration time and weight variation. All results are within the limit given in the USP 30.

Table 14: Post compression evaluation of $IBUAC_{NBC}$.

Formulation	Weight variation (mg)	Hardness (kg)	% Friability	Drug content uniformity (%)	Disintegration time (s)
F1	649±0.05	3.45±0.11	0.78	95.2531	79±2.45
F2	650±0.0023	3.62±0.15	0.61	98.1850	68±1.98
F3	645±0.534	3.11±0.18	0.65	95.3167	75±3.29
F4	646±0.432	3.38±0.17	0.58	99.8140	58±1.51

Stabilitystudies

Optimized formulation was subjected to stability studies. Various parameters such as disintegration time, drug content and *in-vitro* drug release were measured after 0, 30, 60 and 90 days of stability. Result of stability study shown in the table 9.18 it shows, there is no significant change in the disintegration time, drug content and *in-vitro* drug release after stress condition during stability studies. Thus it can be proved from the stability studies that the prepared formulation is stable and not much affected by stress condition.

Table 15: Stability studies of optimized $IBUAC_{NBC}$.

Time in days	Disintegration time in sec	% drug content	% In-vitro drug release
0	58±1.23	95.2531	99.46
30	57±2.05	98.1850	99.30
60	57±1.68	95.3167	99.85
90	56±0.98	99.8140	99.25

In-vivo evaluation of IBUACNBC tablet

Sr. No.	Time (h.)	Increase in paw volume (mL)			% Inhibition	
		F2 tablet (100 mg/kg)	Control	Standard Indomethacine (10 mg/kg)	F2 tablet (100 mg/kg)	Standard Indomethacine (10 mg/kg)
1	0 h	0.891±0.130	0.937±0.126	1.321±0.121	NA	NA
2	30 Min.	1.177±0.144	1.981±0.111	1.643±0.1426	71.55	75.09
3	1 h	1.55±0.126	2.562±0.156	1.134±0.113	83.51	79.16
4	2 h	1.26±0.156	2.129±0.106	1.333±0.193	96.14	98.12
5	3 h	1.211±0.141	2.255±0.102	1.343±0.133	98.42	96.16
6	4 h	0.655±0.101	2.444±0101	1.334±0.134	99.54	98.83
7	24 h	0.859±0.146	1.212±0.137	1.346±0.107	75.79	82.08

CONCLUSIONS

This study gives the use of natural carriers such as Acacia and Ghatti gum in the microwave generated Nanobiocomposite for the enhancement of solubility, dissolution and ultimately bioavailability of poorly water soluble drug Ibuprofen. The solubility and dissolution study gives the complete information for the use of these materials for the solubility and dissolution enhancement. $IBUAC_{NBC}$ shows good result for the solubility and dissolution enhancement. From the study of FT-IR, XRD, DSC, SEM, TEM, Particle size distribution it can be concluded that Ibuprofen converted into the Nanobiocomposite which is responsible for the enhancement of solubility and dissolution. From the characterization it is shows that there is no interaction between drug and polymer. Key characteristic of this study include uniform distribution of drug in the polymer for the formation of Nanobiocomposite which is sufficiently to prepare. From these overall studies it can be concluded that microwave generated Nanobiocomposites. *In vitro* and *In vivo* evaluation of optimized formulation confirms the use of BNCs for increasing solubility and dissolution of drug. The *In vivo* evaluation of *IBUACNBC*tablet revealed same actions as that of standard, indomethacine. is suitable for the enhancement of solubility, dissolution and ultimately bioavailability of drug.

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Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose. The authors alone are responsible for the content and writing of the paper.

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