

# Celecoxib Bionanocomposite: Investigation of the effect of microwave irradiation using natural solubilizer

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## Research Article

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### ABSTRACT :

The main objective of present work was to enhance the solubility and improve the rate of dissolution of drug Celecoxib which is poorly water soluble as it belongs to BCS class II. Enhancement of solubility was achieved by converting the BCS Class II drugs into bionanocomposites (BNCs) by using natural carriers and Microwave assisted Fusion method were employed, which ultimately leads to enhance the bioavailability of drug entity. Bionanocomposites (BNCs) were prepared using microwave assisted synthesis fusion method, where the drug entities were fused with natural carriers such as acacia, gelatin and ghatti gum. Selection of carriers was done based on their wetting and surfactant properties. The FTIR, DSC studies reveals that there was no any interaction between Celecoxib and Natural carriers. Solubility dissolution studies were carried out to investigate the solubility-enhancing property of the BNC. Mixture dissolution and in-vitro dissolution of prepared Celecoxib's BNCs were characterized through DSC, SEM XRD and FTIR. From the study it was found that, the designed and developed nine batches of BNCs among which fourth batch was with Celecoxib: Acacia (1:4) shown the acceptable solubility i.e. 0.0113 mg/ml and its % drug release was found to be 91.58%. The four Batches of Immediate release tablet was prepared and evaluated using official methods viz; weight variation, Content uniformity, *in-vitro* dissolution. BNCs of Celecoxib prepared with Acacia provides significant enhancement in solubility and highlights its use in solubility and dissolution enhancement.

**Keywords:** Bionanocomposite, BCS class II, Celecoxib, microwave-Assisted fusion method and natural carriers.

## INTRODUCTION:

New chemical entities (NCEs) are novel drugs or active pharmaceutical ingredients (APIs) inflowing the drug discovery pipeline due to technological innovation and pressure of competition. The resulting NCEs are mainly characterized as lipophilic with high molecular weight suitable for biological targets, which subsequently exhibit low aqueous solubility and dissolution rate. Both patients and the pharmaceutical industry are overwhelmed with limited aqueous solubility of active pharmaceutical ingredients<sup>1</sup>. Moreover, Poor solubility results in to poor absorption in GI tract, poor bioavailability and therefore, high drug dosage to be administered to achieve desired therapeutic effect, which may leads to increased side-effects of such NCEs. Despite several efforts to ease these issues solubility remains the leading challenge in drug development<sup>2</sup>. Drug absorption from the gastro intestinal tract can be limited due to the low aqueous solubility and slow dissolution. The aqueous solubility of drug is of primary significance. Since,

often a solution of drug is required to conduct pharmacological, pharmacokinetic and toxicological studies. Therefore, poor aqueous solubility limits drug pharmacological applications as well as challenges its pharmaceutical development. As a result, investigations on development of new solubilizers and techniques for solubility enhancement are need of the hour<sup>3</sup>.

Almost 90% of drugs are given through oral administration. The functional viz. absorption, sufficient & reproducible bioavailability and pharmacokinetic profile of these drug substances are highly dependent on solubility in aqueous medium<sup>4</sup>. The Biopharmaceutical Classification System is predictive tool by which drugs can be classified based on its gastrointestinal absorption. This classification was proposed by the recognition that the basic parameters on which the rate and extent of drug absorption depend are drug solubility in aqueous media and its permeability through the gastrointestinal cell wall<sup>5</sup>. The drugs belongs to

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class II and IV which have poor aqueous solubility are difficult to design in formulation, based on physicochemical and biopharmaceutical properties for oral administration<sup>6</sup>. Many approaches have been employed to enhance the solubility such as Salt Formation, Co-crystallization, Co-solvency, Hydrotropic, Solubilising agent and Nanotechnology by Chemical modification. Under Physical Modifications the Particle size reduction, Modification of the crystal habit, Complexation, Solubilization by surfactants and drug dispersion in carriers.<sup>8-14</sup>

A Nanocomposite is a combination of two or more different materials with different properties of each and that are fused, by an effort to blend the best properties of both. A composite consists of two materials of varying natures and combination of those shows improved in their properties greater than that of individual. A physical mixture of drug and Natural or bio carrier in the composite by nanotechnology and their evaluating parameters as drug release profile by *in-vivo* and *in-vitro* and bioavailability in biological system hence termed Bionanocomposite<sup>15</sup>. Bionanocomposite prepared by microwave irradiation method used to prepare Bionanocomposites. This can be applied for various approaches like enhancement of solubility, dissolutions and bioavailability of drug candidates for poorly water soluble drugs.

Among the different techniques, Melting or Fusion technique is one of the simple and efficient one in the preparation bionanocomposite for the solubility enhancement. As particle size reduction provides more surface area for absorption and rapid dissolution.<sup>16</sup>

Microwave radiation consists of electromagnetic waves with frequencies between those of infrared and radio waves, in the range 0.3–300 GHz. It passes through materials and causes their molecules to oscillate, generating heat. Microwaves, with their ability to penetrate any substance, allow heat to be produced at any point in a sample at a given time.<sup>17-18</sup>

The bionanocomposites are the nanocomposites which are prepared by using drug and bio carriers by using microwave-induced fusion technique for the enhancement of solubility of the drug from BCS Class II drug. Thus, Bionanocomposites were prepared by microwave induced fusion method and nanocomposite shows significant increase in solubility and dissolution rate of drug. Further, the versatile vehicle was used with impact of its potential significance in drug delivery system and drug development.<sup>16, 19 & 20</sup>

Promotion and use of Natural carriers with its advantages such as they are Biodegradable, Biocompatible and non-toxic, Economic, safe and devoid of side effects and Easy availability were employed in the BNCs preparation<sup>21</sup>. Celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor and a nonsteroidal anti-inflammatory drug (NSAID), having anti-inflammatory analgesic and antipyretic activity and used in treatment rheumatoid arthritis, osteoarthritis, and familial adenomatous polyposis (FAP). Because of its lack of platelet effects, celecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is not known if there are any effects of celecoxib on platelets that may contribute

to the increased risk of serious cardiovascular thrombotic adverse events associated with the use of celecoxib<sup>22</sup>. Inhibition of PGE<sub>2</sub> synthesis may lead to sodium and water retention through increased fluid reabsorption in the renal medullary thick ascending loop of Henle and perhaps other segments of the distal nephron<sup>23</sup>. Celecoxib drug is poorly absorbed from the gastrointestinal (GI) tract. Thus, there is need to enhance its water solubility and dissolution rate. Natural carriers such as Gum Acacia, Gelatine, gum ghatti used in the preparation of Celecoxib BNCs and prepared celecoxib BNCs compared with that of the pure drug celecoxib at the same experimental conditions for each study. The prepared BNCs of Celecoxib were characterized through differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-Ray Diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) studies and solubility studies.

## Materials and Methods

### Materials

Celecoxib was a generous gift from Gene pharmaceuticals, Pune, Maharashtra (India). Ghatti gum, Gelatin, cassia gum, Ethanol, Disodium Hydrogen Phosphate, Potassium Di-hydrogen Phosphate, Micro Crystalline Cellulose, Sodium Saccharine, Talc, and Magnesium Stearate were purchased by Unique biological, (Kolhapur, Maharashtra, India) and Cross carmellose sodium, were purchased from Vergo, Goa (India). All the materials were of analytical grade. The materials were used as received without any further purification.

### NATURAL CARRIER GUM

#### Swelling characteristics

Natural carrier was weighed accurately about 10 g and placed in a 100 ml measuring cylinder. The initial volume of powdered gums was noted, and the cylinder was filled up to 100 ml with distilled water. The cylinder was kept aside for about 24 hr, and noted the volume of swelled powder. Swelling index (SI) was expressed as a percentage and calculated according to the following equation:

$$\% \text{Swelling} = \frac{(X_t - X_0)}{X_0} \times 100$$

Where,  $X_0$  = initial height of the powder measuring cylinder,  $X_t$  = height occupied by swollen gum after 24 hr.

#### Viscosity

Viscosity of formulation was measured at different shear rates. A typical run comprised changing shear rates from 1–100  $\text{sec}^{-1}$  with equal stay for each shear rate. The shear rate was reversed (from 100–1  $\text{sec}^{-1}$ ) with similar stay. The average of three readings was used to calculate the viscosity<sup>[21]</sup>.

#### Foaming index

The foaming index of the carrier was measured for the surfactant properties. 1 gm of carrier was dispersed in distilled water about 100 ml and shaken vigorously for 2 min. The foaming index was calculated by the following equation:

$$\text{Foaming index} = V_f - V_i$$

Where,  $V_f$  = the volume of 1% w/v solution of carrier after shaking,  $V_i$  = the volume of 1% w/v solution of carrier before shaking.

## PREPARATION OF BIONANOCOMPOSITES (BNCS)

A physical mixture of drug with natural carriers was prepared by simple blending of drug with carrier in required ratios (drug: carriers) for 10 min.

For each sample, a physical mixture of Drug and natural carrier was made by uniform mixing. The weight-to-weight (w/w) ratio of drug to the carrier was taken as per required by ratios keeping amount of mixture constant. Then 4 ml of water was added for each gram of the drug-carrier mixture to make homogeneous slurry (the water was added for hydration of the carrier). A fixed amount of the slurry (5 g) was placed in a glass beaker with a Teflon stirrer (transparent to microwaves) and treated with microwave irradiation for different times at power of 560 W. The temperature of the mixture at the end of treatment was recorded using an inbuilt temperature measurement probe (Table 1). The samples were then ground in a glass mortar and sieved to achieve a particle size of 80–250  $\mu\text{m}$ .

Table No.1: Development of batches of Bionanocomposites of celecoxib

Drug + Carrier (w/w)	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
CXB-A	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
CXB-G	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
CXB-GG	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9

### Drug content

To study the amount of drug converted in the BNCs was extracted by dissolving them in adequate 25 ml solvent. The 0.2 $\mu\text{m}$  membrane filter was used to filter the resulting solution. From the extracted solvent the drug content was analyzed by UV-Visible spectrophotometer at its  $\lambda_{\text{max}}$  254 nm.

### Solubility study

The solubility of drug and physical mixture was determined remarkably in pH 6.8 phosphate buffer. The solubility of drug, physical mixtures and BNCs was determined by taking an excess amount of drug (30 mg) and BNCs (equivalent to 30 mg of drug) and adding it to 10 ml of solvent (pH 6.8 buffer), in Teflon-facing screw-capped vials. The samples were kept at equilibrium for a period of 48 hrs on an orbital shaking at  $37 \pm 0.5$  °C and 50 rpm. The supernatant fraction taken from the vials and filtered through a 0.2 $\mu\text{m}$  membrane filter, later analyzed by UV-Visible spectrophotometer at a  $\lambda_{\text{max}}$  254 nm. Ratio optimization i.e. drug: carrier was done depending on the best solubility results obtained.

### Dissolution study

The powder dissolution test was performed on Celecoxib BNCs following the USP XXIV Apparatus 2 (paddle) method in 900 ml of pH 6.8 phosphate buffer as dissolution media maintained at  $37 \pm 0.5$  °C at 50 rpm. Powder containing 5 mg (or equivalent to 5 mg of) Celecoxib was added to dissolution media. At predetermined times (5, 10, 15, 30 and 45) 5-ml samples were collected periodically and replaced with fresh dissolution medium. After filtration through a 0.2 $\mu\text{m}$  membrane filter samples were analysed spectrophotometrically at 254 nm. A cumulative correc-

tion was made for the removed samples while determining the total amount of drug dissolved. All experiments were run in triplicate. Comparatively dissolution profiles were performed for Celecoxib BNCs and pure Celecoxib drug at the same experimental conditions.

## CHARACTERIZATION OF BIONANOCOMPOSITE

### Fourier-transform infrared spectroscopy (FTIR)

Fourier-transform infrared spectra of pure drug and pure carriers and BNCs of individual API with individual carriers were taken to access interaction, if any, between drug and gum in mixtures. BNCs of drug with each carrier were mixed with in a ratio of 1:1. The prepared mixtures were then scanned using an FTIR spectrophotometer. The FTIR spectra of mixtures were compared with that of the carriers and pure drug to assess any change in the principal peaks of spectra of pure drug and carrier.

### Differential scanning calorimetry

Differential scanning calorimetry (DSC) studies of pure drug and carriers and BNCs of individual drug with individual carriers was performed to assess what changes had actually occurred when BNCs were formed and by what phenomenon these enhanced drug solubility. The test samples were weighed in aluminium pans, approximately 2–4 mg, based on the drug content in the formulation, and was sealed. An empty aluminium pan was used as a reference. DSC thermograms were obtained by differential scanning calorimeter at a heating rate of 10°C/min from 0 to 300°C in nitrogen atmosphere.

### X-ray diffraction studies

To determine the physical state of pure Celecoxib and BNCs, X-ray diffraction was applied. A transmission diffractometer Rigaku (Rigakuminiflex, Mumbai, India) was used to investigate crystallinity in BNCs of optimized batch, and Celecoxib. Diffraction patterns were obtained at a voltage of 45 kV and at a current of 40 mA. Samples were scanned in a 2 theta range from 5° to 70° with a scanning speed of 2°/min and an intensity of 1000 cps.

### Scanning electron microscopy

BNCs that showed the best results in the solubility and dissolution studies were subjected to scanning electron microscopy (SEM) studies to confirm the changes made during the formation of BNCs. Samples were prepared by mounting powder onto a brass stub using graphite glue and coated with gold under vacuum before use. Images were recorded at the required magnification at an acceleration voltage of 10 KV using a scanning electron microscope.

## PREPARATION OF IMMEDIATE-RELEASE TABLETS

The ratios of BNCs that showed the best results in solubility and dissolution studies were selected for formulating the immediate-release tablets. Super disintegrant croscarmellose sodium was used for formulating immediate-release tablets. All the components of the tablets (Table 2) were sieved through a #60 sieve, weighed, mixed and compressed by direct compression into tablets using a 13mm punch for CXB-A tablets on rotary tablet minipress.

Table No.2: Composition of Immediate release tablets of Celecoxib BNCs

Ingredient	Quantity in batch(mg)			
	F1	F2	F3	F4
CXB-A	250	250	250	250
Microcrystalline Cellulose	220	215	210	205
Cross carmellose sodium	20	25	30	35
Sodium saccharine	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5

### Evaluation of prepared immediate release tablets

#### Weight variation

The USP weight variation test was run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

#### Friability

20 tablets were weighed and placed in the Electrolab friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 revolutions the tablets were de-dusted and weighted again. The friability was determined as the percentage loss in weight of the tablets. The % weight loss should be less than 0.5 to 1% the total weight of tablets.

#### Hardness & Dimensions

Hardness was measured using the Pfizer hardness tester. The tablet was compressed between the holding anvil and piston connected to a direct force reading gauge. The dial indicator remains at the reading where the tablet breaks and it returned to zero by depressing a reset button. The thickness and diameter of the tablets was determined by using a vernier caliper. Six tablets from each formulation were used and average values were calculated.

#### Disintegration test

Disintegration test, one tablet was placed in the each tube of the USP disintegration apparatus and the basket rack was positioned in a one liter beaker of 0.1N HCL, at 37°C  $\pm$  2°C, such that the tablets remain 2.5 cm below the surface of liquid on their upward movement and descend not closer than 2.5 cm from the bottom of the beaker. Then motor-driven device is used to move the basket assembly containing the tablets up and down through a distance of 5 to 6 cm at a distance of 28 to 32 cycles per minute. To be in compliance with the USP standards, the tablets must disintegrate, and all particles must pass through the 10 mesh screen in the specified time. If any residue remains, it must have a soft mass with no palpably firm core.

#### Assay

20 tablets were accurately weighed and finely powdered. A quantity equivalent to 50 mg of Celecoxib was transferred to a 100 mL volumetric flask 50 mL of ethanol was added and shaken for 1 hour to dissolve the drug. The solution was then filtered and suitably diluted with Phosphate Buffer 6.8. The drug content was determined spectrophotometrically at 254 nm.

### In-vitro dissolution

In-vitro dissolution testing of optimized tablets was carried out following the USP XXIV Apparatus 2 (paddle) method in 900 ml of pH 6.8 phosphate buffer as dissolution media, maintained at 37  $\pm$  0.5°C at a speed of 50 rpm. A tablet containing 50 mg of Celecoxib was added to the dissolution media. At predetermined times (5, 10, 15, 30 and 45) 5-ml samples were collected and replaced with fresh dissolution medium. After filtration through a 0.2-micron membrane filter, samples were analyzed spectrophotometrically at 254 nm. A cumulative correction was made for the removed sample while determining the total amount of drug dissolved. All experiments were run in triplicate (US Pharmacopoeia). Solubility studies are not always a reliable means to access the solubility enhancing properties of any material; instead, dissolution studies of drug along with gums give more specific information about the solubility of drug<sup>57</sup>.

#### Physical stability study of prepared tablets

The accelerated stability study of BNC-containing tablets was carried out at 40°C/75% relative humidity up to three months. The tablets were filled in cap vials packed in aluminium strips and stored for three months in a stability chamber (CHM 10S; REMI Instruments Ltd., Thane, Maharashtra, India). Samples removed and analysed for *in-vitro* drug release at 0, 30, 60 and 90 days<sup>58-61</sup>.

### RESULT AND DISCUSSION

#### Preliminary Investigation of Celecoxib

Saturation solubility of pure Celecoxib in water, Ethanol and phosphate buffer pH 6.8 were determined. The results suggest that Celecoxib has very less solubility (0.0033 mg/ml) in water. The melting point was observed 165  $\pm$  1.24°C

#### NATURAL CARRIER GUM

##### Swelling characterisation of carriers

Swelling characteristics and viscosity of the gums are primary characteristics of gum (Table 3). It can be concluded that the swelling characteristics and viscosity of ghatti gum, gelatin and acacia gum are low. High viscosity and toughness may limit their application as carriers for dissolution enhancement. The results indicate that, because of less swelling and low solution viscosity, they are more prone to dissolution enhancement. They are less prone to the formation of the tough matrix which will assist rapid liberation of the nanocrystals from the BNCs. Moreover, the foaming index clearly indicates the greater foaming ability of Acacia among the various carriers. Hence, Acacia enhances the solubility more efficiently than the other carriers.

Table No.3: Physical characterisation of polymers

Material	Swelling index	Viscosity (cps)	Foaming index (ml)
Gelatin	65.67% $\pm$ 1.78	4.11 $\pm$ 0.28	17 $\pm$ 1.10
Acacia	64.43% $\pm$ 1.15	3.98 $\pm$ 0.25	18 $\pm$ 0.91
Gum ghatti	74.34% $\pm$ 1.40	5.35 $\pm$ 0.21	14 $\pm$ 0.70

\*All values represent mean  $\pm$  standard deviation (n=3)

#### Drug content analysis

Drug content analysis was performed in order to study the

amount of drug incorporated in the BNCs. It was found that almost 76–92% of drug was incorporated in the BNCs, indicating uniform dispersion of drug (Table 4). Celecoxib with carriers like gelatin, acacia gum and ghatti gum are denoted by CXB-G, CXBA, CXB-GG respectively.

**Table No. 4: Drug content of BNCs of celecoxib**

Drug :polymer	CXB-A	CXB-G	CXB-GG
1:1	76.15±1.12	90.15±1.78	91.24±0.47
1:2	77.74±0.81	79.19±1.30	78.72±0.52
1:3	80.46±0.32	77.43±0.76	76.76±0.87
1:4	85.65±1.78	86.95±0.76	85.14±0.87
1:5	82.78±0.29	85.15±1.39	84.42±0.42
1:6	80.46±0.45	83.22±0.47	82.22±1.87
1:7	78.48±0.36	81.67±0.45	80.66±0.34
1:8	87.25±1.13	88.17±0.41	87.46±1.89
1:9	76.15±1.12	77.43±0.76	76.76±0.87

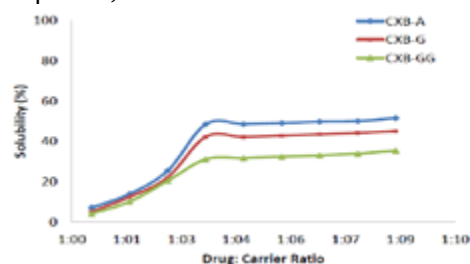
\*All values represent mean ± standard deviation (n=3)

**Solubility studies**

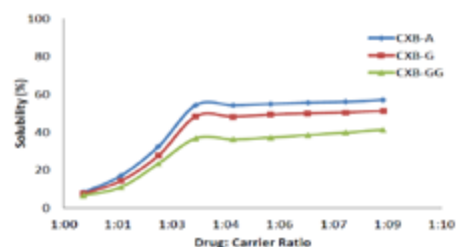
Solubility studies were performed to analyze the solubility enhancing properties of BNCs. Solubility studies provided the basis for selection of the best ratio that was to be forwarded for formulation. Pure drug Celecoxib and physical mixtures of Celecoxib with individual carriers in various ratios, as well as BNCs of Celecoxib with individual carriers in various ratios were analyzed for solubility determination. The solubility of pure Celecoxib was found to be 0.0074 mg/ml. In the form of BNCs the solubility was enhanced as shown in Figure 1 & 2.

Solubility studies reveals that physical mixtures improves the solubility of Celecoxib significantly compared with pure Celecoxib; this may be due to the surfactant and wetting property of gelatin, acacia gum and ghatti gum. In case of Celecoxib BNCs solubility data indicates a tremendous rise in solubility compared with pure Celecoxib; this may be due to reduction of crystal size of the drug to a nanocrystalline form. On the other hand, other microstructural aspects of the composites also play an important role in the drug dissolution.

This aspect is to be investigated by performing SEM and X-ray photoelectronic spectroscopy analyses. Solubility studies of physical mixtures and BNCs clearly indicated that as the ratio of drug to carrier increases solubility also increases. It was also found that after certain ratio (i.e. 1:4), the solubility remains constant; hence 1:4 ratio was considered optimal. This optimized ratio was then confirmed by powder dissolution studies and taken forward to formulation development, dissolution studies.



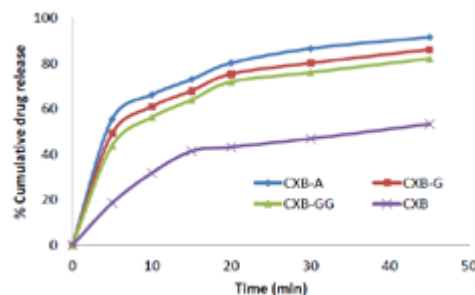
**Figure 1: % solubility data of pure Celecoxib (Physical Mixture) with carriers like gelatin, acacia gum and ghatti gum (CXB-G, CXB-A, CXB-GG).**



**Figure 2: % solubility data of pure Celecoxib (Bionanocomposites) with carriers like gelatin, acacia gum and ghatti gum (CXB-G, CXB-A, CXB-GG).**

**Dissolution study**

A powder dissolution test was performed as solubility studies are not always a predictable means to retrieve the solubility-enhancing properties of any material; instead dissolution studies of Celecoxib and Celecoxib BNCs give more specific information about the solubility and dissolution of drug. Figure No.3 shows the dissolution profile of Celecoxib and Celecoxib BNCs, there was evidently a remarkable improvement of the dissolution rates in all Celecoxib BNCs compared with the pure Celecoxib. Of the BNCs, the best result was shown by CXB-A which released 91.58±0.13% in comparison to pure CXB which released 53.34±0.26% after 45 min. From the solubility and dissolution studies the CXB-A was selected for formulating the tablet.



**Figure 3: Comparative results of drug release from plain Celecoxib and the BNC's in different natural gum; (Mean ±S.D. n =3)**

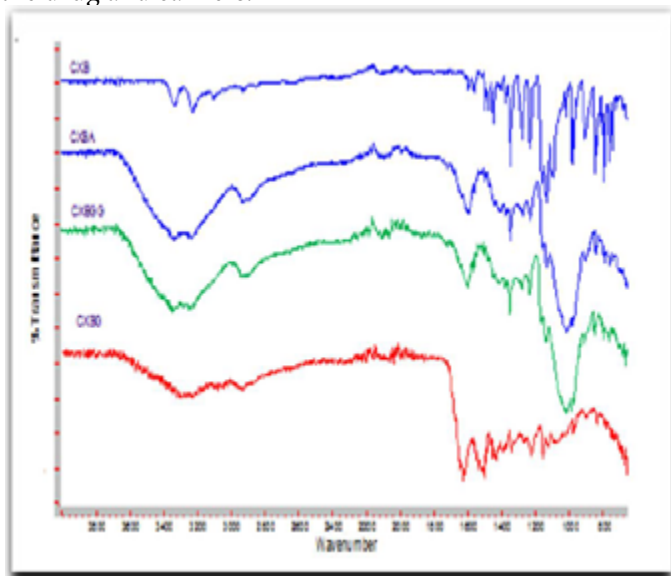
**CHARACTERIZATION OF BIONANOCOMPOSITE Fourier-transform infrared spectroscopy (FTIR)**

The interaction between a drug and its carrier often leads to identifiable changes in the infrared spectrum. The presence and absence of characteristic peaks associated with specific structural characteristics of the drug molecule were noted. FTIR studies of pure Celecoxib (Figure 4) and BNCs of Celecoxib with individual carriers (i.e.CXB-A, CXB-G, CXB-GG) was done. Presence of peak at 1157.81 and 1346.48 confirms the S = O stretch of the SO<sub>2</sub> moiety. In this case, any sign of interaction would be reflected by a change in N–H or S = O vibrations, depending on the extent of interaction. Any kind of physicochemical interactions that may take place, such as the formation of hydrogen bonds between the carrier and drug, will automatically lead to frequency shifts or splitting in absorption peaks. FTIR spectroscopy suggested the presence of a secondary interaction between carriers and Celecoxib within the BNCs. Most of the natural carriers' interaction occurs at the hydroxyl group. All the characteristic peaks of Celecox-



ib were at the same positions as those in the spectrum of .CXB-A, CXB-G, CXB-GG (Figure 4).

From FTIR spectra of the hydroxyl groups region, it is obvious that the intensity of the characteristic peak at 3337.99/cm changed according to a comparison with CXB-A indicating reduction in crystal size. The spectra of Celecoxib BNCs were equivalent to the addition spectrum of GELATIN, acacia gum and ghatti gum and Celecoxib individually. From this it can be concluded that principal peak values of the drug remain unchanged in the microwave-treated BNCs indicating no chemical interaction. Thus, it can be concluded that there is no chemical interaction between the drug and carriers.

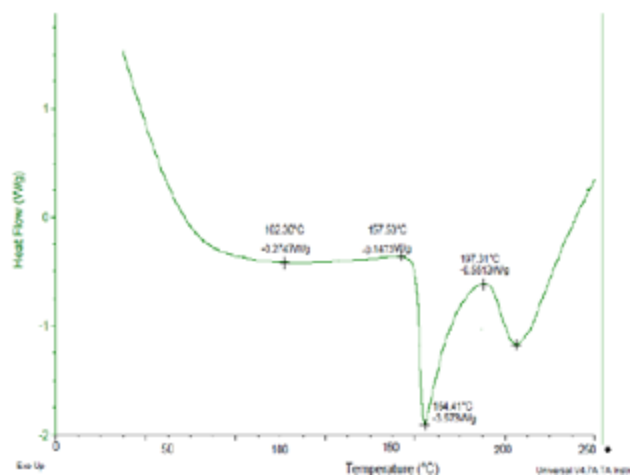


**Figure 4: Compatibility study of pure Celecoxib and BNCs**

**Differential scanning calorimetry**

DSC study of Celecoxib (Figure 5) and Celecoxib BNCs with individual carriers CXB-G, CXB-A, CXB-GG was carried out. In practice, in the DSC profile of a BNC containing micro- and nanocrystals of drug, besides the peak relative to the melting of the microcrystals, there exist one or more other peaks, located at lower temperatures, which relate to the melting of the nanocrystals. This was not the case for the BNCs generated by MIND, whose DSC profiles only contained the peaks relative to the melting of the nanocrystalline drug. The Studies have shown that as the crystal size of a crystalline nanoparticle reduces its melting point also reduces minutely

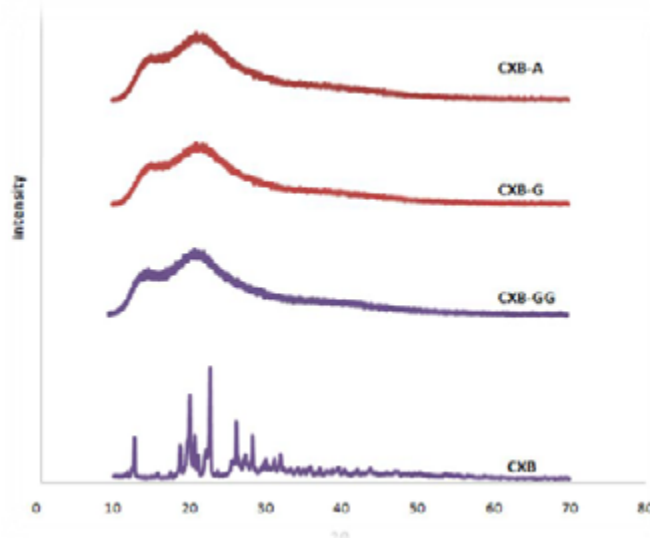
The crystalline nature of Celecoxib can be easily recognized by the presence of a sharp endothermic peak at around 164.41°C. The same endothermic peak with reduced intensity was observed in the DSC profile of CXB-G, CXB-A and CXB-GG indicating melting of drug nanocrystals. The peak broadening also indicated that most of the drug is embedded in the BNCs in the nanocrystalline form. Little shift in the melting point was observed due to reduction of drug to the nanocrystalline form. This phenomenon is responsible for the solubility enhancement as the crystallinity has been reduced to nanocrystalline form.



**Figure 5: Differential Scanning calorimetry (DSC) of Pure Celecoxib**

**X-ray diffraction studies**

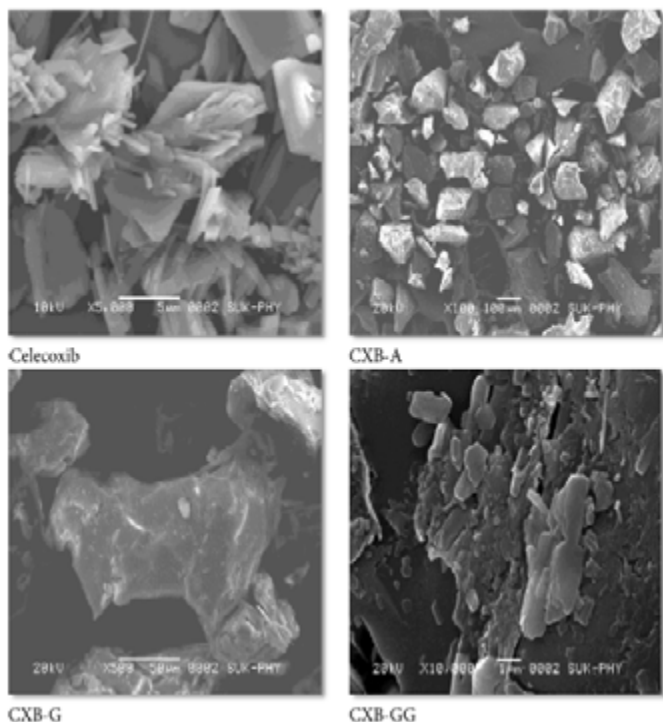
XRD analysis was performed to determine the physical state of the drug (Figure 6) and its BNCs. Powder XRD patterns of Celecoxib, CXB-G, CXB-A, and CXB-GG are shown in Figure No.6. The pure Celecoxib exhibited an intense crystalline peak between 5 and 40. Characteristic diffraction peaks at 10.20, 13.80, 18.30, 19.50, 20.90, 23.60, 26.60 and 28.00 were observed with an intense peak at 23.60 indicating the crystalline nature of Celecoxib. On the other hand, in CXB-G, CXB-A and CXB-GG it is observed that peak intensity was reduced indicating a reduction in crystallinity.



**Figure 6: Compatibility study of pure Celecoxib and BNCs by XRD**

**Scanning electron microscopy**

SEM studies are usually done to study the surface morphology of drug particles. Celecoxib and CXB-A, CXB-G and CXB-GG were characterized by SEM. Celecoxib particles were plate shaped with a smooth surface, while CXB-A particles were of irregular shape and size. Figure No. 7 clearly shows that the crystal shape of Celecoxib was completely changed in CXB-A showing embedded Celecoxib crystals in the Acacia matrix.



**Figure 7: Scanning electron microscopy (SEM) images of CXB and CXB-BNC.**

**Formulation of immediate-release tablets**

The formulation has been done in four batches and ingredients were weighed accordingly as shown in Table No. 5.

**Table No. 5: Formulation of immediate-release tablets**

Ingredient	Quantity in batch(mg)			
	F1	F2	F3	F4
CXB-A	250	250	250	250
Microcrystalline Cellulose	220	215	210	205
Cross carmellose sodium	20	25	30	35
Sodium saccharine	5	5	5	5
Magnesium Stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5

**Evaluation of immediate-release tablets**

All the formulation mixtures were subjected to evaluation of pre and post compression characterization. From the angle of repose, Carr’s index and Hausner’s ratio data, it can be clearly concluded that CXB-A and its mixture with different formulation components have excellent flow properties and fair-to-good compressibility, which allows these formulation mixtures to be directly compressed into tablets and good flow of the mixture from the hopper with good content uniformity in the final tablets.

Prepared formulations were subjected to various compendia tests for post-compression evaluations such as hardness, friability, content uniformity of prepared tablets, DT (Table 6). According to weight variation, drug content and disintegration time results the Batch F4 was found to be optimized.

**Table No. 6: Physical Characterization of CXB-BNC Tablet**

Code	Angle of repose (θ)	Carr’s index (%)	Hausnerratio	Weight variation (mg)	Hardness (kg)	Friability (%)	Drug content (%)	Disintegration time (seconds)
CXB-A	23.54 ±2.92	11.56±1.36	1.161±0.01	-	-	-	-	-
F1	22.11±1.22	11.96±0.31	1.156±0.01	498.8±3.55	3.1±0.15	0.42±0.03	101.83	57.00±2.64
F2	24.14±1.64	12.36±0.18	1.187±0.01	496.2±4.42	2.8±0.12	0.62±0.03	97.32	51.33±2.08
F3	21.15±1.88	10.88±0.69	1.150±0.00	499.1±2.71	2.7±0.20	0.73±0.05	99.57	44.66±3.20
F4	23.18±1.41	10.88±1.13	1.142±0.01	500.4±4.24	3.0±0.10	0.80±0.06	96.32	38.67±1.72

**Stability study**

Optimized formulation was subjected to stability studies according to ICH guidelines. Various variables, such as drug content, disintegration time and *in-vitro* drug release, were measured before and after 30, 60 and 90 days of storage (Table 7). There was no significant change in the above-mentioned variables. Following the elevated temperature and humidity conditions imposed during the stability study. Thus, it can be concluded that the prepared formulation is stable and not much affected by elevated humidity and temperature.

**Table No.7: Stability study of optimized CXB-A formulation (F4)**

Time(days)	Disintegration time(s)	Drug content (%)	Drug release (%)
0	39±2	98.51±0.4	99.03±0.82
30	38±1.3	97.85±2.3	98.68±4.91
60	38±2.5	98.16±1.3	98.21±2.4
90	37±3.6	97.65±0.7	97.41±1.8

## CONCLUSION

This study successfully demonstrated the use of acacia gum, Gelatin and ghatti gum as carriers for the formation of microwave-generated BNCs in the solubility and dissolution enhancement of celecoxib. Solubility and dissolution studies confirmed the use of these materials for solubility enhancement. This demonstrates the possibility of using BNCs as drug delivery systems, particularly using the MIND technique. The Acacia BNCs showed the best results regarding solubility and dissolution enhancement. From the FTIR, DSC, XRD, SEM characterization it can be concluded that celecoxib had been converted to nanocrystals in the composites and this was responsible for the solubility enhancement. Characterization confirmed that there was no interaction between the drug and polymers.

*In-vitro* assessment of optimized formulations further confirmed the use of BNCs for enhancing solubility and dissolution by use of natural carriers. The stability studies showed that the BNC-containing formulations were stable. Here we have demonstrated that it is indeed possible to prepare BNCs using celecoxib as a model drug. Key feature of this study include the uniform distribution of drug in carrier in a nanocrystalline form, which is sufficiently stable and easy to prepare. Finally from these studies overall we can conclude that microwave-generated BNCs can be successfully used for the enhancement of solubility, dissolution and bioavailability.

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