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Original Article

FORMULATION AND EVALUATION OF A NANOEMULGEL CONTAINING INDOMETHACIN AND BROMELAIN FOR LOCALIZED ANTI-INFLAMMATORY ACTIVITY

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ABSTRACT

Objective: This study aimed to develop and evaluate a topical nanoemulgel containing indomethacin and bromelain for effective localized anti-inflammatory therapy.

Methods: Nanoemulsions were formulated using eucalyptus and nirgundi oils as the oil phase, Tween 20, and propylene glycol as the surfactant and co-surfactant. Pseudo-ternary phase diagrams identified the largest nanoemulsion region at Smix 1:1. The nanoemulsions were incorporated into Carbopol 934 to obtain nanoemulgel. Preformulation studies and FTIR and DSC analyses confirmed drug-excipient compatibility, while molecular docking showed strong binding of indomethacin and bromelain to inflammatory targets, including COX-2 and TNF-α. The physicochemical parameters of nanoemulgel, including globule size, PDI, zeta potential, pH, viscosity, spreadability, and extrudability, were evaluated. *In vitro* anti-inflammatory activity was assessed using protein denaturation and HRBC membrane stabilization assays, while permeation was studied using Franz diffusion cells.

Results: The formulations (F1-F5) demonstrated nanoscale droplets ranging from 119.6 to 189.4 nm, with zeta potential between −12.0 and −19.2 mV. The pH values were between 6.50 and 6.73, and the viscosity was approximately 21.355–21.392 mPa·s. The spreadability was measured between 33.01 and 39.32 g·cm/s, and extrudability ranged from 61.00% to 74.81%. The *in vitro* anti-inflammatory activity of formulations F3 and F4 was significant and comparable to that of a marketed indomethacin gel. Franz diffusion studies indicated an increase in cumulative permeation over time, with high flux and permeation coefficients.

Conclusion: The developed nanoemulgels, particularly F3, exhibited satisfactory rheological properties, enhanced drug permeation, and significant anti-inflammatory activity comparable to that of a marketed indomethacin gel formulation.

Keywords: Nanotechnology, Nanoemulgel, Rheumatoid arthritis, Topical drug delivery, Anti-inflammatory activity, Indomethacin, Bromelain

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial inflammation, cartilage degradation, and bone erosion, which leads to pain, stiffness, and functional disability [1, 2]. Although systemic pharmacotherapy using NSAIDs, corticosteroids, and DMARDs remains central to RA management, long-term systemic administration often causes significant adverse effects such as gastrointestinal irritation, renal toxicity, hepatotoxicity, and immunosuppression [3, 4]. These limitations necessitate alternative drug delivery approaches capable of providing effective localized therapy while minimizing systemic exposure [1, 5].

Topical drug delivery systems have emerged as a promising strategy for managing localized inflammatory conditions, offering site-specific drug action, avoidance of first-pass metabolism, reduced systemic side effects, and improved patient compliance [6, 7]. However, the efficacy of conventional topical formulations is often limited by the stratum corneum barrier, which restricts drug penetration into deeper tissues, such as synovial joints. Thus, advanced carrier systems are required to enhance skin permeation and drug retention at target sites. Nanotechnology-based drug delivery systems have gained attention for topical applications because of their ability to improve drug solubility, stability, and skin permeation [8]. Among nanocarriers, nanoemulsions are particularly effective because of their small droplet size, high kinetic stability, and enhanced interfacial surface area, which facilitate improved drug diffusion across the skin barrier [8–12].

Indomethacin is a potent NSAID used to manage inflammatory disorders, including RA, through cyclooxygenase enzyme inhibition and prostaglandin synthesis suppression. Despite its efficacy, oral indomethacin causes severe gastrointestinal and renal adverse effects, limiting its long-term use [13]. Bromelain, a proteolytic enzyme derived from pineapple (Ananas comosus), exhibits anti-inflammatory, anti-edematous, and immunomodulatory properties, along with a favorable safety profile [14-16]. The combination of indomethacin and bromelain offers complementary therapeutic effects, potentially enhancing anti-inflammatory efficacy while reducing the dosage of synthetic NSAID. This study aimed to develop and evaluate a nanoemulgel-based topical delivery system for indomethacin and bromelain co-delivery for localized anti-inflammatory therapy.

MATERIALS AND METHODS

Materials

Indomethacin was procured from Yarrow Chemicals and bromelain from Vital Herbs. Eucalyptus oil was purchased from Loba Chemie Pvt. Ltd., and Nirgundi oil was sourced from R V Essentials. Sesame oil was obtained from the local market, and Karanja oil was supplied by Research Lab Fine Chem Industries, India.

Methods

Solubility of drugs in oils, surfactants, and Co-surfactants [18]

The solubility of indomethacin and bromelain in selected oils, surfactants, and co-surfactants was determined using the shake flask method. An excess amount of each drug was added to 2 ml of each excipient and vortexed for 10 min. The mixtures were then shaken at 3000 rpm for 48 h at room temperature and centrifuged at 15,000 rpm for 10 min. The supernatant was filtered through a 0.45 µm membrane filter, diluted with methanol, and analyzed using a UV spectrophotometer at 320 nm and 280 nm for indomethacin and bromelain, respectively. Solubility is expressed in mg/ml.

Screening of surfactant and Co-surfactant [18]

Surfactants were screened based on their emulsification efficiency and transparency. The oil phase (300 mg) was mixed with an equal amount of surfactant and heated to 40 °C. From this mixture, 50 mg was diluted to a final volume of 50 ml using distilled water. The ease of emulsification was evaluated by counting the number of flask inversions required to obtain a uniform emulsion. The percentage transmittance was measured at 440 nm using distilled water as a blank.

Co-surfactants such as PEG 400, PEG 600, propylene glycol, and isopropyl alcohol were screened similarly by preparing mixtures of oil, selected surfactant (Tween 20), and co-surfactant, followed by the evaluation of the emulsification efficiency and transparency.

Construction of pseudo-ternary phase diagrams [18, 19]

Pseudo-ternary phase diagrams were constructed using the water titration method to identify the nanoemulsion region and optimize the surfactant to co-surfactant ratio. Smix ratios (1:1, 2:1, and 1:2) were prepared, vortexed, and equilibrated at 40 °C. The data obtained from these experiments were used to construct pseudo ternary phase diagrams using Chemix School-Portable Chemistry Software 7.0. The phase boundaries were recorded, and the nanoemulsion regions were identified.

Drug–excipient compatibility studies

FTIR analysis

FTIR spectroscopy was performed to assess the compatibility between indomethacin, bromelain, and the selected excipients by comparing the characteristic functional group peaks.

Differential scanning calorimetry

DSC analysis was conducted to evaluate the thermal behaviour, crystallinity, and potential interactions between the drugs and excipients by analyzing the changes in the melting endotherms.

Molecular docking study [20]

Molecular docking studies were performed using AutoDock Vina to predict the binding affinity and interaction patterns of indomethacin and bromelain with inflammatory target proteins, including COX-1, COX-2, TNF-α, IL-6, phospholipase A2, and phospholipase D2. The binding energies (kcal/mol) were used to assess the interaction strength.

Formulation development

Preparation of drug loaded nanoemulsion

Blank nanoemulsions within the nanoemulsion region were identified based on pseudo-ternary phase diagrams constructed using eucalyptus oil, nirgundi oil, Tween 20, propylene glycol (Smix 1:1) and water. The formulation exhibiting visual clarity and stability without phase separation after 24 h was selected for drug loading.

Indomethacin was dissolved in the oil phase, and bromelain was dissolved in an aqueous phase. The oil phase (eucalyptus oil: nirgundi oil, 1:1) was mixed with Smix (Tween 20: propylene glycol, 1:1) under magnetic stirring. Distilled water was added dropwise to form a coarse emulsion, which was then homogenized at 8000 rpm for 15–20 min to obtain a nanoemulsion. Five nanoemulgel formulations (F1–F5) were prepared by varying the proportions of indomethacin and bromelain (table 1), while the oil phase composition and Smix ratio were maintained constant.

Table 1: % w/w of indomethacin and bromelain in each formulation

Component	F1	F2	F3	F4	F5
Indomethacin (% w/w)	1.0	0.25	0.5	0.75	–
Bromelain (% w/w)	–	0.75	0.5	0.25	1.0

Preparation of nanoemulgel

A gel base was prepared by dispersing Carbopol 934 (1% w/v) in distilled water and allowing it to hydrate for 24 h. The prepared nanoemulsions (F1–F5) were incorporated into the gel base in a 1:1 (w/w) ratio under gentle stirring to obtain uniform nanoemulgels. Preservatives were added prior to incorporating the nanoemulsion.

Evaluation

Evaluation of nanoemulsion

a) Organoleptic properties of nanoemulsion

The prepared nanoemulsion formulations were evaluated for their organoleptic properties, such as appearance, colour, odour, and clarity, which were visually examined and recorded.

b) pH determination of nanoemulsion

The pH of the prepared nanoemulsion formulations was measured using a calibrated digital pH meter at room temperature

c) Droplet size and polydispersity index

The droplet size and polydispersity index (PDI) of the nanoemulsion formulations were determined using dynamic light scattering (DLS).

d) Zeta potential

The zeta potential of the nanoemulsion formulations was measured using a zeta sizer to determine the surface charge and electrostatic stability of the droplets.

Evaluation of nanoemulgel

a) Organoleptic properties of nanoemulgel

The prepared nanoemulgel formulations were evaluated for their organoleptic properties, including appearance, color, odour, and texture, through visual inspection.

b) pH determination of nanoemulgel [21]

Approximately 1 g of nanoemulgel was dispersed in 10 ml of distilled water and allowed to stand for 2 h, after which the pH was measured at room temperature using a calibrated digital pH meter.

c) Viscosity of nanoemulgel [21]

Viscosity measurements were performed using a Brookfield viscometer fitted with an appropriate spindle (spindle no. 6) at 32.6 °C and 10 rpm.

d) Spreadability of nanoemulgel [21]

The spreadability was determined using the slip-and-drag method. Approximately 2 g of nanoemulgel was placed between two ground glass slides. A weight of 1 kg was applied for 5 min to ensure uniform thickness. The upper slide was pulled using a 70 g load, and the time required to move a distance of 7.5 cm was recorded for each sample. Spreadability was calculated using the following equation:

$$S = \frac{m \times l}{t}$$

e) Extrudability of nanoemulgel [22]

Extrudability was assessed by filling the nanoemulgel into collapsible aluminium tube. A 500 g weight was applied, and the amount of extruded gel was collected and weighed. Extrudability was expressed as the percentage of gel extrusion.

f) Drug content

The drug content was determined using UV–Visible spectrophotometry. For single-drug formulations, the drug content was calculated directly from calibration curves. For combination formulations, simultaneous estimation was performed at 280 nm

and 320 nm using absorptivity coefficients and Beer-Lambert's law. One g of nanoemulgel was dissolved in phosphate buffer (pH 7.4), sonicated, filtered, diluted, and analyzed spectrophotometrically. The percentage drug content was calculated based on theoretical drug loading.

g) *In vitro* anti-inflammatory activity

Protein denaturation assay [23]

The anti-inflammatory potential of the nanoemulgel formulations was evaluated using a protein denaturation method, with bovine serum albumin (BSA) as the protein model. A 5% w/v bovine serum albumin (BSA) solution was prepared in phosphate buffer (pH 6.3). The test formulations were diluted to 100–500 µg/ml, and a marketed indomethacin gel (Inmecin 1%, 100 µg/ml) was used as the reference standard. The percentage inhibition of protein denaturation was calculated as follows:

$$\%\text{Inhibition} = \frac{A_{\text{control}} - A_{\text{sample}}}{A_{\text{control}}} \times 100$$

Membrane stabilization assay (HRBC method) [24]

The membrane stabilization method was used to assess the ability of the formulations to protect human red blood cells (HRBCs) from haemolysis. Fresh blood was collected from a healthy volunteer, washed with isotonic saline, and a 10% v/v HRBC suspension was prepared using the blood. The percentage of haemolysis inhibition was calculated as follows:

$$\%\text{Inhibition} = 100 - \left(\frac{\text{OD}_{\text{sample}}}{\text{OD}_{\text{control}}} \times 100\right)$$

h) *In vitro* permeation study [19]

The drug release of the nanoemulgel formulations (F1–F5) and the marketed gel was evaluated using a Franz diffusion cell with a cellophane membrane. The receptor compartment contained phosphate buffer (pH 7.4) at 37 °C with stirring. One g of gel was applied to the donor side, and 1 ml samples were withdrawn at 15–480 min intervals, replaced with fresh buffer, and analyzed using UV spectrophotometry (320 nm for indomethacin and 280 nm for bromelain).

The cumulative drug permeation was plotted against the time. The flux (J) and permeation coefficient (Kp) were calculated as follows:

$$J = \frac{dQ}{dt} \times \frac{1}{A}, K_p = \frac{J}{C_d}$$

Where A diffusion area, and C_d is the initial drug concentration.

RESULTS AND DISCUSSION

Preformulation studies

Preformulation studies such as melting point determination, UV spectroscopic analysis, and construction of calibration curve were carried out using standard pharmacopeial procedures.

Melting point

The melting points were determined using the capillary method. The melting point of indomethacin was determined to be 162 °C.

Determination of λmax of indomethacin and bromelain

The λmax of Indomethacin and Bromelain was found to be 320 nm and 280 nm, respectively.

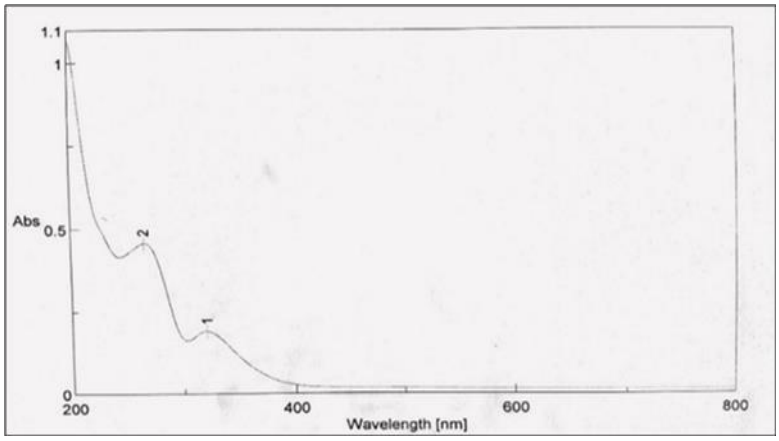

Fig. 1: λmax of indomethacin

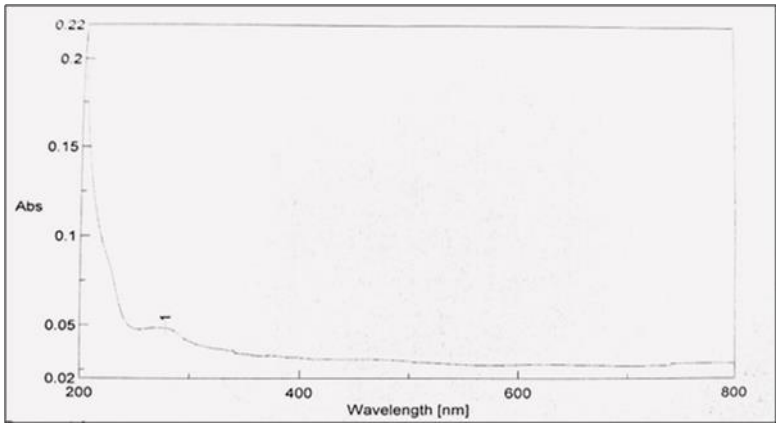

Fig. 2: λmax of bromelain

Calibration curves

For preparation of calibration curves, stock solutions (100 µg/ml) of indomethacin and bromelain were prepared using phosphate buffer pH 7.4. Aliquots were further diluted to obtain concentrations ranging from 5–25 µg/ml.

Solubility of drugs in different vehicles

Indomethacin showed maximum solubility in eucalyptus oil (253.32 mg/ml) and nirgundi oil (214.98 mg/ml), while bromelain exhibited higher solubility in eucalyptus oil (94.16 mg/ml).

Screening of surfactant and Co-surfactant

Surfactants were evaluated for their emulsification efficiency with the selected oil blend (eucalyptus and nirgundi oil) based on the ease of emulsification and the percentage transmittance at 440 nm. Tween 20 exhibited the highest transmittance (82.39%), followed closely by Tween 80 (81.82%).

Co-surfactants were screened in combination with Tween 20 and an oil blend. Propylene glycol exhibited the highest transmittance (94.23%), indicating superior emulsification with the selected surfactant and oil phase.

These results guided the choice of Tween 20 as the surfactant and propylene glycol as the co-surfactant for the nanoemulsion formulation.

Construction of pseudo-ternary phase diagram

Analysis of the pseudo-ternary phase diagrams indicated that a Smix ratio of 1:1 (Tween 20: Propylene glycol) provided the largest nanoemulsion region, reflecting superior emulsification efficiency and stability of the nanoemulsion. Therefore, this ratio, along with the selected oil blend, was chosen as the optimal composition for further nanoemulsion and nanoemulgel formulation.

Drug-excipients compatibility studies

Fourier transformed infrared (FT-IR) spectroscopic analysis (FTIR)

The FTIR spectrum of indomethacin exhibited characteristic peaks corresponding to the C–Cl, C–N, C–O, N–H, and O–H functional groups, confirming its structural integrity.

The FTIR spectrum of bromelain showed characteristic peaks corresponding to the N–H, C–H, C–O, and C=C functional groups, confirming its proteinaceous structure.

The FTIR spectrum of the physical mixture exhibited all the major characteristic peaks of indomethacin and bromelain, confirming their compatibility.

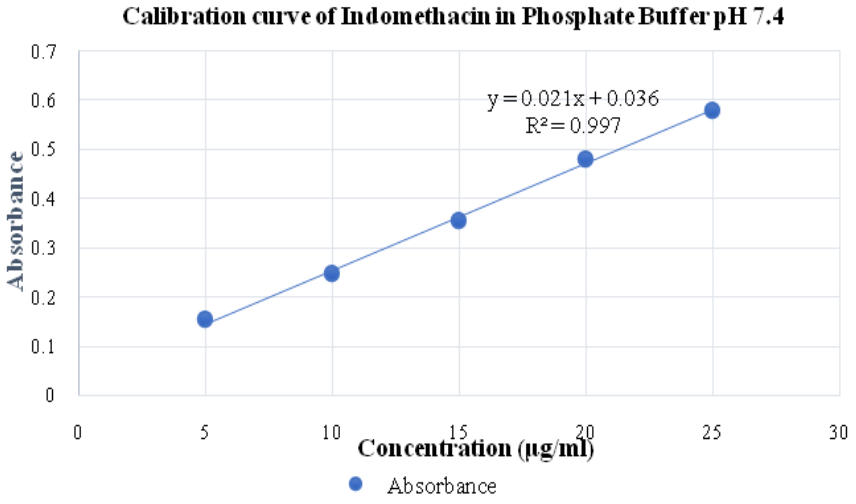

Fig. 3: Calibration curve of indomethacin

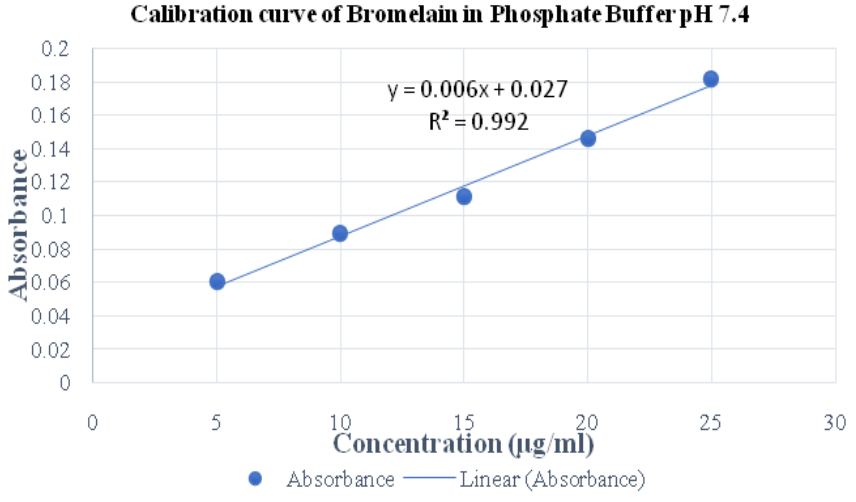

Fig. 4: Calibration curve of bromelain

Table 2: Solubility of indomethacin and bromelain in various vehicles

S. No.	Vehicle	Solubility of indomethacin (mg/ml)	Solubility of bromelain (mg/ml)
1.	Eucalyptus	253.32	94.16
2.	Nirgundi	214.98	32.75
3.	Sesame	82.90	22
4.	Karanja	111.24	14.5
5.	Tween 20	126.27	8.35
6.	Tween 40	65.622	2.43
7.	Tween 60	62.34	2.55
8.	Tween 80	108.90	12.35
9.	Span 20	5.06	15.86
10.	Span 80	19.72	11.33
11.	PEG 200	30.82	0.31
12.	PEG 400	23.36	0.633
13.	PEG 600	91.42	0.25
14.	Propylene glycol	102.44	17.13
15.	Isopropyl alcohol	31.65	0.06
16.	Oleic acid	6.03	26.7

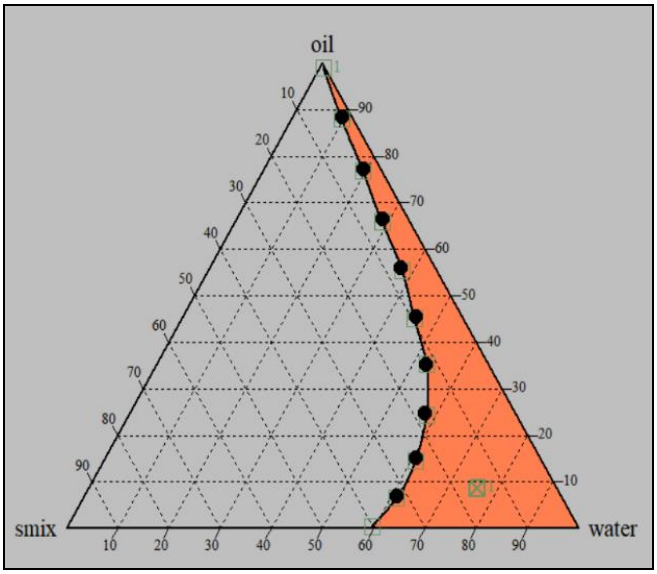

Fig. 5: Pseudo ternary phase diagram 1:1 ratio

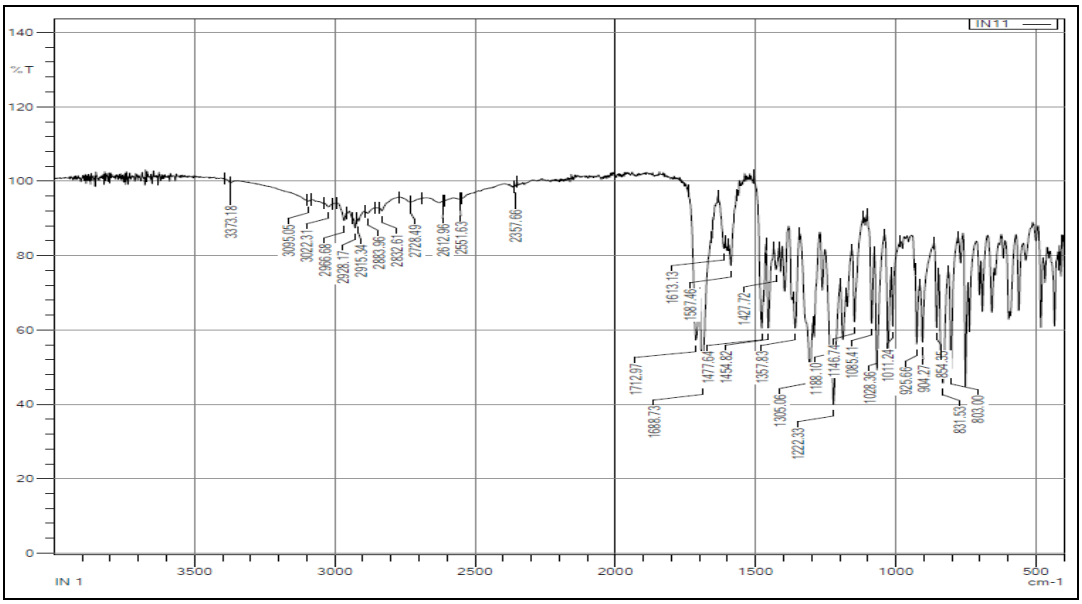

Fig. 6: FTIR spectra of Indomethacin

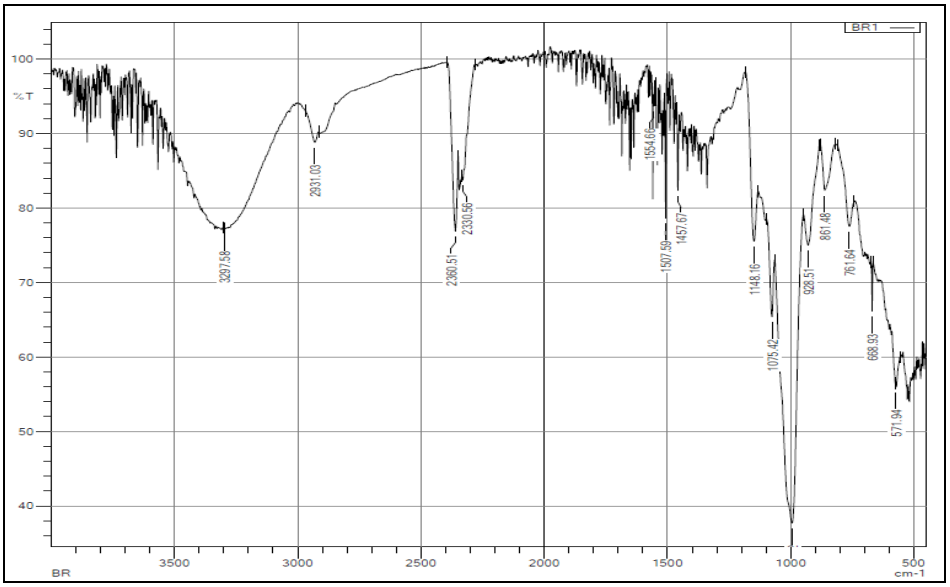

Fig. 7: FTIR spectra of bromelain

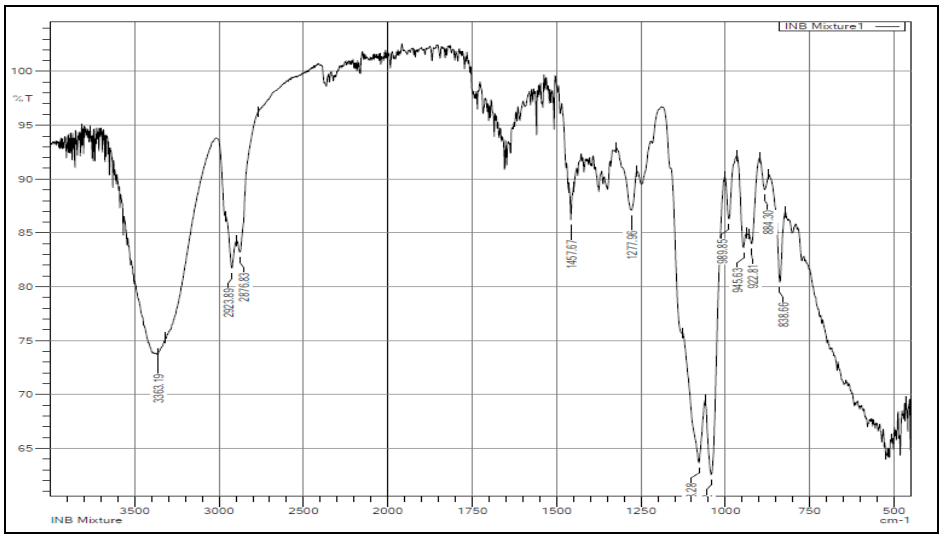

Fig. 8: FTIR spectra of physical mixture

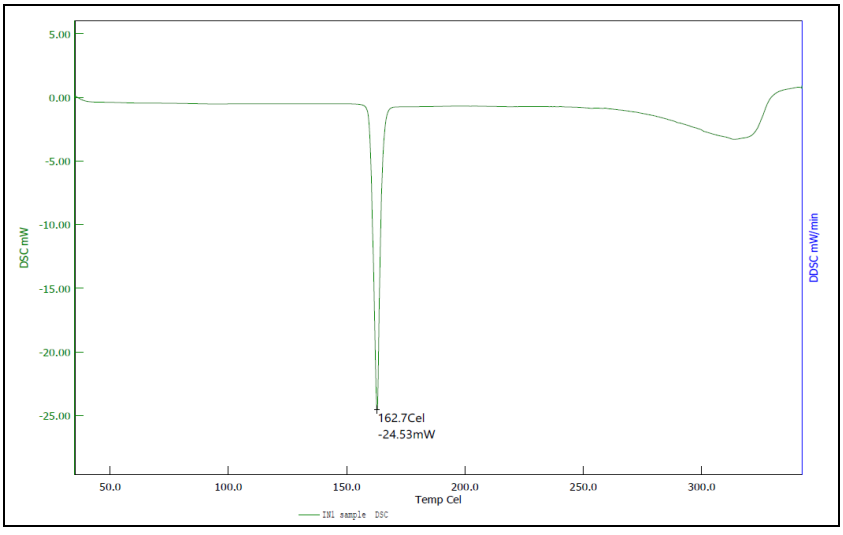

Fig. 9: DSC of indomethacin

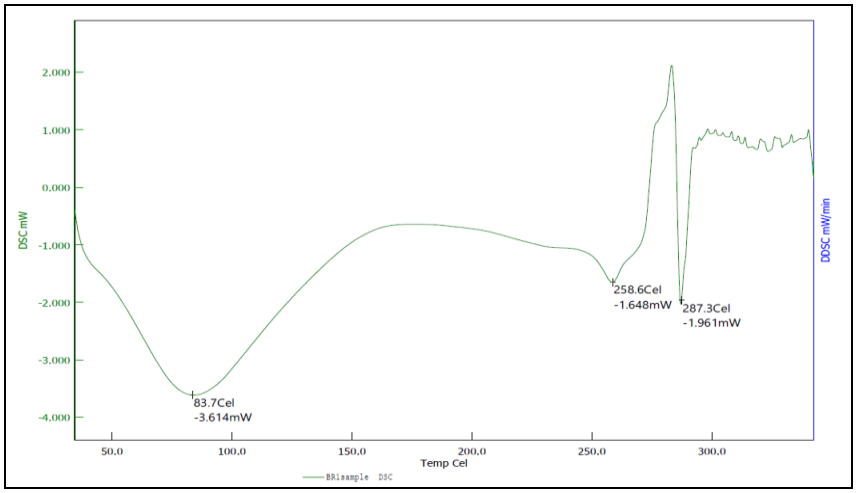

Fig. 10: DSC of bromelain

Differential scanning calorimetry (DSC)

The DSC thermogram of indomethacin showed a sharp endothermic peak at 162.7 °C corresponding to its melting point, confirming its crystalline nature. The DSC thermogram of bromelain exhibited a broad endothermic transition rather than a sharp melting peak, which is characteristic of protein denaturation rather than melting.

Molecular docking study

The binding energies (kcal/mol) represent the stability and strength of the interaction between a drug and a receptor. The docking results suggest that Indomethacin has strong interactions with COX-2 and TNF-α, indicating its potential for anti-inflammatory activity through the inhibition of these key mediators. A similar analysis was performed for bromelain, confirming its complementary binding interactions with the inflammatory target COX-2 (table 3). These results support the rationale for combining both drugs in a nanoemulgel formulation for synergistic localized anti-inflammatory effects.

Evaluation of nanoemulsion and nanoemulgel

Evaluation of nanoemulsion

a) pH

The pH values ranged from 5.60 to 5.97, which is within the acceptable topical range (5.5–7.0) (table 4).

b) Droplet size, PDI, and zeta potential

The mean globule size ranged from 119.6 nm to 189.4 nm, with a PDI between 0.462 and 0.753, indicating a nanoscale and moderately uniform distribution of globules.

Zeta potential ranged from –12.0 to –19.2 mV, suggesting good stability (table 4)

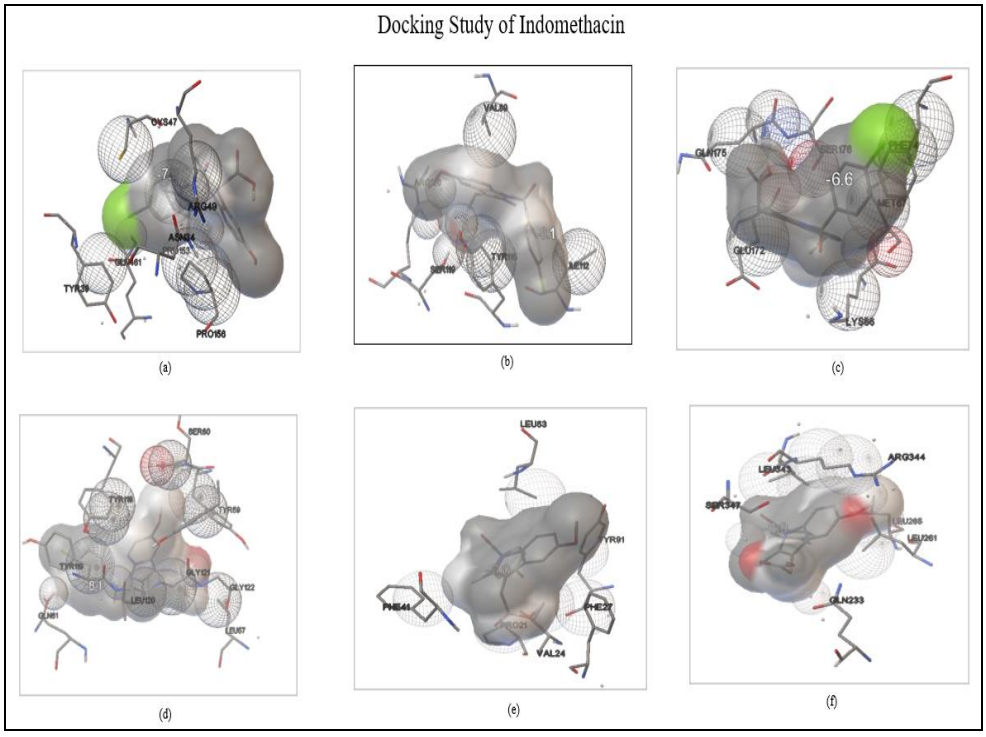

Fig. 11: Docking study of Indomethacin with (a) COX1; (b) COX2; (c) IL 6 (d) TNF Alpha; (e) Phospholipase A2; (f) Phospholipase D2

Table 3: Binding energy of indomethacin and bromelain with receptors

S. No.	Receptor	Binding energy (kcal/mol)	Binding energy affinity (kcal/mol)
1	COX-1	-7.7	-7.7
2	COX-2	-8.1	-8.6
3	TNF-α	-8.1	-8.0
4	IL-6	-6.6	-7.1
5	Phospholipase A2	-8.0	-7.2
6	Phospholipase D2	-6.9	-8.1

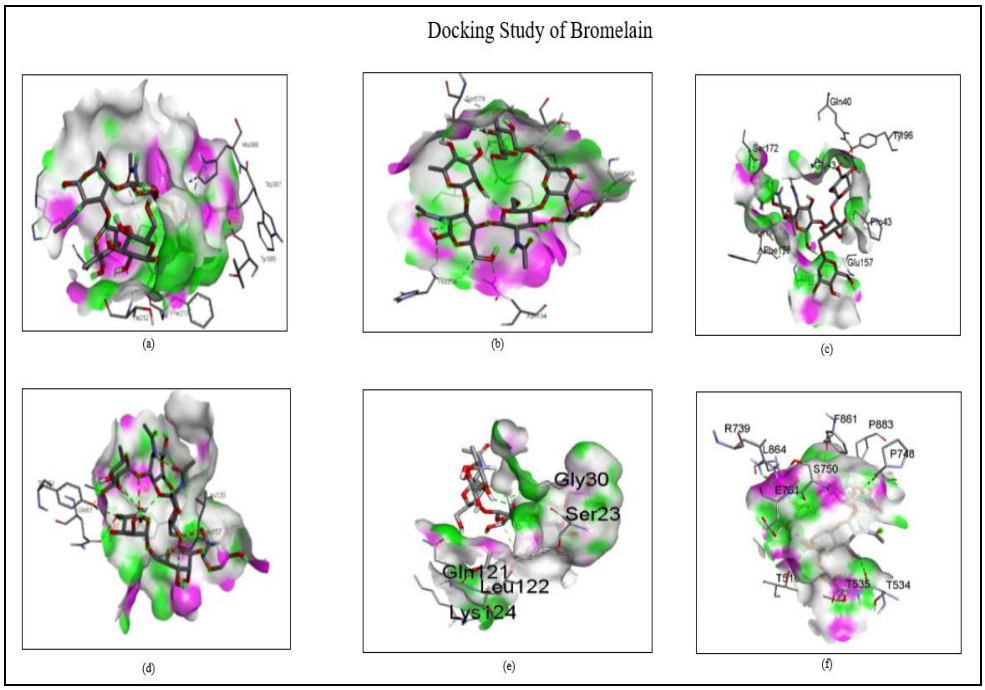

Fig. 12: Docking study of Bromelain with (a) COX1; (b) COX2; (c) IL 6 (d) TNF Alpha; (e) Phospholipase A2; (f) Phospholipase D2

Table 4: Physicochemical properties of nanoemulsion (F1–F5)

Formulation	pH	Mean globule size (nm)	PDI	Zeta potential (mV)
F1	5.85	119.6	0.753	-13.5
F2	5.60	189.4	0.738	-19.2
F3	5.94	154.0	0.462	-12.0
F4	6.01	182.9	0.466	-16.7
F5	5.97	146.6	0.553	-15.4

Evaluation of nanoemulgel

a) pH

The pH ranged from 6.50 to 6.73, which is within the acceptable range for topical formulation (table 5).

b) Viscosity

The viscosity ranged from 21,355 to 21,392 mPa·s, ensuring good skin adherence and ease of application (table 5).

c) Spreadability

The spreadability values ranged from 33.01 to 39.32 g·cm/sec, indicating acceptable spreading characteristics for the formulations (table 5).

d) Extrudability

All formulations exhibited satisfactory extrudability, ranging from 61.00% to 74.81%, indicating easy dispensing from the container (table 5).

Table 5: pH, viscosity, spreadability and extrudability of nanoemulgel (F1–F5)

Formulation	pH	Viscosity (mPa·s)	Spreadability (g·cm/sec)	% Extrudability
F1	6.53	21,359	35.00	63.37
F2	6.50	21,355	37.23	65.02
F3	6.55	21,361	34.32	74.81
F4	6.65	21,369	33.01	73.00
F5	6.73	21,392	36.45	72.64

e) Drug content

Table 6: % Drug content of nanoemulgel (F1–F5)

Formulation	% Indomethacin	% Bromelain
F1	90.0	-
F2	86.8	91.1
F3	95.0	93.0
F4	92.86	93.0
F5	-	89.6

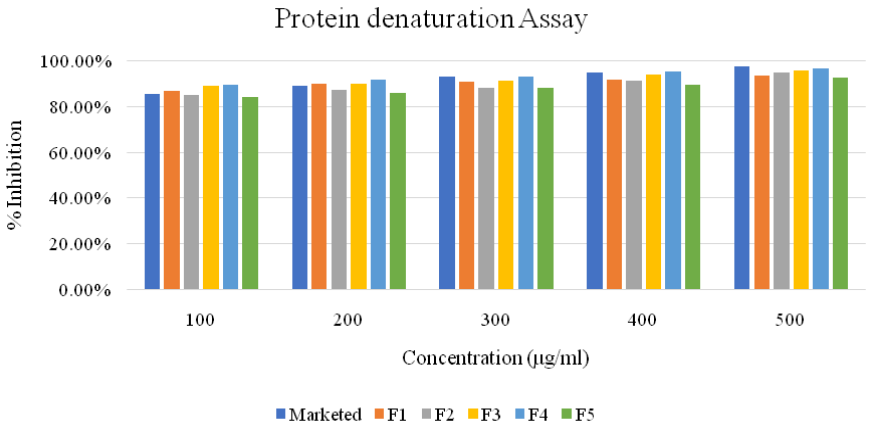

Fig. 13: Graph showing % inhibition for protein denaturation assay

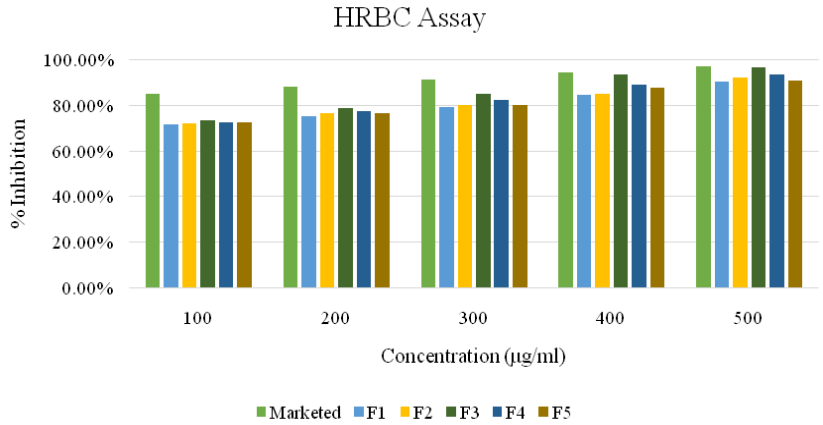

Fig. 14: Graph showing % inhibition for HRBC assay

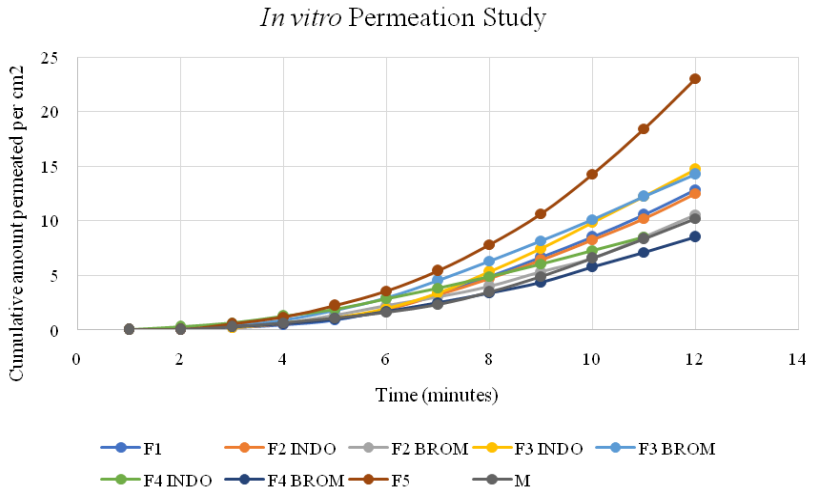

Fig. 15: *In vitro* permeation study

f) Anti-inflammatory activity

Protein denaturation assay

All formulations showed concentration-dependent inhibition of protein denaturation. F4 exhibited the highest inhibition (96.51% at 500 µg/ml), comparable to the marketed gel (97.23%).

Membrane stabilization assay (HRBC method)

The formulations also showed concentration-dependent membrane stabilization. F3 (96.49% at 500 µg/ml) was most effective, approaching the marketed formulation (97.11%).

g) *In vitro* permeation study

Franz diffusion cell studies have demonstrated efficient transdermal drug delivery. The cumulative drug permeation increased over time for all the formulations (table 16). Flux (J) and permeation coefficients (Kp) were high, indicating enhanced skin penetration and potential for localized therapy.

CONCLUSION

In the present study, we successfully formulated and evaluated a topical nanoemulgel containing Indomethacin and Bromelain for localized anti-inflammatory therapy. Preformulation and compatibility studies confirmed the stability of both drugs with the selected excipients. The nanoemulgel formulations demonstrated desirable physicochemical properties, including appropriate globule size, PDI, pH, viscosity, spreadability, and extrudability. Among all formulations, F3 emerged as the most optimized, exhibiting the highest drug content for both actives, effective dual-drug permeation, and a sustained release profile. *In vitro* anti-inflammatory assays, including HRBC membrane stabilization and protein denaturation, confirmed significant activity comparable to that of the marketed indomethacin gel, likely due to the synergistic action of Indomethacin and Bromelain. Molecular docking studies further supported this synergistic potential by demonstrating the strong binding affinities of both drugs toward key inflammatory targets such as COX-2 and TNF-α. Overall, F3 offers a stable, effective topical formulation with enhanced therapeutic potential for the localized management of arthritis, providing a promising alternative to conventional topical therapies.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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