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Preparation And Evaluation Of Microwave Generated Nanobiocomposite For Solubility Enhancement Of Naproxen And Its Prepared Gel For Anti-Inflammatory Activity

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Abstract

Naproxen is an NSAID, or non-steroidal anti-inflammatory medicine. The creation of an oral dosage form for naproxen, which is a member of BCS class II and has a low solubility, has proven difficult. A cutting-edge method for improving solubility is nanocomposite creation. For the creation of nanocomposites, microwaves were used. Nanocomposites were created using polymers such as HPMC, tragacanth, acacia, and avicel as carriers. HPMC and tragacanth were employed for additional research after the physical characterization of polymers, such as their foaming index, viscosity, and swelling index. Eight distinct formulations were made using varied dosages of medication and carrier, and equivalent physical combinations were also made. From many nanocomposites' formulations, NTHN (1:4) and NTTN (1:4) demonstrated good solubility and were the best ratios. Compared to pure naproxen, which demonstrated a dissolution of 49.32 % in an in-vitro drug release study, the medication disintegrated 86.73%. Numerous characteristics, including FTIR, DSC, and SEM, were examined for the prepared nanocomposites. In-vitro drug release, appearance, or drug content of the nanocomposites did not alter significantly over the course of a three-month stability trial. According to the overall findings, Naproxen's solubility can be increased by using microwave aided nanocomposites formulation.

Keywords: Naproxen, Nanocomposites, Solubility enhancement, BCS, Microwave, etc.

Introduction

Given its many benefits, including ease of manufacture, simplicity in administration, and accuracy in dosing, the oral route is the most promising method of drug delivery [1]. When a medicine is taken orally, the cellular membrane of the gastrointestinal system either passively absorbs it or actively absorbs it. Drug bioavailability is determined by two critical parameters: solubility and permeability. A problem for the creation of oral dosage forms is that, according to the US Pharmacopoeia, close to 40 % of medications are either insoluble or poorly soluble in aqueous media [2]. According to the solubility and permeability of a

medicine, a biological classification system divides it into four different types. High permeability and solubility medications are classified as Class I medicines. Drugs in class II have high permeability but low solubility. Drugs with high solubility and low permeability fall under Class III. poor solubility and poor permeability medications are classified as class IV [3]. Class I medications do not present many challenges to produce oral dosage forms, but BCS class II medications with limited solubility could present challenges. Increased solubility of such medications is therefore a significant challenge. To increase solubility, a variety of strategies are employed, including slat formation, solid dispersion, cocrystals, complexation, use of prodrugs, use of surfactants, and many more [4].

One of the cutting-edge methods for increasing solubility is the creation of nanocomposites. Nanocomposites are materials that contain one of their phases at the nanoscale. Nanocomposites are made up of two or more different physical components that are physically distinct from one another and have various physicochemical properties. The matrix of a nanocomposite is the substance in which another material is incorporated, and the nanomaterial, which is the filler material incorporated, is the embedded nanoscale material [5]. The production of nanocomposite enhances the characteristics of both components [6].

The internal structure of drug particles is broken by microwave radiation in microwave ovens, increasing solubility. The primary mechanism for microwave oven heating is the interaction of reaction material charged particles with electromagnetic wavelengths of frequency. By collision, conduction, or occasionally both, electromagnetic radiation can cause heat to be produced. With each wave cycle, all wave energy shifts its polarity from positive to negative. This causes molecules to rapidly reorient and orient, which causes heating from collisions [7,8]. aproxen (NPX) is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of moderate to severe pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, injury (like fractures), tendinitis and bursitis These days Statistical models are extensively used by scientist of formulation and development to strengthen the art of drug formulations. A 3.

Naproxen's usefulness is limited by a short duration of action (8 h) when administrated orally. Repeated administrations are required for maintenance of the pharmacological action. Patients with chronic inflammatory diseases require long term therapy with such NSAIDs. But chronic usage of NASIDS may lead to gastrointestinal disorder, gastritis, ulcer and bleeding. A sustained release Nanoparticles formulation based on Eudragit RS 100 could retard the release of drug extending the pharmacological action of the NPX and reducing the frequency of administration which in turn reduces the drug related adverse effects. [6, 7]

The non-steroidal anti-inflammatory medicine naproxen (6-methyl-2-naphthyl acetic acid), which is classified as a BCS class II drug and has a low water solubility (pka = 4.15), appears to be a weak acid [9]. The extremely poor solubility of naproxen results in patient pain and changes in plasma drug concentration that may have negative effects. When taken in normal or low doses, naproxen might cause liver damage, hepatotoxicity, and hepatic responses [10]. Serious gastrointestinal side effects, such as upper GI tract haemorrhage, can result from naproxen's poor solubility and dissolution [11]. Through the creation of bio-nanocomposite employing the biodegradable natural polymer, namely acacia and tragacanth, by microwave diffusion method, we are improving the solubility and dissolution of BCS class II medication Naproxen in this work.

Material and Method

Material

Naproxen (NAP) was purchased from Joshi Agrochem Pharma Pvt Ltd, in Mumbai, India. Avicel, Tragacanth, Acacia, and Hydroxy Propyl Methyl Cellulose (HPMC) were acquired from Modern Science in Nashik. Each piece of the material was of analytical quality and was used without further purification.

Drug and Excipient Compatibility Study

Fourier Transform Infrared Spectroscopy (FTIR) [15]

For the compatibility research, a physical combination of the medication and excipients was used. FTIR spectroscopy was used to conduct a compatibility evaluation. Solid state KBr dispersion media was used to scan samples of pure drugs and excipients as well as physical mixtures of drugs and excipients. The scanning range was maintained between 4000 and 400 cm-1.

Differential Scanning Calorimetry (DSC) [16]

A differential scanning calorimeter (Mettler Toledo) was used to measure the thermal behaviour of a pure drug, optimised bio nanocomposite batch at a heating rate of 10°C/min. The measurements were carried out in nitrogen atmospheres with a heating range of 30-400 °C.

Preparation of Nanobiocomposite (NBC)

By thoroughly combining an exact weighted amount of each medication and each polymer, the nanobiocomposite was created. In this instance, a weight-to-weight (w/w) ratio of 1:1 to 1:4 was used while maintaining a consistent mixed volume. We measured the amounts of pure medicine and polymer for various ratios. 4 ml of water were added to this mixture (drug and polymer) for every gramme of polymer to create a homogeneous slurry. In a glass round-bottom flask, the predetermined volume of slurry was placed, and for 5 minutes, it was continuously stirred while being exposed to microwave radiation at a strength of 556 W (CATA-2R, Catalyst System). To reach particle sizes of 80 to 250 nm, nanobiocomposite were mashed in a mortar and sieved. A drug-polymer HPMC and Tragacanth nanobiocomposite was created [17].

Table 1: Ratio of Naproxen and Tragacanth For Preparation of Physical Mixture and Nanocomposites

Ratios (for physical mixture)	Quantity (mg)			Ratio (for nanocomposite)	Quantity (mg)		
	NAP	TRG	HPMC		NAP	TRG	HPMC
$NAPT_P$ 1:1	500	500	-	$NAPT_N$ 1:1	500	500	-
$NAPT_P$ 1:2	500	1000	-	$NAPT_N$ 1:2	500	1000	-
$NAPT_P$ 1:3	500	1500	-	$NAPT_N$ 1:3	500	1500	-
$NAPT_P$ 1:4	500	2000	-	$NAPT_N$ 1:4	500	2000	-
$NAPH_P$ 1:1	500	-	500	$NAPH_N$ 1:1	500	-	500
$NAPH_P$ 1:2	500	-	1000	$NAPH_N$ 1:2	500	-	1000
$NAPH_P$ 1:3	500	-	1500	$NAPH_N$ 1:3	500	-	1500
$NAPH_P$ 1:4	500	-	2000	$NAPH_N$ 1:4	500	-	2000

NAP: Naproxen, **TRG**: Tragacanth, **HPMC:** Hydroxy Propyl Methyl Cellulose

Determination of Solubility

In distilled water with phosphate buffer pH 6.8, the solubility of an anti-inflammatory medication was assessed. To 10 ml of the appropriate solvent, further medication was added. The mixture was left to equilibrate after 24 hours of continuous stirring at 37 °C. The samples were taken out after 24 hours, put through a membrane filter, and then put through a UV-visible spectrophotometer for analysis [17].

Fourier transforms infrared spectroscopic (FTIR) studies of pure drug

In a ratio of 1:99, the dry drug sample was combined with KBr. The sample was triturated, put in a sample holder, and then compressed using a motorised pellet press at a 15-ton pressure. Then, using a Shimadzu FTIR spectrophotometer (IR Affinity-1S), the pellets were scanned across a frequency range of 4000-400 cm-1. The spectrum was analysed using the functional group's standard absorbance range [17].

Physical characterization of polymer Swelling Index (SI)

A modified method for calculating the polymer's swelling index was disclosed. Accurately weighing 1gm of tragacanth and acacia, 100 ml of the mixture were then transferred. The original volume that the powder occupied was noted. Using distilled water, the volume was increased to 100 ml. Aluminium foil was used to close the cylinder's open end, which was then left unattended for 24 hours. After 24 hours, the polymer had grown in bulk. The formula below was used to compute the polymer's swelling index [18].

$$SI = \frac{Hf - Hi}{Hi} \times 100$$

Where,
SI- Swelling index of polymer, Hi - Initial height of powder,
Hf - Final height of powder after 24 hr.

Foaming index

The foaming index can be used to determine a polymer's surfactant property. 1 g of powder was precisely weighed and then put into a 250 ml measuring cylinder. To make the dispersion, 100 ml of distilled water were added to the measuring cylinder. The resulting dispersion was shaken ferociously for two minutes. The

polymer's foaming index, determined using the formula below [18],

Foaming index = Hf – H*i*
Where,
Hf = Height of solution of polymer after shaking H*i* = Height of solution of polymer before shaking.

Viscosity
Acacia and Tragacanth were dissolved in one gramme each in 100 ml of water (1% w/v solution) to determine the polymer's viscosity. Using spindle VI at 200 rpm on a Brookfield viscometer, the viscosity of the carrier dispersions of Tragacanth and Acacia was measured [18].

Drug- Excipient compatibility Studies
It was determined through a compatibility analysis that there was no interaction between the medicine and the excipients utilised in the formulation. The vial was filled with the medicine and a physical mixture of the drug and polymer (1:1). During one month, the desiccator kept the sealed vials at a particular temperature. After a month, the mixture was analysed by IR (Shimadzu: IR Affinity-1S) [19].

Fourier –Transform Infrared Spectroscopy Study
Anti-inflammatory medications FTIR spectrum was measured at 4500 cm-1. The traditional KBr plate approach was used to obtain the infrared spectra of both the pure drug and the physical mixing of the drug with polymers [19].

Preparation of physical mixture
Drug and polymer were simply mixed in a 1:1 to 1:4 ratio to create a physical combination for the medication Tragacanth. The physical mixture created to evaluate how well nanocomposites increase solubility when compared to physical mixture [19].

Solubility of formed bio nanocomposites
In a phosphate buffer with a pH of 6.8, the solubility of the produced formulation was assessed. An excess amount of the drug (10 mg) and the NBCs (10 mg of drug equivalent) were added to 10 ml of the solvent (pH 6.8 buffer), in Teflon-facing screw-capped vials, to assess the solubility of the drug, physical mixes, and NBCs. The samples were maintained in equilibrium for 24 hours in a Remi Instruments orbital shaker at 37°C at 50 rpm. Shimadzu's UV-visible spectrophotometer was used to measure the supernatant fraction after it had been removed from the vials and filtered through a 0.45-micron membrane filter. The best solubility data were used as the foundation for ratio optimization (drug: carrier) [19].

Dissolution test
A USP apparatus II (Paddle) method was used to conduct an in-vitro powder dissolution test on an anti-inflammatory medication and a nanobiocomposite, utilising 900 ml of pH 6.8 phosphate buffers as the dissolution medium. While keeping the temperature at 37 0.5°C and the paddle's rotation speed at 75 rpm, powder containing an exact dose of the medicine was introduced to the dissolving media. By substituting 5 ml of pH 6.8 phosphate buffer solution in the dissolution media, 5 ml of sample were removed at intervals of 0, 5, 10, 15, 20, 25, and 30 minutes. Samples were filtered using a 0.45 membrane filter before being spectrophotometrically evaluated [19].

Drug content analysis
By dissolving the nanocomposites mixture in 25 ml of methanol, a drug content analysis of the nanobiocomposite was carried out to determine the amount of drug integrated into it. The resultant solution was filtered through a 0.45-micron membrane filter before being tested for the presence of an anti-inflammatory medicine against methanol as a blank using a UV-visible spectrophotometer at a specified wavelength [19].

Characterization of optimized nanobiocomposite [20,21]
The NBCs that displayed better results were chosen for further characterisation from the findings of solubility and dissolution testing.

Fourier–Transform Infrared Spectroscopy (FTIR)
The optimised nanobiocomposite ratio underwent an FTIR analysis. In a ratio of 1:99, potassium bromide (KBr) of IR grade was combined with nanobiocomposite before being compressed using a pellet press operating at 15 tonnes of pressure. The next step involved scanning the pellets with an FTIR (Shimadzu; IR Affinity-1S). To determine if there had been any changes to the main peaks of the optimised nanobiocomposite FTIR spectra, they were compared to those of the pure medication.

Differential Scanning Calorimetry (DSC)
An optimised nanobiocomposite was subjected to a DSC investigation to determine what modifications had been made throughout the formulation process and how these improvements improved drug solubility. By using a differential scanning calorimeter and heating a sample from 50 to 200 °C at a rate of 10 °C/min in a nitrogen environment, the DSC curves were obtained.

Scanning Electron Microscopy (SEM)
The morphology of the exterior surface was investigated using scanning electron microscopy. SEM was used to examine the morphologies and fine-grained particle structural characterizations of the pure drug and nanobiocomposite. To corroborate the alterations produced during NBC formation, scanning electron microscopy (SEM) examinations were performed on NBCs that displayed the best results in the solubility and dissolution tests. The samples were made by gluing powder to a brass stub with graphite and then coating them in gold under vacuum before usage. Using a scanning electron microscope and an acceleration voltage of 10 KV, images were captured at the necessary magnification.

Formation of Carbopol 940 gel containing optimized naproxen-loaded nanobiocomposite
A gelling agent, Carbopol 940 (0.1%), was utilised. To create Ca-940 solutions, Ca-940 was continuously stirred at 800 rpm for 1 hour in distilled water using a homogenizer. The pH of the gel was kept between 6.2 and 6.8 by applying 0.05% triethanolamine. The main criteria used to choose the gelling agent were its ideal viscosity, distinct visual appeal, compatibility with polymers, and spreadability. The above-mentioned Ca-940 solutions were then thoroughly mixed with 50 mg of NAP-containing nanobiocomposite [22].

Table 2: Formulation of naproxen loaded optimized nanobiocomposite gel batches

Gel batches	Optimized naproxen loaded nanobiocomposite (mg)	Carbopol 940 (%)	Triethanolamine
NG1	10 mg	0.1 %	0.5 ml
NG2	20 mg	0.1 %	0.5 ml
NG3	30 mg	0.1 %	0.5 ml
NG4	40 mg	0.1 %	0.5 ml
NG5	50 mg	0.1 %	0.5 ml

Characterization of Naproxen-Loaded nanobiocomposite-Containing Ca-940 Gel
The above-formulated NAP-loaded nanobiocomposite-containing Ca-940 gel was subjected to evaluation for the following parameters:

Appearance, pH, Viscosity, and Spreadability
Visual inspection was used to examine the colour, clarity, homogeneity, and presence of lumps in all generated NAP nanobiocomposite-containing gel preparations [23]. To measuring the pH of the Ca-940 gel formulations, a digital pH metre was employed. Gels containing NAP nanobiocomposite were transferred to a graduated beaker and filled to a final capacity of 50 millilitres using distilled water. A digital pH metre was completely submerged into the gel system to measure the freshly made gel formulations until a stable reading was obtained. The average pH of each formulation was calculated and measured in triplicate [24,25]. Using a Brookfield RST Cone Plate Rheometer with spindle CP 62 at 4 rpm for 50 s, the viscosity of the NAP gel was determined at 25 °C [26].
Spreadability is one of the most important factors to consider when evaluating the optimal quality because the therapeutic effectiveness of the gel formulation depends on its spreading value. In order to assess the spreadability of the NAP-loaded gel, 0.5 g of the gel formulation was placed on a glass plate within a circle that was previously marked with a 1 cm diameter. 100 g of weight was placed on the upper glass plate and left there for five minutes. The spreadability of the gel formulations was assessed in triplicate by computing an increase in diameter [27].

Drug Content

A sample of gel containing NAP nanobiocomposite (100 mg) was dissolved in a total of 100 mL of ethanolic phosphate buffer (EPB). For 4 hours, a motorised shaker was employed to completely dissolve the medication in EPB. Following filtering, the sample's UV absorbance was measured at 262 nm with a phosphate buffer (pH 7.4) used as a blank [28].

Skin Irritation Studies for Naproxen-Loaded Gel

The Draize patch test was used to assess the risk for skin irritation in gels containing NAP nanobiocomposite. Each albino Wistar rat (200 g), regardless of gender, received food and water, and their own space in the animal house. Twenty rats (n = 2) were divided into two groups, group 1 receiving all NAP formulations containing nanobiocomposite gel and group 2 receiving pure NAP (control gel). The rats had a specific portion of their backs shaved 24 hours before the formulation administration. On the hairless skin of the rats, the needed quantity of gel (equivalent to 5 mg naproxen) was applied. The test site was left intact for 48 hours before the gel was removed; the ensuing skin reactions were then noticed after 48, 72, and 96 hours. Based on the severity of the erythema, a score from 0 to 4 was assigned [29].

Stability Studies

Gels containing NAP nanobiocomposite underwent stability investigations (accelerated stability studies) by being prepared under various stability settings. The nanobiocomposite compositions were separated into four batches and stored for three months at four different temperatures: room temperature (27 °C), 4 °C, 37 °C, and 45°C. The samples' absorbance was measured at 262 nm with a phosphate buffer (pH 7.4) at weekly intervals, and their physicochemical attributes were calculated [30].

***In Vivo* Anti-Inflammatory Studies in Rats Animals**

In the animal home, albino rats weighing 150 + 10 g were bred and fed a conventional lab food along with water. Rats were housed in polypropylene cages with a room temperature of 25 + 1 °C, a photoperiod of 12:12 h of light and dark, and a humidity level of 55–60%. The Pharmacy Animal Ethics Committee (08-2020/PAEC) gave its approval to the investigations involving animal testing.

Treatment Protocol

The following treatments were given to the animals: normal control, formalin, formalin + NAP NBC gel (15 mg/kg), and formalin + NAP control gel. The animals were divided into 4 groups of six each. On the first and third days of the experiment, intradermal formalin (0.1 mL of 2% v/v) was injected into each rat's right hind paw to cause inflammation. The paw volume was measured 1, 3, and 5 hours after treatment using a paw edoema metre. The formula below was used to determine the level of paw swelling and the pace at which edoema was inhibited.

Percentage inhibition = 1 − VT/VC × 100

where VT and VC stand for the treatment groups and control group's respective paw volumes. At the end of the seven days, the rats were decapitated and slaughtered. A histological analysis of the samples was then carried out.

Histopathology Analysis

The tissues from the right paw were taken out, fixed in 10% formalin, and paraffin embedded. Three-millimetre-thick tissue samples were chosen and put on the slides. Hematoxylin-stained tissues are used to look for histopathological alterations under a light microscope [31-33].

Statistical Analysis

The data were subjected to statistical analysis in order to assess the impact of independent variables on the response variables. To carry out statistical analysis, Design-Expert software (9.0.6.2) was used as the statistical tool. An ANOVA test was utilised to determine the importance of each independent variable. Significant data was defined as a value of "p" less than 0.05.

Result and Discussion

Fourier transform infrared spectroscopic studies (FTIR)

A sampler was used to collect the powdered mixture of naproxen and KBr, and an FTIR spectrophotometer was used to scan in the 4000-400 cm-1 wavelength range and record the spectrum. The FTIR spectrum of naproxen, as shown in fig., contains all the peaks corresponding to the functional groups found in naproxen's structure.

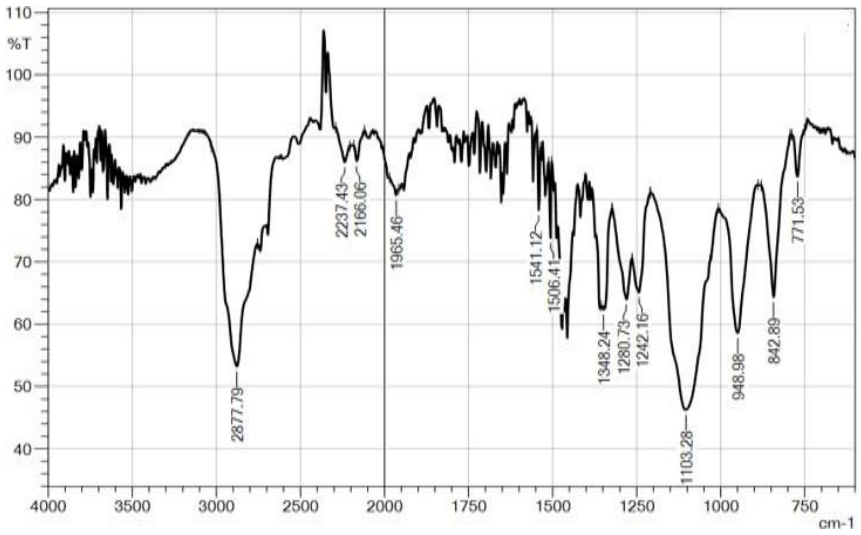

Fig.1 FTIR spectra of Naproxen

After interpretation of FT-IR Spectrum of drug, it was concluded that all the characteristic peaks corresponding to the functional group present in the molecular structure of naproxen were found within the reference range and confirming its identity.

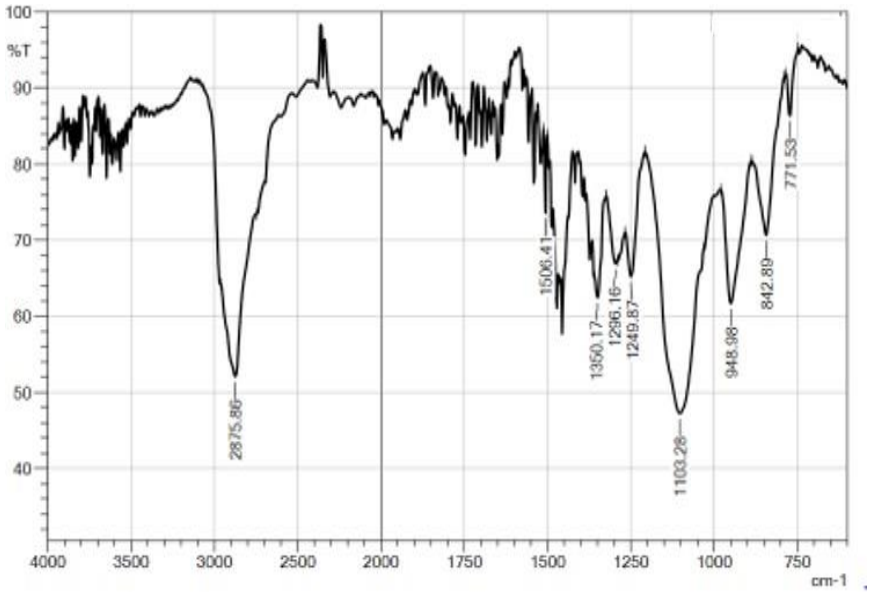

Fig.2 FTIR Spectra of HPMC

After interpretation of FT-IR Spectrum of polymer, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of HPMC were found within the reference range, confirming its identity.

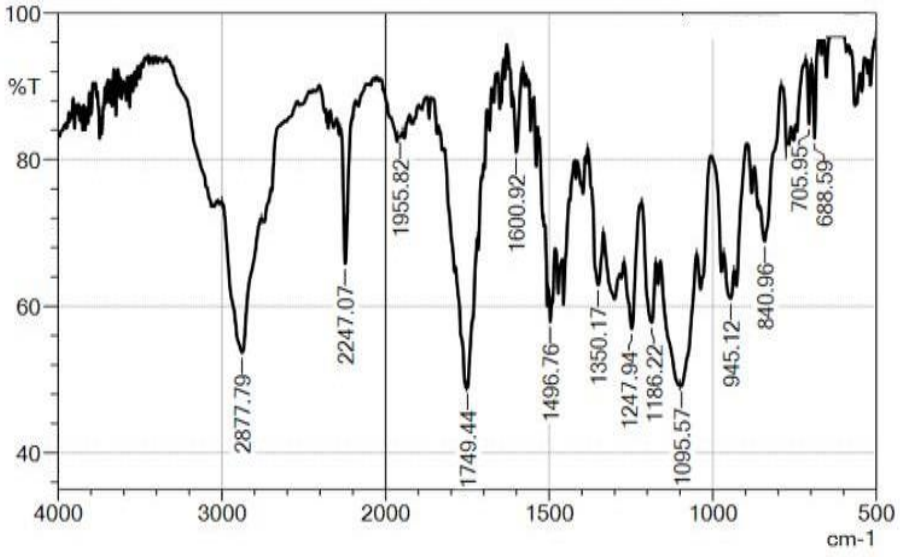

Fig.3 FTIR Spectra of Tragacanth

After interpretation of FT-IR Spectrum of polymer, it was concluded that all the characteristic peaks corresponding to the functional group present in molecular structure of Tragacanth were found within the reference range, confirming its identity.

Physical characterization of carriers

The table below displays the physical characterization's results. It is clear from the results that Acacia has extremely high viscosity and minimal swelling characteristics compared to Tragacanth. High viscosity and hardness may restrict their use as carriers for improving dissolution. They are more susceptible to dissolving enhancement due to minimal swelling and low solution viscosity. They are less likely to produce a dense matrix that will speed up the release of the nanocrystals from the nanocomposites. Tragacanth and HPMC were employed for the subsequent operations based on the physical characterisation of the polymer, such as swelling index, viscosity, and foaming index.

Table 3: Physical Characterization of Polymers

Polymer	% Swelling	Viscosity (cp)	Foaming Index
Tragacanth	62.90 ± 1.31	2.51 ± 0.12	7.10 ± 0.45
Acacia	67.88 ± 1.20	2.34 ± 0.15	8.30 ± 0.75
HPMC	61.40 ± 1.32	2.24 ± 0.12	7.75 ± 0.45
Avicel	64.68 ± 1.26	2.61 ± 0.15	8.50 ± 0.75

Solubility study of physical mixture

To determine how well nanocomposites enhance solubility, solubility studies were conducted. The best ratio was chosen based on solubility studies, which served as the foundation. To determining solubility, pure drug Naproxen, physical mixes of Naproxen with various carriers, as well as nanocomposites of Naproxen with various carriers, were all examined. The following Table displays the findings from experiments on how well physical mixtures and nanocomposites dissolve in water.

Table 4: Solubility of Physical Mixture of Naproxen And Polymer

Drug polymer Ratio	$NAPH_P$ (mg/ml)	$NAPH_N$ (mg/ml)	$NAPT_N$ (mg/ml)	$NAPT_P$ (mg/ml)
1:1	0.503 ± 0.02	1.066 ± 0.03	0.728 ± 0.04	0.342± 0.08
1:2	0.630 ± 0.07	1.399 ± 0.05	1.106 ± 0.09	0.521 ± 0.08
1:3	0.651 ± 0.08	1.568 ± 0.05	1.246 ± 0.13	0.618 ± 0.07
1:4	0.813 ± 0.05	1.633 ± 0.09	1.211 ± 0.03	0.700 ± 0.06

Abbreviations: $NAPH_P$ – Naproxen- HPMC physical mixture, NAPHN – Naproxen -HPMC nanobiocomposite, $NAPT_N$- Naproxen Tragacanth Nanobiocomposite, $NAPT_P$- Naproxen tragacanth physical mixture.

Physical combinations considerably increase the solubility of naproxen when compared to the pure medication, according to solubility tests. This might be because acacia and tragacanth have surfactant and wetting properties. The solubility results for nanocomposites show a sharp increase in solubility when compared to pure drug; this might be because the drug's crystal size was reduced to a nanocrystalline form. Studies on the solubility of physical mixes and nanocomposites clearly showed that solubility increased up to a certain ratio when the ratio of medication to carrier increased. Additionally, it was discovered that the formulation of nanocomposites had good solubility, with nanocomposites made with HPMC exhibiting the best solubility results at a 1:4 ratio being deemed ideal. $NAPH_N$ was discovered to have a solubility of 1.633 mg/ml. The best ratios from several drug: polymer nanocomposites formulations, $NAPH_N$ (1:4) and $NAPT_N$ (1:4), showed great solubility; as a result, they were put through an in-vitro drug release research with pure drug and drug content analysis.

***In-vitro* Drug release study**

Following figure depicts the dissolving profile of a pure drug and its nanocomposites. According to the dissolution profiles of the nanocomposites, the dissolution rates in all of them were noticeably better than they were for pure naproxen. The best outcome among all nanocomposites was demonstrated by $NAPH_N$, which demonstrated a drug dissolution of 89.73 % in contrast to pure Naproxen, which demonstrated a dissolution of 41.30 %.

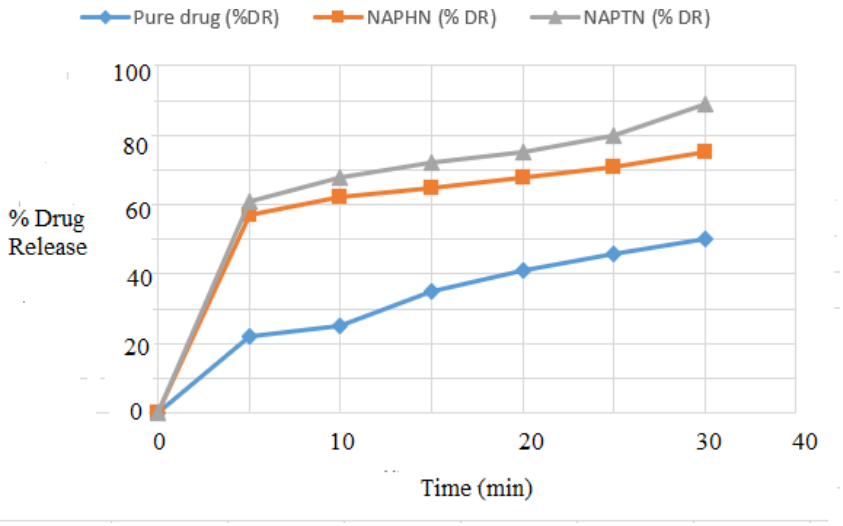

Figure 4: Dissolution profile of pure drug, $NAPH_N$ and $NAPT_N$

Drug content analysis of nanocomposites

Analysing the drug content of the nanocomposites can reveal if the drug is distributed uniformly throughout. It was discovered that the medicine was incorporated into the nanocomposites by 46–93%. $NAPH_N$ (1:4) depicting homogeneous drug dispersion in nanocomposites. Drug incorporation rates in $NAPH_N$ and $NAPT_N$ were respectively 92.65 ± 0.53% and 66.69 ± 0.51%.

Characterization of optimized nanocomposite

The solubility, dissolution, and drug content of each ratio were investigated. From the various batches, nanocomposites made with HPMC performed better, and the optimum optimised ratio is 1:4. The following parameters further describe the optimised ratio $NAPH_N$.

Fourier transform infrared spectroscopy (FTIR)

FTIR tests are conducted to characterise the drug and examine how it interacts with the polymers in the formulation. The optimised nanocomposites NAPHN (1:4) underwent an FTIR analysis. In the figure, FTIR spectra of nanocomposites are displayed. Nanocomposites' spectrum was comparable to naproxen's. This leads to the conclusion that there is no chemical interaction because the drug's principal peak values in the microwave-treated nanocomposites remain constant. The medicine and gum carrier do not interact chemically, it can be said.

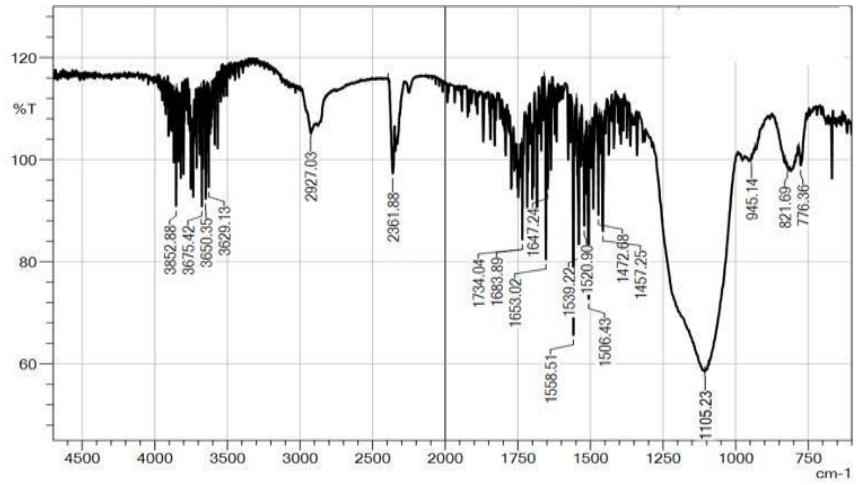

Figure 5: FTIR spectra of optimized Naproxen nanocomposites ($NAPH_N$)

Differential Scanning calorimetry (DSC)

To find the interaction between Naproxen and the polymer, DSC was used. A strong endothermic peak that corresponded to the melting point of the crystalline drug at 150 °C was visible in the DSC thermogram of the pure drug in Figure. The DSC of the optimised nanocomposites $NAPH_N$ 1:4 exhibits a little difference in the endothermic peak compared to the pure drug, and the peak intensity is reduced. This may be caused by a reduction in the drug's crystalline size. As seen in fig., the DSC thermogram of $NAPH_N$ displayed a large endothermic peak. The peak broadening revealed that most of the medication is present as nanocrystalline nanocomposites. Due to the medication being reduced to a nanocrystalline state, little change in melting point was seen. Since the crystallinity has been decreased to a nanocrystalline state, this phenomenon is to blame for the solubility improvement.

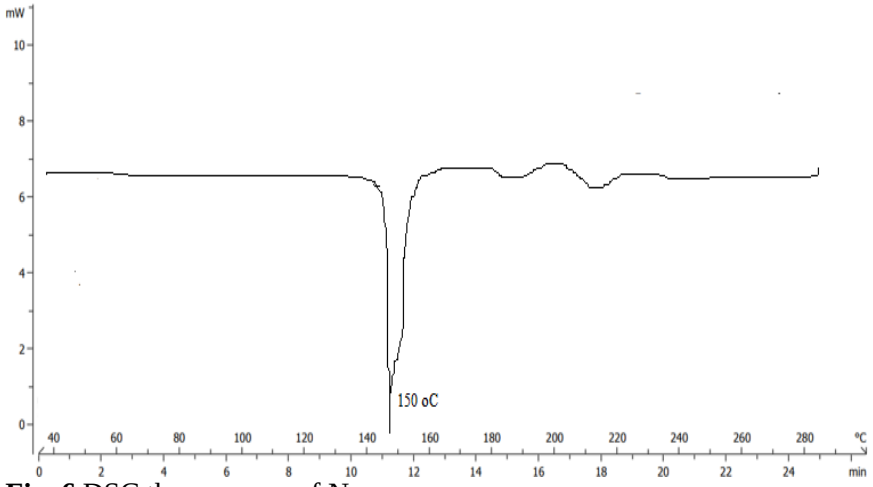

Fig. 6 DSC thermogram of Naproxen

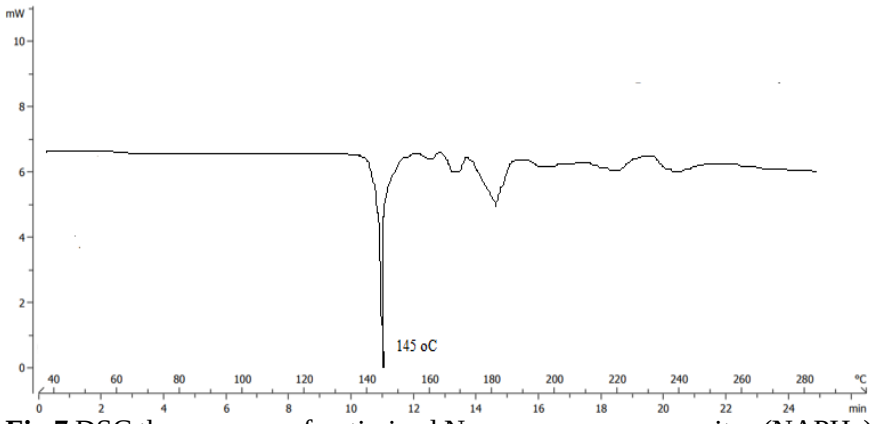

Fig.7 DSC thermogram of optimized Naproxen nanocomposites ($NAPH_N$)

Scanning electron microscopy

The results of SEM examinations, which are often conducted to analyse the surface morphology of drug particles, are shown in fig. SEM was used to describe $NAPH_N$ 1:4 optimised nanocomposites. SEM results show that the $NAPH_N$ nanocomposites were of erratic size and form. Nanocomposites completely alter naproxen. It is possible to see naproxen crystals in the matrix of the polymer (HPMC, tragacanth).

A) **B)**

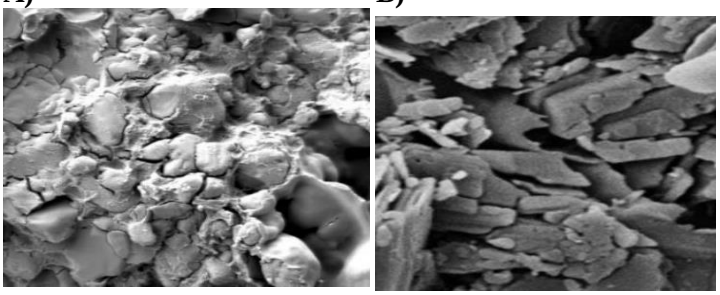

Fig. 8 SEM images of (A) Naproxen with HPMC (B) Naproxen with tragacanth Nanocomposites Characterization of Naproxen loaded optimized NBC containing Carbopol 940 Gel

Appearance, Spreadability, pH, Viscosity, and Drug Content

The colour and spreadability of the NAP-loaded nanobiocomposite gel compositions were visually assessed. All NAP-loaded, NBC-containing gels had a clear look, were transparent, and had a uniform, slick texture. Low shear forces made it simple to disseminate all gel compositions. The next table's compilation of formulation findings shows that all the polymers provided good gel spreadability with only a moderate amount of shear force. To prevent skin irritation, all NAP-loaded, nanobiocomposite-containing gel formulations had pH values between 6.3-6.8. The NAP-loaded, nanobiocomposite-containing gel underwent rheological experiments, and the results showed that all formulations had viscosities that fell between 520 and 559 cps. All the gel preparations had drug concentrations between 86% and 97%, which is appropriate for optimum therapeutic efficacy. Results for each of these evaluation criteria are displayed in the table below.

Table 5: Evaluation of naproxen-loaded, HPMC-tragacanth-nanobiocomposite-containing gel

Formulation Code	**Appearance and Homogeneity**	**pH**	**Viscosity (cps)**	**Spreadability (cm)**	**Drug Content (%)**	**Skin Irritation Score**
NG1	+++	6.8	5398	2.8	84.24 %	0
NG2	+++	6.4	5412	3.1	84.67 %	0
NG3	+++	6.6	5450	3.7	86.34 %	1
NG4	+++	6.3	5523	4.2	88.56 %	0
NG5	**+++**	**6.7**	**5576**	**4.9**	**91.45 %**	**0**

Skin Irritation Studies

Studies on skin sensitivity were carried out to determine the dermal toxicity of all created formulations and control gel. All the gel preparations displayed a Draize score of up to 1, or minor erythema (light pink), demonstrating their tolerance and lesser risk for causing irritation when applied topically.

In-Vivo Anti-Inflammatory Studies on Rats

The formalin-induced edoema (FIE) model showed a substantial increase in paw volume ($p < 0.05$). In contrast to the NAP control gel depicted in the next figure, NAP NBC gel treatment significantly ($p< 0.05$) reduced paw volume and inflammation. At 1, 3, and 5 hours, the NAP NBC gel significantly inhibited 37%, 58%, and 80% of the reaction, respectively. The next table shows that reductions in paw volume also occurred in the NAP control gel group (22%, 46%, and 60%, respectively). As a result of improved penetration, the NAP NBC gel for the treatment of arthritis has more potent anti-inflammatory effects than the NAP control gel.

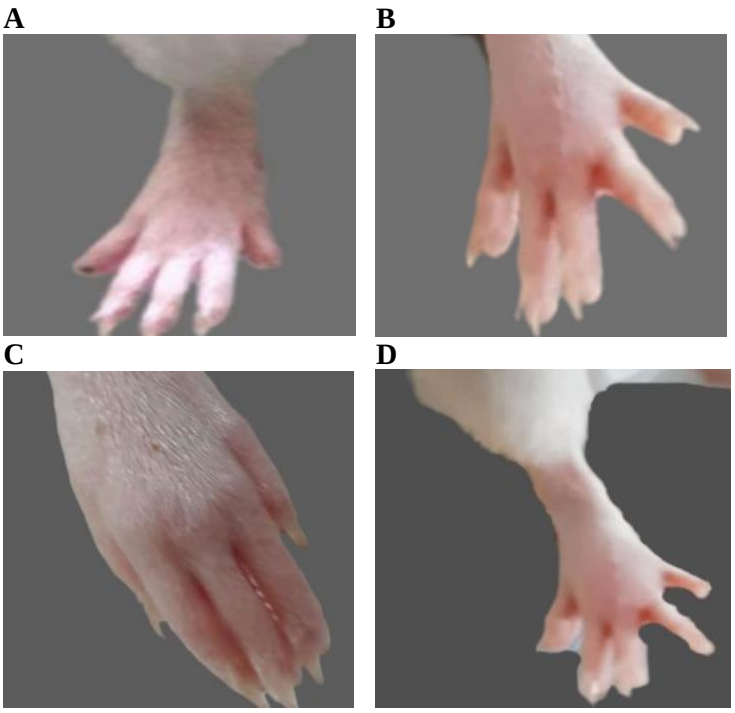

Fig. 9 A) Photograph of control animal rat paw, B) photograph of formalin-induced rat paw, C) photograph of NAP-gel-treated rat paw, D) photograph of control-gel-treated rat paw

Table 6: Percentage inhibition of paw edoema after 1, 3, and 5 h on experimental animals

Percentage Inhibition of Paw Edoema			
Groups	**1 h**	**3 h**	**5 h**
FIE	17	17	17
Formalin + NAP NBC gel	37 ± 0.97	58 ± 0.80	80 ± 0.86
Formalin + NAP control gel	22 ± 0.77	46 ± 2.14	60 ± 2.02

Inflammatory cells increased, there was significant edoema, the epithelial layer was loosened, and collagenous materials accumulated in the rat paw tissue, according to histopathological analysis. Most of the inflammatory histological alterations returned to normal at the end of the fifth hour in rats given treatment with NAP nanobiocomposite (NBC) gel, but there was a slight amount of edoema present. However, in comparison to the group treated with the NAP NBC gel, the group treated with the NAP control gel displayed noticeable histological changes in the buildup of collagenous tissues in the deep dermis and the infiltration of inflammatory cells (fig. C). The enhanced anti-inflammatory properties of the NAP NBC gel.

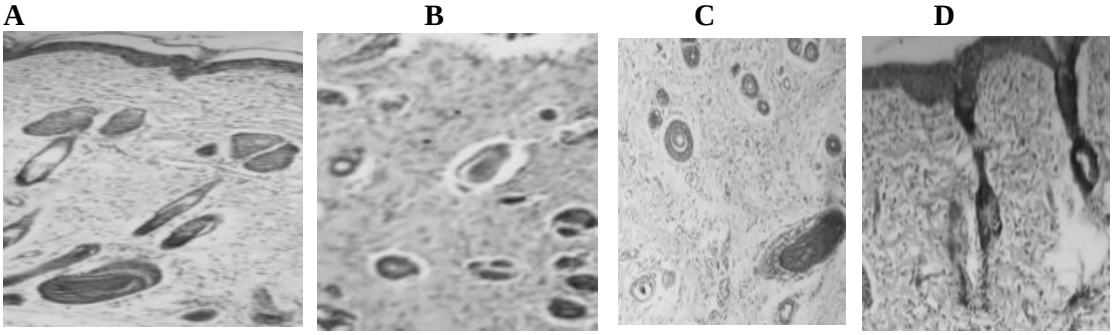

Fig. 10 Histopathological analysis of rat paw tissue revealed normal epidermis, deep dermis, and subcutaneous tissues in (A) significant hyperkeratosis of skin with epithelial growth in (B) groups that were only given formalin. The injury to the paw tissue was much less severe in the FIE + NAP-gel-treated group than in the FIE + control-gel-treated group in (C) and (D), respectively. Compared to the group that received only formalin treatment, most of the histological alterations were significantly reduced and deemed inconsequential. Formalin-induced edoema is known as FIE.

Stability Study of NAP loaded optimized NBC Containing gel

The NAP-loaded nanobiocomposite optimised formulation was added to 0.1% Carbopol 940 gel and used for additional characterisation. In order to create an optimised formulation with an optimised therapeutic effect, as indicated in the accompanying table, stability tests were conducted to examine the interaction between the medicine and Carbopol gel.

Table 7: Stability Study of NAP loaded optimized NBC Containing gel

Time	Appearance	pH	Viscosity (cps)	Spreadability (cm)	Drug content (%)
Day 0	++	6.78	5576	4.90	91.45 %
Day 30	++	6.74	5534	4.93	91.12 %
Day 60	++	6.76	5502	4.95	90.78 %
Day 90	++	6.66	5483	4.99	90.23 %

Conclusion

The current study demonstrated the use of naturally occurring carriers, such as tragacanth, in microwave-generated nanocomposites to enhance solubility and, consequently, drug component dissolution. Nanocomposites made with tragacanth were discovered to be applicable from among the many batches developed based on various assessment criteria. The drug's solubility has grown significantly, and its ability to dissolve has improved significantly as well. The undeviating dispersion of medication in carrier in a nanocrystalline form in optimised nanocomposites is a key aspect of this study. The improved nanocomposites were sufficiently stable and simple to make. Conclusion: Microwave-produced nanocomposites can be used to increase the solubility, dissolution, and subsequently bioavailability of BCS class II medicines that are poor water soluble. This study also showed how to successfully manufacture a gel that contains a nanocomposite loaded with NAP for use as a sustained TDDS. A NAP-loaded nanocomposite was successfully created by using optimised drug and polymer concentrations. This work was started to develop a polymeric nanocomposite-containing gel employing polymers as a unique method for a TDDS that contains nanocomposite material. In contrast to the control gel, the NAP-loaded nanocomposite-containing Carbopol 940 gel demonstrated that an optimised batch produced a gel with good consistency, homogeneity, spreadability, and stability. Histopathological images from in vivo anti-inflammatory experiments supported an improved inhibitory percentage of paw edoema and a notable decrease in inflammation indicators. Considering this, it is anticipated that innovative NAP-loaded nanocomposite gels will be used to treat arthritis through enhanced patient compliance.

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