Optimization bionanocomposites of fenofibrate for enhancement of Solubility and dissolution using microwave induced diffusion technique

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***Abstract*— Dissolution and diffusion through gastrointestinal membrane are the mechanism by which drug get absorbed on oral administration. The major challenge in case of most of drugs is poor water solubility. Hence the objective of present study is to develop bionanocomposites (BNCs) by microwave induced diffusion technique (MIND) to enhance solubility and dissolution of poorly water soluble drug Fenofibrate. Natural drug carriers such as *MoringaOleifera* Gum and *AegleMarmelos(L)* were selected for BNCs preparation based on their wetting and surface active agent property. BNCs were prepared by MIND technique and characterized by Fourier transform infrared spectroscopy, differential scanning calorimetry, X-ray diffraction studies, scanning electron microscopy and transmission electron microscopy. The solubility and dissolution enhancing performance of BNCs were assessed by *In-vitro* solubility and dissolution studies. It was demonstrated that, the dissolution of Fenofibrate enhanced with increase in polymer concentration. The optimized ratio of drug and polymer for the entire composite was found to be 1:3 and 1:4 BNCs with Moringa Oleifera and Aegle Marmelos Gum respectively. The MIND technique employed in this study as green and cost effective method for nanobiocomposites formation. Enhancement in the solubility might be because of generation of drug dispersion at micro and nanoscale level. So the development of BNCs is a promising approach to increase solubility and dissolution of poorly water soluble drug..**

Keyword: **Bionanocomposites, Fenofibrate, Microwave induced diffusion Technique, Natural carriers and Solubility enhancement.**

I. INTRODUCTION

SOLUBILITY of drug is most difficult aspects in the formulation and development [1]. Drug effectiveness can be severely limited by poor aqueous solubility and most of the drug also show side effect due to their poor solubility. Increasing drug solubility increases efficiency and minimizes side effects of certain drugs [2-7].Drugs having poor water solubility are associated with the slow drug absorption and finally inadequate or diverse bioavailability. Today near about 40 % of newly synthesized drugs have problem of poorly water solubility [8].The poor aqueous solubility of drug in the gastrointestinal fluid often causes inadequate bioavailability. These drugs require high dose to achieve therapeutic plasma concentration. At the site of action, aqueous form preferred for oral administration [9]. The designed and developed Celecoxib with Acacia (1: 4) BNCs shown acceptable solubility i.e. 0.0113 mg/ml andits percentage of drug release was found to be 91.58%[10].

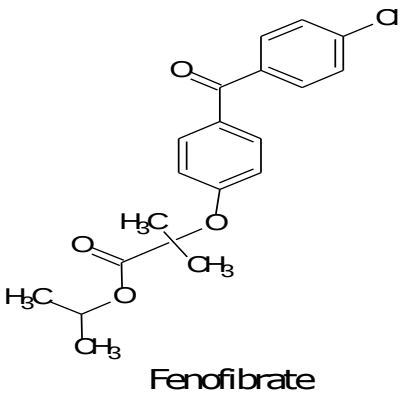

Figure 1

Fenofibrate is a drug of the fibrate class. It is mainly used to reduce cholesterol levels in patients at risk of cardiovascular disease. Like other fibrates, it reduces both, low-density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels, as well as increasing high-density lipoprotein (HDL) levels and reducing triglyceride levels and it is used alone or along with statins in the treatment of hypercholesterolemia and hypertriglyceridemia. Further, Fenofibrate has been used since 1975, is one of the most commonly prescribed fibrates, and has a well-known efficacy and tolerability profile [13]. Fenofibrate is mainly used for primary hypercholesterolemia or mixed dyslipidemia. Fenofibrate appears to decrease the risk of cardiovascular disease and possibly diabetic retinopathy in those with diabetes mellitus [14, 15] and firstly indicated for the reduction in the progression of diabetic retinopathy in patients with type 2 diabetes and existing diabetic retinopathy in Australia [16]. It also appears to be helpful in decreasing amputations of the lower

legs in this same group of people [17]. Fenofibrate also has an off-label use as an added therapy of high blood uric acid levels in people who have gout [18]. They are highly permeable through biological membrane but have limitation of poor aqueous solubility. Drug absorption rate and bioavailability of such poorly water soluble drugs are controlled by rate of dissolution in gastrointestinal fluids. This problem has been tried to solve by many researchers by various methods in the past to enhance solubility and dissolution ultimately bioavailability [19]. As Fenofibrate is poorly aqueous soluble results in poor dissolution rate and decrease in its gastrointestinal absorption.

Oral route is the most common way of drug delivery system for drug administration. The majority of sold pharmaceutical products (drugs) are given orally [20].The increase in surface area by particle size reduction increases dissolution property. Nanosize means the particle size between 100 nm to 1000 nm [19].BNCs produce increased saturation solubility and therefore, shows increased dissolution velocity [21].Continuous advancement in the other drug delivery system leads to pay attention towards oral drug delivery system to increase clinical efficiency and patient compliance. From pharmaceutical point of view a numerous type of polymer are used to control drug release from dosage form. The use of natural polymer rather than synthetic polymer is more preferred. Natural polymers are mainly used because they are readily available, inexpensive, nonreactive, capable of chemical modification and potentially compatible and degradable [22].Due to the development of polymer based BNCs; these are extensively used in the pharmaceutical industry. Polymer BNCs are the polymer that has been reinforced with small quantities of nanosize particles having high aspect ratio [23].

In this study, we have used novel technique called microwave induced diffusion (MIND) which is green and cost effective for the production of BNCs. Microwave heating starts from the direct interaction of electromagnetic energy with the material. The extent to which the material is heated by microwave energy is reliant on the range of parameters, but particularly dielectric properties are more important [24]. Polar liquids like water are very readily heated. Microwave heating can confer several benefits over conventional heating which includes rapid heating and cooling, reduced temperature gradients across the sample, lower energy usage and enhanced reaction rates [25]. BNC is the process of complex formation between drug and natural polymers [(MoringaOleifera Gum and AegleMarmelos (L)] where microwave energy plays significant role in reducing particle size of materials. It breaks intermolecular bonding and reduces the particle size. Now a day's microwave also applied for reducing particle size of drug material up to nanometer (nm). Reduction in particle size increases effective surface area of the drug and thereby enhances solubility and dissolution rate. In present study, fenofibrate BNCs formation enhance solubility ultimately leads to increase in bioavailability of the drug. Microwave heating is a well-established method for processing and drying [26-27].

The natural polymer MoringaOleifera Gum and AegleMarmelos(L) is used for the formation of different BNCs.MoringaOleifera Gum is naturally occurring, water soluble, complex polysaccharides obtained from the incision area on bark tree of MoringaOleifera and AegleMarmelos gum was found in Beal fruit i.e. AegleMarmelos(L). These are selected on the basis of their good surfactant and wetting property which are associated with increase in the solubility and dissolution [25].Fenofibratehave high permeability through biological membrane but shows low aqueous solubility.Fenofibrate has low bioavailability and fast elimination time which is about 1.5 to 2 hours. Thus, it is needed to enhance the solubility and dissolution ultimately bioavailability of Fenofibrate..

II. Material and Experimental Method

Materials

Fenofibrate drug was obtained as gift sample from Taj Pharmaceuticals Ltd., (Valsad, Gujarat, India) and isolation and collection of *Moringa Oleifera* gum was done by making an incisionat different places on stem parts of tress of *Moringa Oleifera* and gumwas collected in suitable air tight container after air drying. Further, isolation and collection of *Aegle Marmelos* (L.) *corr*. i.e. (Beal fruit) gum**:** Fruit contain large amount of gum, and after breaking Beal fruit gum was air dried and neatly collected in suitable air tight container.

2.1 Extraction and Purification of Natural Gums:

Collected both the gum viz. *Moringa Oleifera* and *Aegle Marmelos* gum respectively were dried on ground under sunlight. Dried gum was passed through Sieve No. 80. Dried gum (10gm) was stirred in distilled water (250ml) for 6-8 hours at room temperature. By centrifugation method supernatant was obtained and residue was washed with water and the washing was added to supernatant. The procedure was repeated four times.

Finally, the supernatant was made up to 500ml and treated with twice the volume of acetone by continuous stirring. The precipitated material then washed with distilled water and same was dried at 50˚C-60˚ C under vacuum.

2.2 Characterization of pure fenofibrate

2.2.1Solubility determination

The solubility of fenofibrate drug was determined by taking excess amount of drug into 150 ml of distilled water and kept for 24 h on orbital shaker incubator at room temperature 25 ^{0}C [21].The obtained solution was filtered through Whatmann filter paper no. 1 and the drug concentrations were determined by taking ultraviolet absorbance using UV-Visible Spectrophotometer (UV-Carry 60, Agilent) at 287 nm wavelength.

2.2.2 Fourier transform infrared spectrophotometric studies (FT-IR)

The identification of Fenofibrate was done by FT-IR Spectroscopy. The FT-IR spectrum was obtained by using FTIR spectrophotometer(Agilent Corp., Germany). The wavelength of rang from 400 to 4000 cm^{-1} with a resolution

of 4 cm^{-1} was used. Characteristic peaks of the drug, *Moring Oliefera* and *Aegle Marmelos*gum were compared with the formulated BNCs to check the compatibility of drug-polymer.

2.3 Characterization of polymers

2.3.1 Swelling index (SI)

SI of gums was calculated to check the swelling power. Accurately weighed 10 g of *MoringaOleifera* and A*egleMarmelos* gum were transferred into 100 ml measuring cylinder. The initial volume occupied by gum was noted. Distilled water was added in the cylinder up to 100 ml and the open end of cylinder was sealed with an aluminum foil. Measuring cylinder was kept aside for 24 h and volume of swelled gum was noted. The swelling index of gum was calculated by the following formula;

$$\%Swelling = \frac{Xt - X0}{X0} X\ 100$$

Where, *X*0 is the initial height of the powder in the graduated cylinder and *Xt*denotes the height occupied by swollen gum after 24 h.

2.3.2 Viscosity determination

Viscosity of gum was determined by taking 1 g of each of *MoringaOleifera* and *Aegle Marmelos* gum respectively and dispersed in 100 ml distilled water (1% w/v). The viscosity of resultant dispersion was measured by viscometer (Brookfield DV-E, Brookfield Engineering Laboratories, Inc., Middleboro, MA, USA) using spindle 3 at 100 rpm[31].

2.3.3 Foaming index

The foaming index was calculated to check the surfactant property of *Moringa Oleifera* and *Aegle Marmelos* gum. Accurately weighed 1 g of gum was transferred in 250 ml measuring cylinder containing 100 ml distilled water to make dispersion. Resultant dispersion was vigorously shaken for 2 minutes. The foaming index of gum was calculated by the following equation,

$$Foaming\ index = Vf - Vi$$

Where, Vf is the volume of 1% w/v solution of carrier after shaking and Vi is the volume of 1% w/v solution of gum carrier before shaking[31].

2.4 Preparation of bionanocomposites

The BNCs were prepared by adding accurately weighed drug Fenofibrate and carrier of *Moringa Oleifera* and *Aegle Marmelos* gum in 1:1 to 1:9 w/w proportions as shown in Table no. 1. Homogeneous physical mixture of drug and carrier was prepared using mortar and pestle. Slurry was prepared by adding 5 ml of distilled 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 700 W (IFB Microwave Oven, Model 17PM-MEC1, Kolkata, India) with continuous stirring [20].

Table No.1: Formulation design for Bionanocomposites batches

Drug :Gum	Drug + Carrier (w/w)	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
DG1	FF-Moringa Oleifera Gum	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9
DG2	FF-Aegle Marmelos Gum	1:1	1:2	1:3	1:4	1:5	1:6	1:7	1:8	1:9

*****D-FE-Drug Fenofibrate, G1-Moringa Oleifera Gum, & G2-Aegle Marmelos Gum**.**

The temperature was noted using inbuilt temperature measurement probe at the end of the treatment. BNCs were grounded using mortar and pestle to obtain required size of 80-250 µm [19]. The formulated BNCs of fenofibrate drug with natural carrier (Moringa Oleifera and Aegle Marmelos gum) were denoted by and respective process variables for preparation of FEMONC and FEAMNC are given in Table No. 2.

Table No. 2: Process variables for preparation of FEMONC and FNAMNC

Drug: Gum	Sample	Ratio(w/w)	Time(min)
DG1 BNC	FEMONC	1:1 to 1:9	7
DG2 BNC	FNAMNC	1:1 to 1:9	7

*****BNC- Bionanocomposite, FEMONC=Fenofibrate+Moringa Oleifera Gum and FNAMNC = fenofibrate+Aegle Marmelos

2.4.1 Drug content analysis of BNCs

The fenofibrate drug incorporated into the BNCs (FEMO (Fenofibrate Moringa Oleifera gum) and FEAM (Fenofibrate Aegle Marmelos gum) was calculated by dissolving bionanocompositesmixture in the 25 ml methanol. The resulting solution was filtered by 0.2 µ membrane filter and analyzed by UV-Visible spectrophotometer (UV- Carry 60, Agilent) at the wave length of 287 nm against the methanol as a blank.

2.4.2 Solubility study

The solubility study of BNCs (FEMONC and FEAMNC) was carried out by adding excess amount of pure fenofibrate drug (equivalent to 30 mg) and BNCs to 150 ml distilled water in a separate flask. The resultant mixture was stirred for 24 h at 25°C temperature by using orbital shaker incubator. The supernatant liquid was collected and filtered through 0.2 µ membrane filter and analyzed by UV-Visible spectrophotometer at 287 nm wavelength. The solubility of pure fenofibrate drug was observed to be 0.11 mg/ml. The

drug: carrier ratio was optimized from the result of solubility study [28].

2.5 Characterization of bionanocomposites

Characterizations of BNCs were carried out by FTIR, DSC, XRD, SEM and TEM to ensure the compatibility of drug and polymer.

2.5.1 Fourier-transform infrared spectroscopy (FT-IR)

FT-IR spectra of pure drug (fenofibrate), pure polymers (Moringa Oleifera and Aegle Marmelos gum) and BNCs of drug with individual polymers (Moringa Oleifera and Aegle Marmelos gum) was carried out to check compatibility of drug with polymer. BNCs of drug with each polymer ($FEMO_M$ and $FEAM_M$ were mixed with potassium bromide (KBr) of IR grade in the ratio of 1:100. The pellets were scanned using FT-IR Spectrophotometer (Agilent Corp., Germany). Infra-red spectrum of material gives the information regarding drug-polymer interactions. The materials were scanned through a range from 400 to 4000 cm^{-1} with a resolution of 4 cm^{-1}. Characteristic peaks of the drug, Moringa Oleifera and Aegle Marmelos gum were compared with the formulated BNCs to check the compatibility of drug-polymer.

2.5.2 Differential scanning calorimetry (DSC)

DSC studies of pure drug (fenofibrate), pure polymer (Moringa Oleifera and Aegle Marmelos gum) and BNCs of drug with individual polymer (Moringa Oleifera and Aegle Marmelos gum) were performed to access the enhanced solubility of drugs. DSC thermos-gram was obtained usingdifferential scanning calorimeter (DSC 60; Shimadzu) at heating rate of 11°C/min from temperature 0°C to 250°C. The DSC gives the information related to melting point, type of heating reaction (either endothermic or exothermic) and physical, chemical interaction between drug and polymer.

2.5.3 X-ray diffraction studies (XRD)

XRD study of drug (fenofibrate), pure polymers (Moringa Oleifera and Aegle Marmelos gum), and BNCs of drug (fenofibrate) with individual polymers (Moringa Oleifera and Aegle Marmelos gum) were determined to evaluate the changes in the crystallinity made when drug was mixed with gums. The crystallinity property is associated with physicochemical properties of material. The XRD patterns of the drug, polymers and BNCs were recorded using (Bruker, D8) and Cu-kα radiation. The scanning angle ranged from 1° to 42° of 3θ.

2.5.4 Scanning electron microscopy (SEM)

The surface morphology of fenofibrate BNCs 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 15 kV and working distance of 8 mm on XL30-SFEG Philips (Labexchange, Burladingen, Germany). The mean particle size, standard deviation and 95% confidence interval were calculated by a written program which randomly selects 100 particles of the SEM images.

2.5.5Transmission electron microscopy (TEM)

TEM study was performed to confirm size and shape of drug crystals dispersed in the polymer. The sample for TEM (Hitachi Model H600-3, Tokyo, Japan) was mounted on a carbon-coated copper grid made up of disc type with thinned central area of size 3 mm.

III. RESULTS AND DISCUSSION

3.1 Physical characterization of carriers

The % swelling, viscosity and foaming index were represented in Table No. 3. The swelling property and viscosity of Moringa Oleifera and Aegle Marmelos gum was low. Due to the less viscosity of Moringa Oleifera and Aegle Marmelos gum, they were considered for solubility and dissolution enhancement of drug [20]. Moringa Oleifera and Aegle Marmelos both showed low viscosity and high foaming index. Hence both the gums were more suitable for increasing solubility and dissolution rate of drug.

Table No. 3: Physical characterization of Moringa Oleifera and Aegle Marmelos gum.

Material	Swelling Index	Viscosity(cps)	Foaming index
Moringa Oleifera	19.7 ± 2.21	4.16 ± 0.25	17 ± 0.92
Aegle Marmelos	20.3 ± 1.01	4.67 ± 0.11	16 ± 0.65

All values are represented as means ± SD, n = 3.

3.2. Solubility studies

The solubility study showed that Moringa Oleifera and Aegle Marmelos gum enhances solubility. Solubility studies of physical mixtures and BNCs clearly indicated that as the ratio of drug to polymer increases solubility also increases. No significant increase in solubility was showed after 1:3 and 1:4 ratio of drug to polymer (FEMONC &FEAMNC) the optimized ratio was found 1:3 and 1:4. This optimized ratio was then confirmed with powder dissolution and found to be increase in solubility [20, 28]. Enhancement of solubility found for FEMONC and FEAMNC this may be due to more foaming index of Moringa Oleifera than Aegle Marmelos

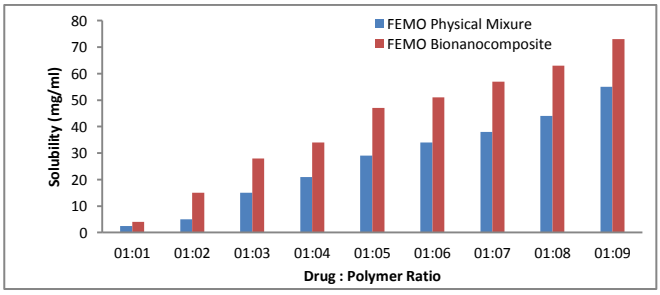

Figure No. 1:Solubility comparisons between FEMOMC physical mixture and FEAMNC bionanocomposites

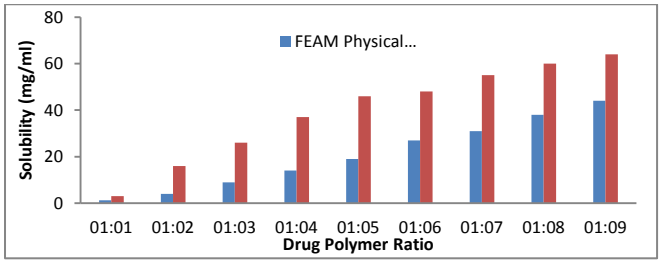

Figure No. 2: Solubility comparisons between FEMO physical mixture and FEAM bionanocomposites. FE-Fenofibrate, MO-Moringa Oleifera, AM-Aegle Marmelos gum. Data are mean +/- SD, *n* = 3, Values are expressed as % of solubility of pure fenofibrate.

3.3 Powder dissolution test

The powder dissolution test was carried out to check solubility enhancing properties of the materials. The dissolution profile of BNCs showed remarkable improvement in the dissolution rate in fenofibrate BNCs when compared with the pure fenofibrate. BNCs of fenofibrate with Moringa Oleifera gum demonstrated good result. It released 81% in comparison to pure fenofibrate which released 61% after 60 min. The dissolution profile of fenofibrate and fenofibrate BNCs were shown in figure no.3. FEMONC powder released 84 % of drug in a solution compared to pure drug which was released only 64%. Therefore, it can be concluded that dissolution rate of fenofibrate drug has been enhanced with BNCs.

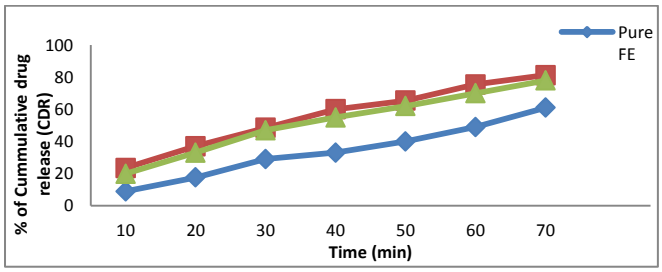

Figure No. 3: Powder dissolution studies of pure fenofibrate, FEMONC and FEAMNC powder.

3.4 Drug content analysis of bionanocomposites

Uniform dispersion of drug in the BNCs was determined by drug content analysis. It was found that 95-98% drug was incorporated in the BNCs showing uniform dispersion of drug.

3.5 FT-IR studies

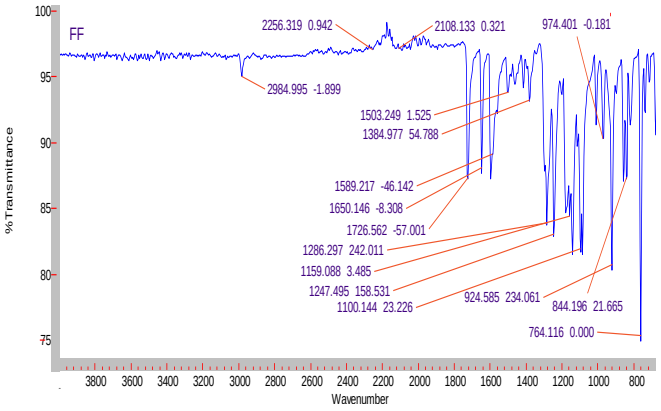

Figure No. 4: FTIR of Pure drug Fenofibrate

The FTIR spectrum of pure fenofibrate as in Figure No. 4 shows two absorption peaks at 1726 and 1650 cm^{-1} i.e. C=O Stretching which indicates the presence of two carbonyl frequencies of ester and ketone, respectively. The ester peak is confirmed by its characteristic absorption at 1159 and 1247 cm^{-1}. The appearance of the absorption peaks at 2800 - 3400 cm^{-1} (particularly at 2985 cm^{-1}) are associated with carbon-hydrogen (C–H) stretching vibrations. Further, study after the BNCs formulation by FTIR spectrum all the peaks showed in the pure drug was unchanged in the FT-IR spectra of FEMONC and FEAMNC as shown Figure no. 5. It indicates that there is no chemical reaction between drug and polymer after microwave irradiation of fenofibrate.

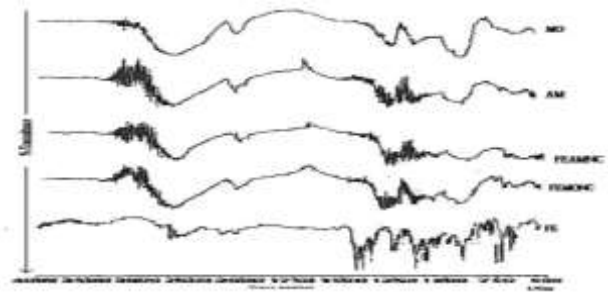

Figure No 5:FT-IR studies of pure Moringa Oleifera (MO) Aegle Marmelos(AM), pure fenofibrate (FE), bionanocomposites of fenofibrate with Moringa Oleifera Gum (FEMONC) and bionanocomposites of fenofibrate with Aegle Marmelos Gum (FEAMNC).

3.6 DSC studies

DSC thermos-grams of pure drugs (FE), polymers (MO and AM) and BNCs of individual drug with individual polymer were shown in the figure 6. DSC of pure fenofibrate exhibited sharp endothermic peak at 94^{o}C indicating melting of fenofibrate. DSC of FEMONC and FEAMNC shown same endothermic peak as that of pure drug but with reduced intensity which might be due to decrease in the crystalline nature of drug. Slight shift in the melting point indicated reduction of drug to nanocrystalline form. Broadening of peak indicated that most of the drug converted into nanocrystalline form. No chemical interaction between drug and polymer was observed. Physical interaction was the mechanism by which drug bound to the polymer. These studies confirmed that as the crystal size of crystalline

nanoparticle reduces; its melting point also reduces minutely.

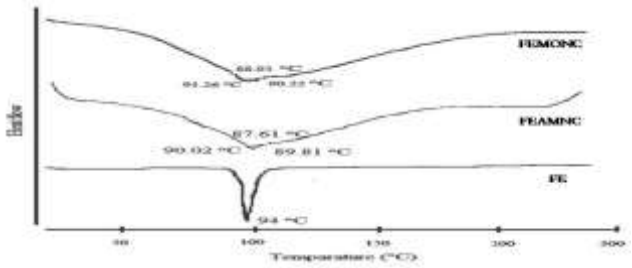

Figure No. 6:DSC studies of fenofibrate and Moringa Oleifera bionanocomposites (FEMONC), fenofibrate and Aegle Marmelos bionanocomposites (FEAMNC) and pure fenofibrate (FE)

3.7 X-ray Diffraction Studies (XRD)

XRD was performed to check the physical state of drug and its BNCs. XRD pattern of pure drug (FE), pure polymer (MO and AM) and its bionanocomposites were shown in the following figure no.7. The XRD pattern of pure fenofibrate showed crystalline peak between 100 and 600. It demonstrated characteristic diffraction peaks at 5, 13, 14.50, 17.50, 19, 21, 24, 25.50, 28, 30, 32 and 35 with intense peak at 24 indicating crystalline nature of fenofibrate. XRD pattern of FEMONC and FEAMNC showed reduced peak intensity due to decreased crystallinity. Reduced peak intensity of bionanocomposites might be due to reduction in the drug size to the nano level.

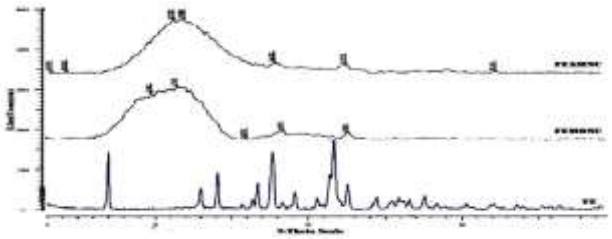

Figure No. 7:XRD studies of bionanocomposites of fenofibrate with Aegle Marmelos (FEAMNC), bionanocomposites of fenofibrate with Moringa Oleifera (FEMONC) and pure fenofibrate (FE).

3.8 Scanning Electron Microscopy (SEM)

The SEM study was done to check surface morphology of the drug particles. The SEM of polymer (MO) and its BNCs are shown in the following Figure no.8. Fenofibrate particles were plate shaped with a smooth surface, while FEMO particles were of irregular shape and size. Figure no. 8, clearly demonstrates crystal shape of fenofibrate was completely changed in FEMONC showing embedded fenofibrate crystals in the matrix.

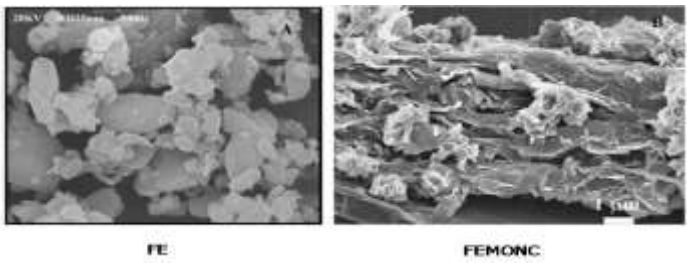

Figure No.8:SEM images of fenofibrate (FE) and bionanocomposites of fenofibrate with Moringa Oleifera gum (FEMONC).

3.9 Transmission Electron Microscopy (TEM)

TEM were carried out to confirm particle size of embedded fenofibrate drug particles. The TEM images of pure drug (FE) and bionanocomposites fenofibrate with Moringa Oleifera (FEMONC)were showed in the Figure no. 9. The TEM results demonstrated that rapid release of fenofibrate drug from the bionanocomposites due to lose network structure which enhances solubility and dissolution characteristics of fenofibrate drug. It was clear that the FE nanoparticles were rod shaped morphology having 1µm (1000nm) diameter. TEM of FEMONC showed surface dark spots of acacia polymer in which the drug has been dispersed. The structure of FE BNCs was looser, smaller size with average diameter of 110nm. This revealed that MIND process was responsible for agglomeration and change in size of the particles which might be due to cross linking among the different nanoparticles with polymers.

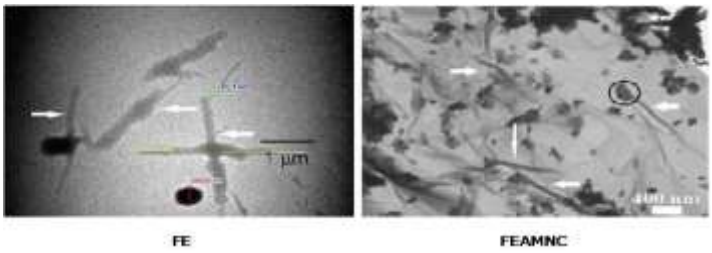

Figure No. 9:TEM images of Pure Fenofibrate (FE) and Bionanocomposites Fenofibrate with Aegle Marmelos gum (FEAMNC)

IV. CONCLUSION

Present study revealed use of natural carriers such as Moringa Oleifera and Aegle Marmelosgum in the microwave generated BNCs for the enhancement of solubility, dissolution. Result of FT-IR, XRD, DSC, SEM and TEM shows that Fenofibrate converted into the BNCs is responsible for enhancement of solubility and dissolution. It also shows that, there is no significant interaction between drug and polymer. *In vitro* evaluation of optimized formulation confirms the use of BNCs for increasing solubility and dissolution of drug. On the basis of present research study it can be concluded that microwave generated BNCs is one of the potential approach to enhance solubility, dissolution and ultimately bioavailability of drug.

Conflict of interest:

The Authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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