DEXIBUPROFEN NANOSPONGE BASED TOPICAL GELS: PREPARATION AND *IN VITRO*EVALUATION

MahalakshmiK[1], MonishaK[2], RohithS[3], Sharan Babu RS[4], SowmyaC[5]*

[1]Department of Pharmacognosy, Sri Ramachandra faculty of pharmacy, Sri Ramachandra institute of higher education and research, Chennai - 600116, India. E Mail: mahakkgd@gmail.com.

[2]Department of Quality Assurance, Sri Ramachandra faculty of pharmacy, Sri Ramachandra institute of higher education and research, Chennai - 600116, India. E Mail: monishak778@gmail.com

[3]Department of Pharmaceutics, Sri Ramachandra faculty of pharmacy, Sri Ramachandra institute of higher education and research, Chennai - 600116, India. E Mail: rsp0118013@gmail.com

[4]Department of Pharmacy Practice, Sri Ramachandra faculty of pharmacy, Sri Ramachandra institute of higher education and research, Chennai - 600116, India. smmsharan@gmail.com

[5*]Department of Pharmaceutics, Sri Ramachandra faculty of pharmacy, Sri Ramachandra institute of higher education and research, Chennai - 600116, India. Email: drcsowmya@sriramachandra.edu.in

Address of Corresponding author

Dr. C.Sowmya, Assistant Professor

Department of Pharmaceutics,

Sri Ramachandra faculty of pharmacy,

Sri Ramachandra institute of higher education and research (SRIHER) (DU), Chennai - 600116, India.

Email: drcsowmya@sriramachandra.edu.in

ABSTRACT

Objectives: The goal of this study is to prepare and evaluate a topical gel loaded with Dexibuprofen (DIB)nanosponges.

Methods: DIB nano sponges (DIBNS)had been prepared by using emulsion solvent diffusion technique and subsequently characterized for size, potential and surface morphology by scanning electron microscopy. Optimized DIBNSformulation (F2) was incorporated into Carbopol gel and evaluated for drug content, spreadability, viscosity and drug diffusion studies.

Results: FTIR and DSC studies confirmed the absence of drug -excipient interactions**.** The average size of prepared DIBNS is 813.5 nm with 0.8 PDI and 32 mVs zeta potential. SEM studies revealed that the DIBNS are round in shape with smooth surface and available as clusters. DIBgel showed pH of 6.8, 70467.03 cps viscosity, 4.7 gm/cm/s spreadability and 64.27 % drug content. *In vitro* drug diffusion studies showed that, 52.14% drug has been released in 60 mins.

Conclusion: From the results it has been concluded that, DIBNS loaded topical gels have been prepared successfully and evaluated. It could be an alternative topical formulation to the existing analgesic and anti-inflammatory gels. However, theclinical potential of DIBNSgels need to be evaluated.

Keywords: Nanosponges, Dexibuprofen, Topical gels

INTRODUCTION

DIBU, S (+)-ibuprofenis a physiochemically distinct enantiomer of racemic ibuprofen that is pharmacologically efficacious. Due to a larger concentration of the active S enantiomer than ibuprofen, it is thought to have a superior safety profile and be more pharmacologically active and tolerated. It acts by inhibiting the COX-2 isoform of the arachidonic acid COX, similar to other NSAIDs, to reduce prostanoid production in inflammatory cells[1].

The typical diameter of Nanosponges, which are spongy, virus-sized NPs, is between 250 nm and 1 m. It can be utilised in parenteral, nasal, topicaland oral drug delivery systems. Medicines can easily bind to them due to their small size and porous form, which raises the drug's solubility and bioavailability. These colloidal nano-sized carriers have been proposed for drug administration to prolong the release of lipophilic pharmaceuticals and solubilize them. Nanosponge lowers the unpleasantness of medications without reducing their effectiveness[2].

Nanosponges can contain materials that are hydrophilic and lipophilic. Additionally, they alter the pharmacokinetic properties of drugs and improve their bioavailability. Nanosponges are efficient delivery systems for both lipophilic and hydrophilic chemicals because of their hydrophobic internal core and hydrophilic external surface, which both offer good flexibility. Additionally, using a gel topical formulation as a delivery method instead of other topical formulations can reduce irritation[3].

The study's objective was to create a topical delivery system employing DE ibuprofen Nanosponges hydrogels to promote LX skin absorption and hence enhance therapeutic

effectiveness. Dexibuprofen Nanosponges were developed using the emulsion solvent evaporation technique using ethyl cellulose as the polymer to accomplish this. The developed Nanosponges were then combined with a gel.

Materials and Methods

Materials

Dexibuprofen received as a gift sample from (Solara activePharma Sciences, Tamil Nadu, India), Ethyl acetate was purchased from (Avantor Performance Materials India Private Limited Haryana, India), Carbopol 934 was purchased from (HI Media LaboratoriesPvt.Ltd, Mumbai, India),Polyvinyl alcohol (PVA)and Ethyl cellulose (EC) were acquired from (Loba Chemie Pvt.Ltd, Mumbai, India.)

METHODS

Pre-Formulation studies of Dexibuprofen Nanosponges based gels

Pre-formulation data must be created to facilitate the development process and the physicochemical parameters must be determined before formulation development. Excipients are wisely chosen as a consequence of the study's consideration of the interactions between the drug components and the excipients utilised in the formulation.

Differential Scanning Calorimetry (DSC) studies

DIB, a placeboand DIB in combination with a placebo were studied using differential scanning calorimetry. The heating rate was 10 °C/min with an inert nitrogen flow rate of 10 ml/min and the temperature range was 40 – 400 °C. The samples were loaded into standard platinum pans, and the aluminium pans served as a point of comparison. The reference sample also had a weight of 10 mg and a volume of 10 ml. Every component of the sample had its melting point determined, interpreted, evaluated and its values documented.

Fourier – transform infrared spectral studies

When an infrared beam is pointed at a sample, Fourier-transform infrared spectroscopy (FTIR) examines how much of the beam and at what frequencies the sample absorbs the infrared light. The sample must be cut into a thin enough slice or have a tiny layer of material removed in order for the infrared light to pass through. On some samples, reflectance techniques can be applied without causing harm to the sample. Using a Bruker instrument, an FTIR research of Dexibuprofen, a placebo, and a medication with a placebo was recorded. The resulting FTIR reports were then processed with the help of standard wave numbers and interpreted.

Preparation of DIB loaded Nanosponges

The emulsion solvent diffusion technique was used to prepareDexibuprofen Nanosponges[4]. A predetermined amount of DIB was dissolved in 10 ml of ethyl acetate that included enough ethyl cellulose to create the dispersed phase. To create three batches of Nanosponges (N1, N2, and N3), the dispersed phase was gradually added to an aqueous solution of polyvinyl alcohol with varying concentrations while stirring continuously for 30 minutes.

Characterization of DIB loadedNanosponges

Determination of particle size and zeta potential

The Malvern Particle Size and Zeta Potential Analyzer is used to detect Zeta Potential by utilising dynamic light scattering from less than a nanometer to many microns[5]. Malvern Zeta Sizer was used to analyse the dispersed particle size of Nanosponges, and the findings were published.

Surface morphological study of DIBNS using Scanning electron microscope (SEM)

A concentrated electron beam is used to scan a sample's surface in a SEM, a type of electron microscope, to obtain photographs of the DIB nanosponge samples[6]. The sample's surface topography and chemical composition are revealed by the signals that are created as a result of the electrons' interactions with the sample's atoms. The position of the electron beam and the strength of the detected signal are combined as it is scanned in a raster scan pattern.

Preparation of topical gel by incorporating DIB nanosponges

The Carbopol 934 (1%w/v) solution was made and allowed to swell during the entire night. For the purpose of integrating the Carbopol gel into the Nanosponges[7], Nanosponges were mixed with Carbopol gel for 10-15 minutes while stirring continuously, and the batches were identified as F1, F2, and F3. The resulting gel compositions were placed in firmly covered containers and left at room temperature for 15 uninterrupted minutes to allow any trapped air to escape.

Table 1 Formulation of DIB Nanosponge based topical gels

S.NO	**INGREDIENTS (G)**	Formulation1	Formulation2	Formulation3
1.	Ethyl Cellulose	0.1	0.2	0.3
2.	PolyVinylAlcohol	10	20	30
3.	Carbopol 934	0.5	0.5	0.5
4.	Dexibuprofen	1	1	1

Evaluation of topical gel incorporated DIB nanosponges

Determination of pH of gels:

In order to determine the pH of the created gel compositions, a digital pH metre was employed. Before dipping the pH metre electrode into the mixture to test pH, it was washed with distilled water. Three times through this process, the results were recorded.

Measurement of Viscosity of gels

Using a Brookfield Viscometer with spindle 63, the viscosity of the prepared gel batches were assessed. The formulation whose viscosity was to be evaluated was introduced to the beaker and allowed to settle for 30 minutes at the assay temperature (25 ± 1°C).

Measurement of spreadability of gels

To test the gel's spreadability, 0.5 g of the gel was divided among the glass plates. A half kilogramme of weight was placed on upper glass plate for five minutes and allowed the gel to spread between the plates[8]. After distributing the gel, the area occupied by the gel was measured.

***In vitro* drug diffusion study**

The cellophane membranewas soaked in distilled water for six hours and it was placed between the donor and acceptor compartment of the diffusion cell. 150 ml of phosphate buffer was placed in acceptor compartment and accurately weighed 1.0 g of gel (equivalent to 100 mg of DIB) was taken in donor compartment.The entire setup was placed on magnetic stirrer to control both stirring and temperature. 5 ml of the sample was withdrawn for every 10 min interval till 1 hr[9]. Every time the volume has been preserved by addition of 5 ml of phosphate buffer to the receptor compartment.The acquired samples were analyzed by measuring the absorbance at 222 nm in UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

Preformulation studies:

Preformulation is the examination of the physical and chemical characteristics of the drug's constituent parts before the formulation's compounding procedure. Understanding the nature and characteristics of each component and improving manufacturing conditions are the goals of the study.

DSC studies

The DSC analysis was performed to examine the drug excipients compatibility and physical changes in drug.

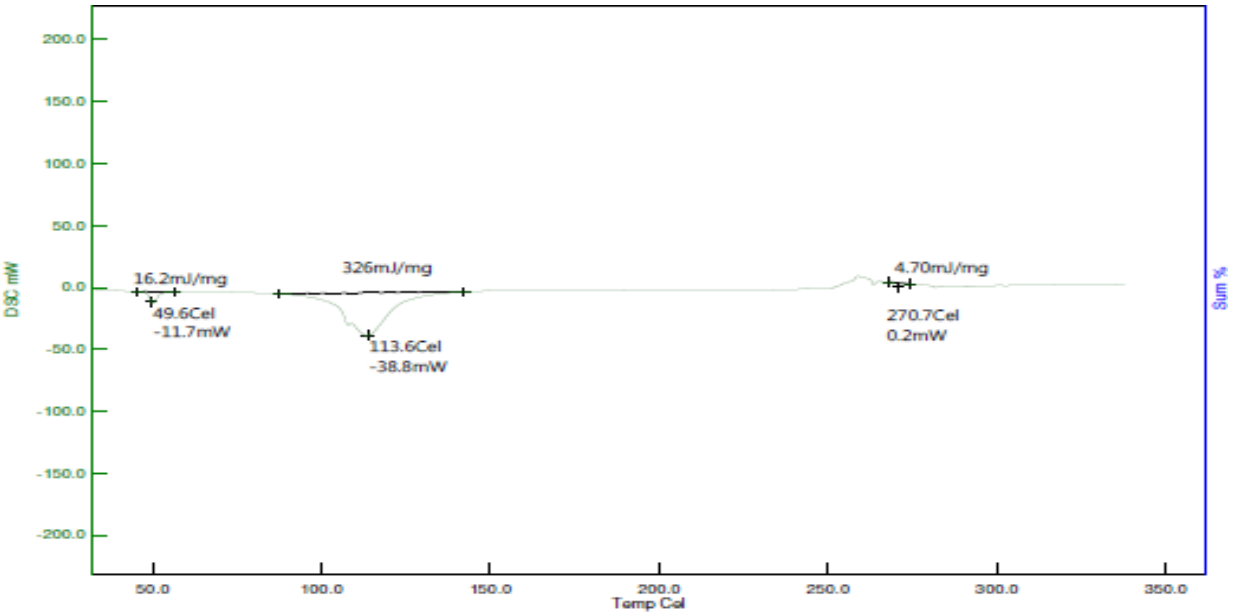


Fig.1 The DSC thermogram of pure Dexibuprofen

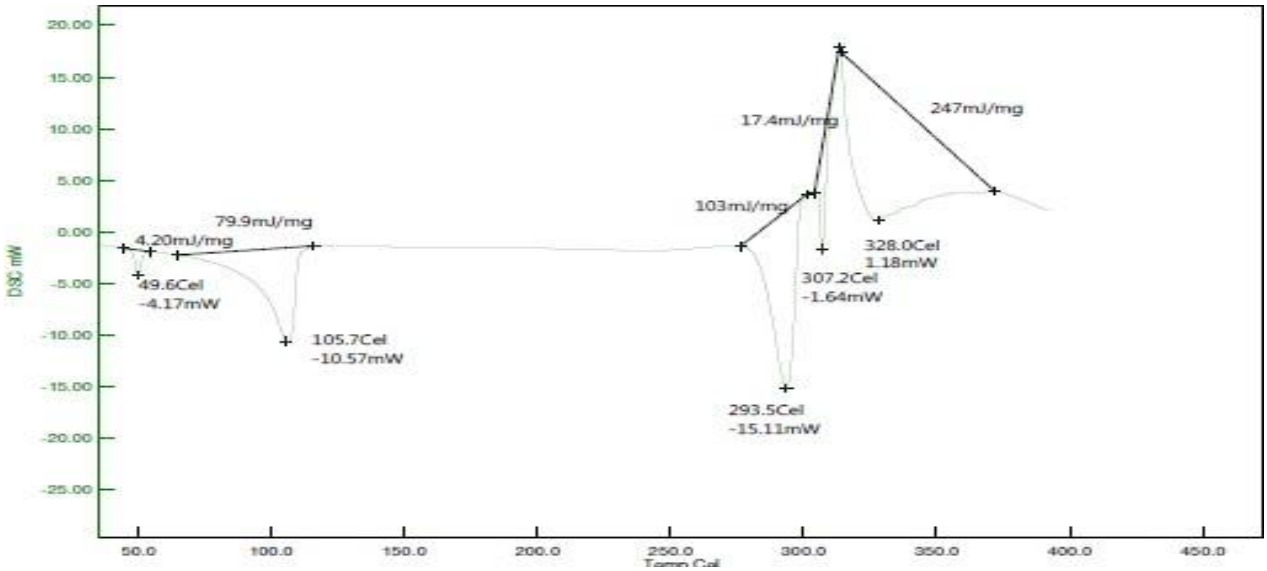


Fig. 2 The DSC thermogram of placebo mixture of Nanosponges associated gel

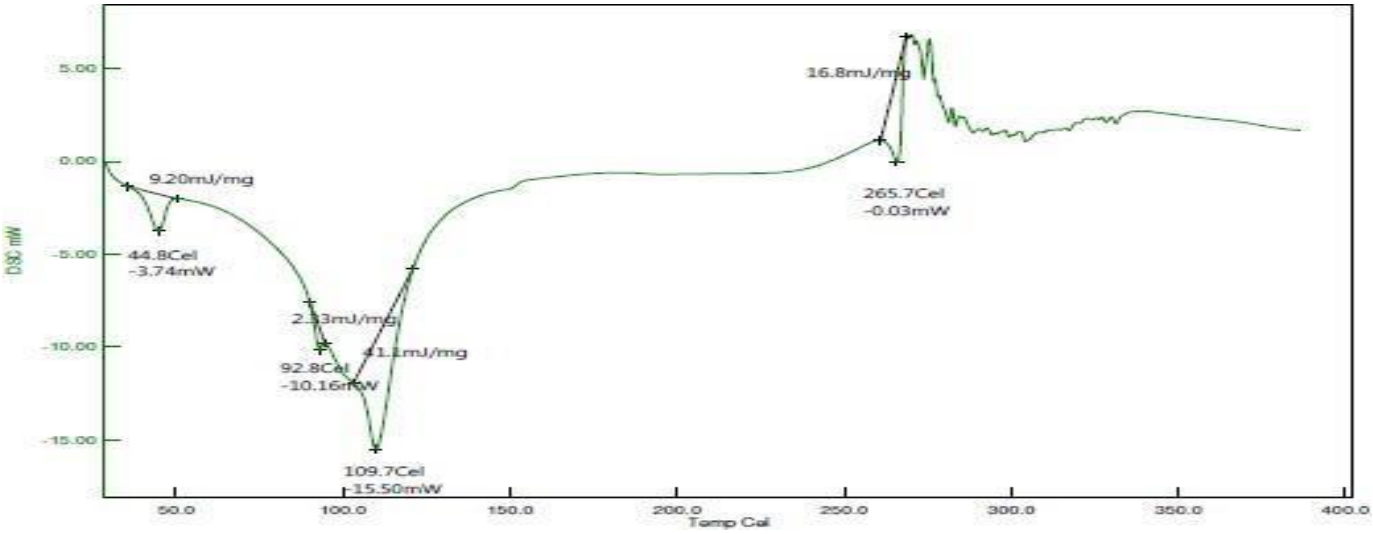
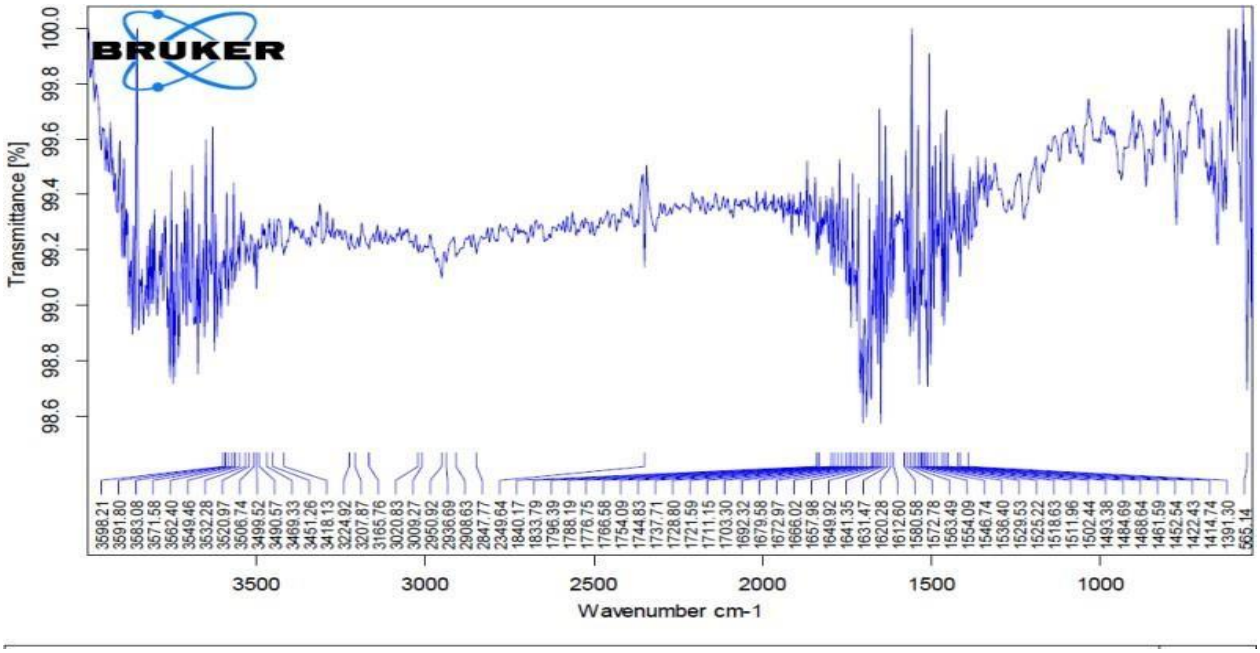


Fig. 3 The DSC thermogram of drug with placebo mixture

The endothermic peak in Fig. 1 was observed at 105^0C, which corresponds to the melting point of the medication Dexibuprofen. Thus, it was established and confirmed sample obtained was Dexibuprofen. The DSC thermogram of aplacebo mixture containing ethyl cellulose, Carbopol and polyvinyl alcohol is shown in Fig. 2. The endothermic peak of the Dexibuprofen in the presence of the placebo was shown in figure 3, it preserved the peak of DIB at 105^0C and did not find any new peaks of interaction[10], thus indicating the absence of



drug-excipient interactions.

FTIR spectral studies

Fig. 4 FTIR spectra of dexibuprofen

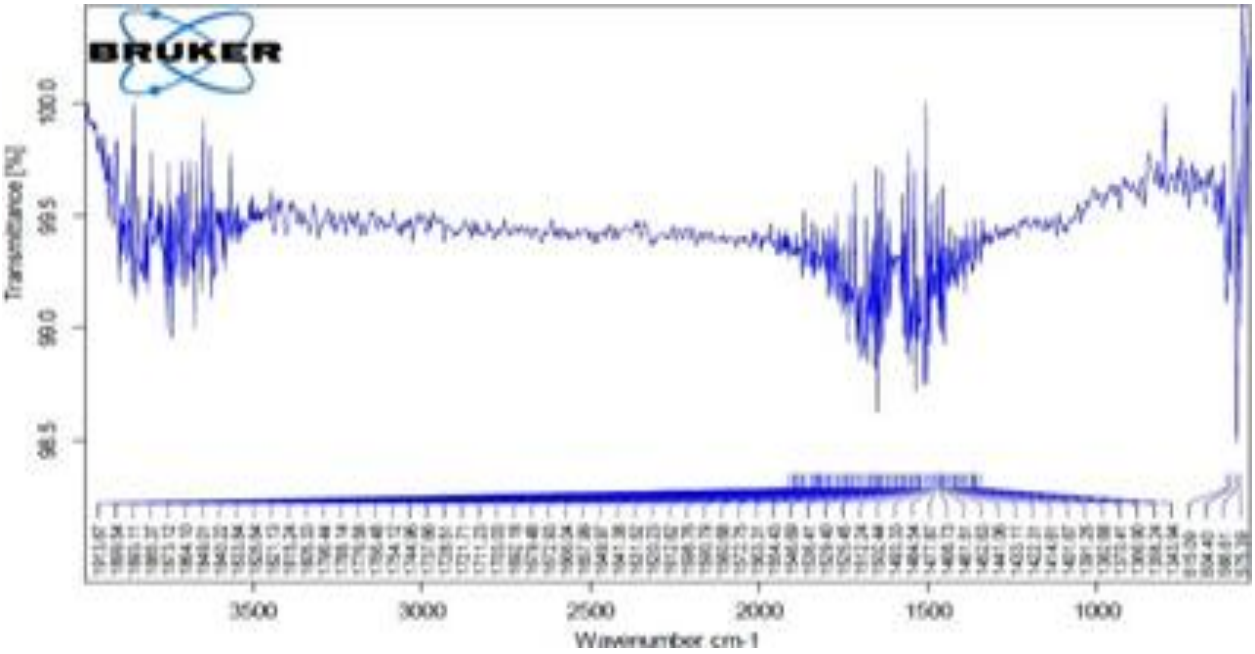


Fig. 5 FTIR spectra of placebo mixture of Nanosponges associated gel

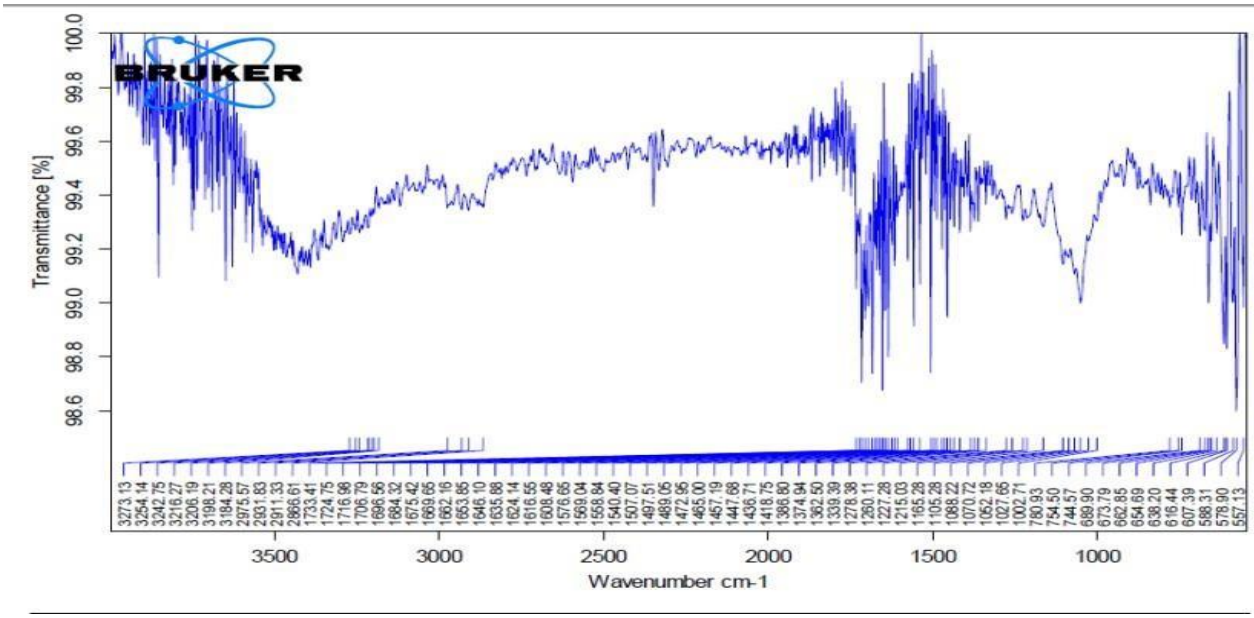


Fig.6. FTIRspectraofdrug with placebo mixture

FTIR investigation was carried out to see whether Dexibuprofen was compatible[11]. Figure 4 showed, the C=O stretch, which is distinctive for Dexibuprofen, is at 1705 cm^{-1}, followed by the aromatic CH_3 stretch at 744 cm^{-1}, the OH stretch at 1068 cm^{-1}, and the C=C benzene stretch at 1465 cm^{-1}. The typical absorbance for the C=O (COOH) peak was visible in the medication Dexibuprofen FTIR spectra at about 1744. The Dexibuprofen is distinguished by absorbance for OH group peak at around 3224. The C-O(S) group has an approximate absorbance of 1391. The spectra of the placebomixture are shown in figure 5. Figure 6 showed the FTIR spectra of drug with placebo mixture contained all of the gropus identified in the drug at wavelengths of 1707 cm^{-1}, 742 cm^{-1}, 1068 cm^{-1}, and 1462 cm^{-1}. This demonstrates unequivocally that neither of the excipient used in the formulation interacts

with the drug. The. The C==O peak at or about 1724 is visible in the combination, which further demonstrates that there is no interaction between the medication and the excipients.

Formulation and evaluation of Dexibuprofen Nanosponges

ParticlesizeanalysisstudiesofDIBNanosponges

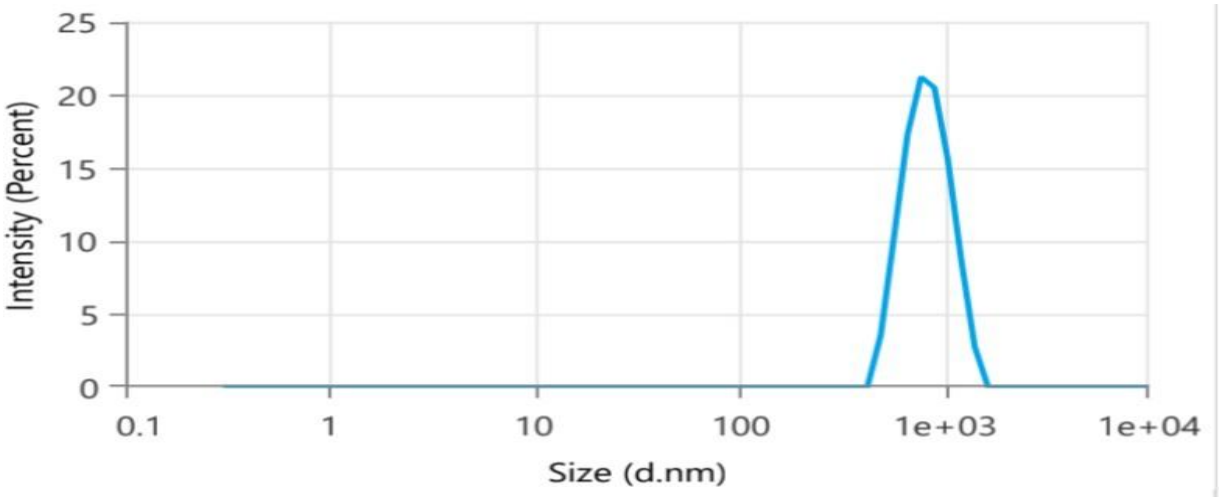


Fig.7 Particle size distribution of DIBnanosponges

The average particle size of nanosponge is 813.5 nm. This size can increase the solubility and penetration of drug through the skin[12].

ZetapotentialanalysisstudiesofDIBNanosponges

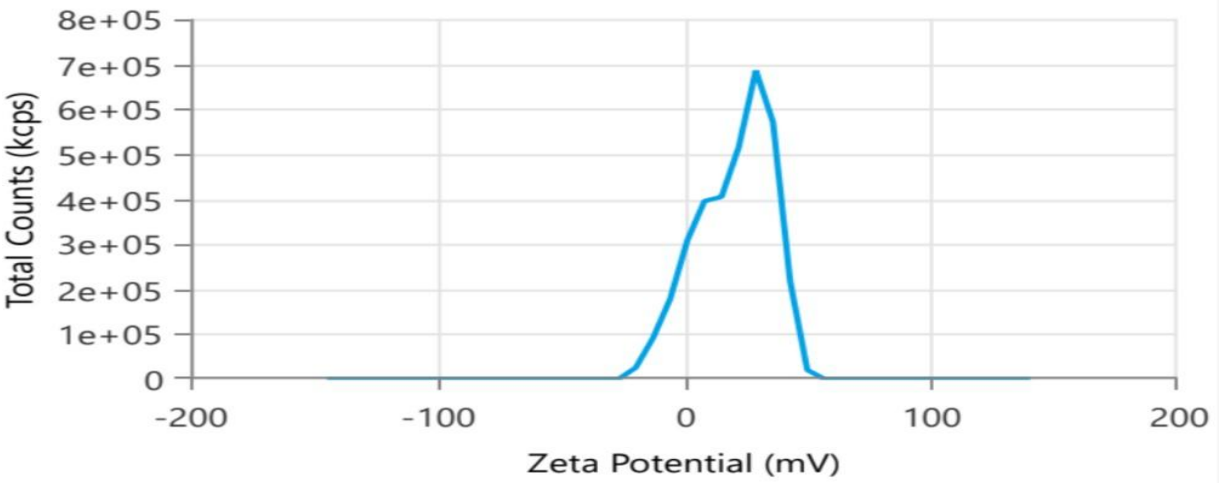


Fig. 8 Zeta potential curve of DIBnanosponges

The average zeta potential value of Nanosponges is 32 mVs and it is ranging from -10 to +42 mVs. The results says that the DIB nanosponges are macroscopically stable[13].

SEM studiesofDIBNanosponges

According to SEM analyses, the Nanosponge exhibited porous, spherical, and nanoscale particles. It also shows the Nanosponge porous and spongy structure[14].

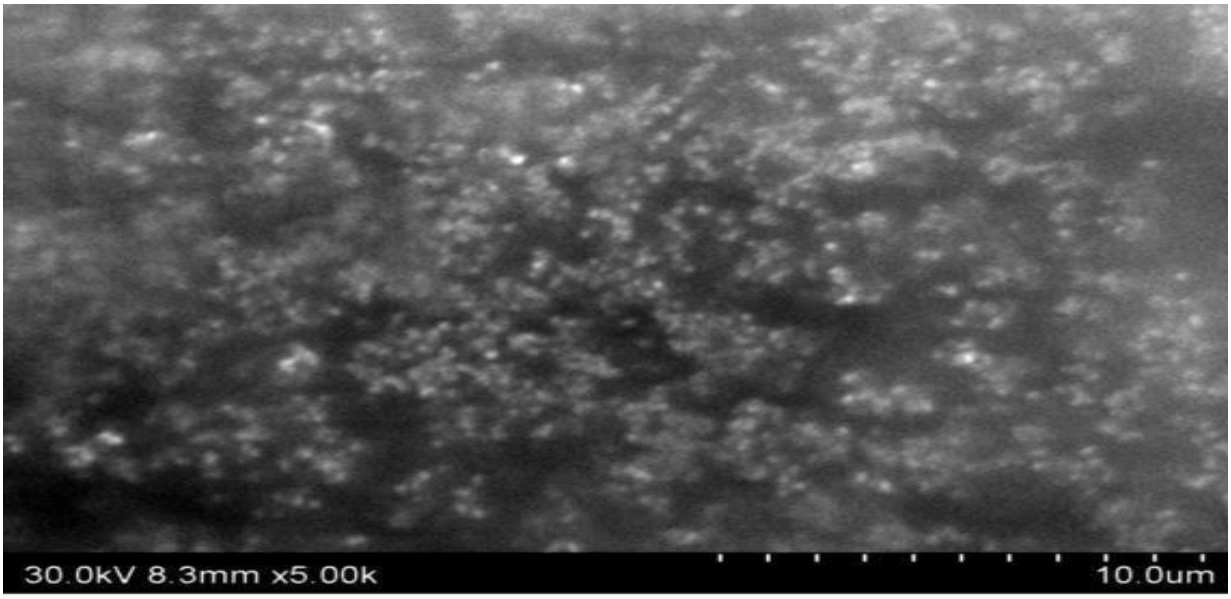


Fig.10 SEM photograph of DIBNanosponges

Evaluation of prepared nanosponge prepared gels:

pH determination

The pH of F1 was found to be 6.8, the pH of F2 was found to be 7.1 and the pH of F3 was found to be 6.9.This clearly indicates that the gel could mimic the pH of the skin and will not contribute to the irritation of skin. The pH of the formulations was found to be satisfactory.

Viscosity measurement

The viscosity of the gel was determined. The viscosity of F1 was found to be 65,240.06 cps. The viscosity of F2 was found to be70,467.03 cps. The viscosity of F3 was found 85,462.37 cps. The viscosity of all the three formulations was in the range of 65000 to 85000 cps, therefore it is meeting the requirements of viscosity of topical Gels, hence the prepared gel is able to stay for longer period on the applied area and can produce therapeutic action.

Spreadability

The spreadability of the formulations were done. Spreadability of F1, F2, F3 was found to be 4.5 gm-cm/s ,4.7 gm-cm/s and 4.9 gm-cm/srespectively. This clearly implies that the formulation will easily get spread on application to skin[15].

Drug content

Drug content was calculated and the results were shown in the table. The drug content of F1 was found to be 63.74 %, drug content of F2 was found to be 64.27%, drug content of F3 was found to be 68.58 %. The drug content was found in the range of 63.54 % to 68.58% which indicates uniform drug distribution in the gel formulation.

Batch no	**pH ***	**Viscosity(cp)***	**Spreadability(cm) ***	**Drug content (%) ***
F1	6.8 ± 0.5	65,240.06± 105	4.5± 0.2	63.74± 2.8
F2	7.1 ± 1.0	70,467.03± 98	4.7±0.8	64.27± 3.0
F3	6.9 ± 0.4	85,462.37± 112	4.9± 0.4	68.58±2.2

Table .2 Evaluation of DIBnanosponge gels for pH, viscosity, spread ability and drug content

*Average of three values

***In vitro* Drug Diffusionof DIB and DIBnanosponge based gels**

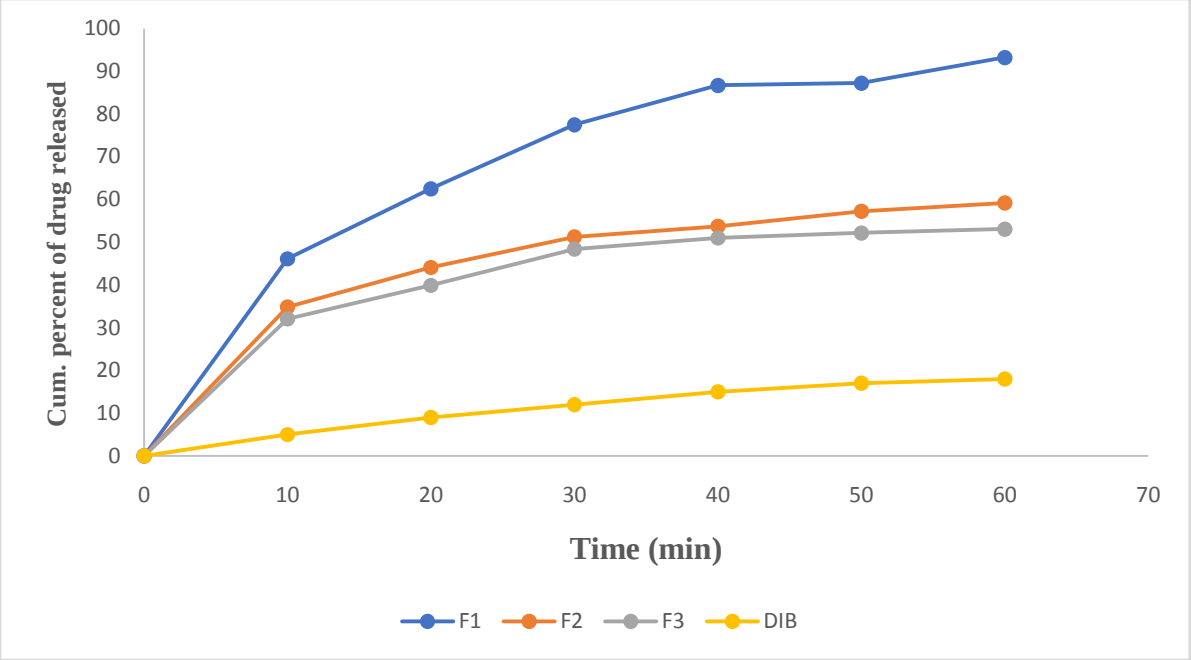


Fig 11. Drug release profiles of DIB andDIBnanosponge based gels

Fig. 11 shows the drug release profiles of DIB pure drug and DIBnanosponges F1, F2, F3.DIB pure drug shows 18 % drug release at the end of 60 min. whereas DIBnanosuspensionformulation F1shows 93.2 %, F2 formulation shows 59.14 % and F3shows 53.06 % after 60 min[16]. Among all the formulations, F1 showed better drug release profile in 60 mins, so it was selected to be the optimized formulation.

CONCLUSION

DIBnanosponge based topical gels have been successfully prepared and evaluated.The research's findings showed that gels based on Nanosponge technology have repeatable quality traits. The developed Dexibuprofen nanosponge-based formulations offer potential dosage forms with positive pharmacological properties, it can be an ideal alternative for DIB oral tablets.However, in order to verify their therapeutic efficacy, ex-vivo and in vivo studies need be carried out. These formulations may be used in the future to treat acute pain and localised inflammation instead of taking DIBU orally.

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