Formulation, Development & Evaluation Of A Bromelain Based Topical Hydrogel Patch

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Abstract:Background:

Inflammation is a common response to tissue injury, infection, and various skin disorders. Conventional topical formulations such as creams and ointments often exhibit poor residence time on the skin, resulting in reduced therapeutic efficacy and the need for frequent application. Bromelain, a proteolytic enzyme obtained from pineapple (Ananas comosus), possesses significant anti-inflammatory, wound-healing, and burn-healing properties, making it a promising candidate for topical drug delivery. The present study aimed to formulate and develop a bromelain-based hydrogel patch to enhance localized drug delivery and improve patient compliance.The hydrogel patch was prepared by the solvent casting method using Hydroxypropyl Methylcellulose (HPMC) and Polyvinyl Alcohol (PVA) as polymeric bases. Pre formulation studies included physicochemical evaluation, solubility studies, FTIR compatibility studies, and UV spectroscopic analysis. The prepared patches were evaluated for organoleptic properties, drug content, folding endurance, tensile strength, thickness, surface pH, swelling index, weight uniformity, moisture content, in vitro drug release, and in vitro anti-inflammatory activity.The developed hydrogel patch showed satisfactory physicochemical characteristics, good mechanical strength, uniform drug distribution, appropriate surface pH, and satisfactory swelling behavior. The optimized formulation exhibited good stability, sustained drug release, and promising anti-inflammatory activity, indicating its potential as an effective topical drug delivery system.The study concludes that the bromelain-based hydrogel patch formulated with HPMC and PVA offers a promising alternative to conventional topical dosage forms for the management of inflammation and burn wounds by improving drug residence time and therapeutic effectiveness.

Keywords: Bromelain, Hydrogel Patch, Anti-inflammatory, HPMC, PVA, Topical Drug Delivery, Solvent Casting.

How to cite this article: Dewe.M. Nandurkar, VijayaV. Rokde, Vaibhav .S. Waghmare, HarM.patil, Chinmay.V. Joshi,. Formulation, Development & Evaluation Of A Bromelain Based Topical Hydrogel Patch. Int J Drug Deliv Technol. 2026;16(79s):594-599. DOI: 10.25258/ijddt.16.79s.112.

Bromelain:

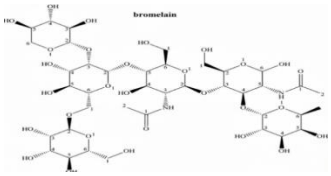

Fig 1 : Structure of bromelain

Bromelain is a proteolytic enzymes obtained from the stem and fruit of the pineapple plant (Ananas comosus). It has strong biological activity and is widely used in medicine due to its anti-inflammatory, analgesic, anti-edematous, fibrinolytic, and wound-healing properties. Bromelain is water-soluble, stable in a wide pH range, and is well-tolerated when used externally or internally. Bromelain works mainly by breaking down inflammatory mediators, reducing swelling, and improving circulation in inflamed tissues. Because of these properties, bromelain has gained significant interest as a natural alternative to synthetic anti-inflammatory drugs.[4]

1. Introduction:

Topical anti-inflammatory therapy is one of the most preferred approaches for managing localized skin inflammation because it ensures direct delivery of therapeutic agents to the affected site while minimizing systemic side effects. Conventional topical formulations such as gels, ointments, and creams often suffer from drawbacks including poor residence time on the skin, rapid removal due to sweat and friction, limited absorption, and inability to provide controlled or sustained drug release. These limitations reduce the therapeutic efficiency of natural biomolecules like enzymes, which are sensitive to environmental conditions. [5]

2.Material & Methods:

Bromelain: Bromelain used as the active pharmaceutical ingredient was procured from Shriji Exbiz Pvt. Ltd., India. It was utilized for the formulation of the hydrogel patch owing to its well-documented anti-inflammatory, proteolytic, and wound-healing properties

Excipients and Instruments:

HPMC and PVA were used as polymeric excipients, while glycerol, PEG 400, DMSO, phosphate buffer solution, and other analytical-grade chemicals were used as received. The study utilized a digital weighing balance, magnetic stirrer, pH meter, UV–Visible spectrophotometer, FTIR spectrophotometer, water .

Table: 1 List of ingredients used in formulation patch

Material	Function	control	Bromelain loaded
Bromelain	Active ingrediant	-	10
PVA	Backing polymer	2.50	2.50
PEG400	plasticizer	10	10
HPMC	Gel base	5	5
DMSO	Penetration enhancer	3	3
Water	solvent	100g	100g

2.1 Physiochemical evaluation

The bromelain was procured and evaluated for its physicochemical properties according to standard procedures reported in the literature.

1.Solubility studies: The solubility of bromelain was determined in different solvents such as phosphate buffer solutions of various pH, HPMC solution, PVA solution, ethanol, and distilled water. Excess bromelain was added to each solvent and stirred until equilibrium was reached

2 pH: The pH of the bromelain solution was determined after stirring for 5 minutes using a digital pH meter. The pH meter was calibrated to neutral before immersing the electrode into the solution. Measurements were carried out in triplicate.

3.Investigation of sample by FTIR:

A sample of bromelain was subjected to Fourier Transform Infrared (FTIR) spectroscopy to evaluate its characteristic functional groups as per standard procedures reported in the literature.

4.Drug polymer interaction studies:

Drug polymer interaction studies were carried out to assess the compatibility of bromelain with the polymers PVA and HPMC. The physical mixtures of bromelain with PVA and HPMC were analyzed using FTIR spectroscopy to detect any possible interaction or shift in characteristic functional groups. The results were evaluated to confirm the compatibility of the drug with the selected polymers for hydrogel formulation.

5.TLC of bromelain:

Thin Layer Chromatography (TLC) of bromelain was performed to assess its purity and homogeneity. The sample was spotted on a silica gel TLC plate and developed using a suitable solvent system. After development, the plate was visualized, and the Rf values were determined. The results were used to confirm the purity and homogeneity of bromelain.

6.UV spectroscopy and calibration curve of bromelain:

The UV absorption spectrum of bromelain was recorded using a UV–Visible spectrophotometer at a suitable(280nm) wavelength. A series of standard bromelain solutions were prepared in an appropriate solvent, and their absorbance was measured. A calibration curve was constructed by plotting absorbance against concentration to establish the linearity of bromelain for quantitative analysis.

2.2 Formulation of Drug-Loaded Hydrogel Patch

The drug-loaded hydrogel patch was prepared by first accurately weighing all the required ingredients, including bromelain, polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), polyethylene glycol 400 (PEG 400), dimethyl sulfoxide (DMSO), and distilled water using a digital balance. PVA (2.5 g) was dissolved in hot distilled water with continuous stirring until a clear solution was obtained, while HPMC (5 g) was separately dispersed in hot distilled water to form a smooth gel base. The two polymer solutions were then mixed thoroughly with continuous stirring to obtain a uniform polymer matrix. Bromelain was dissolved in a suitable quantity of distilled water or ethanol and incorporated gradually into the polymer mixture with constant stirring. Subsequently, PEG 400 (10 g) was added as a plasticizer, followed by DMSO (3 g) as a penetration enhancer. The resulting mixture was stirred using a magnetic stirrer for 20–30 minutes until a homogeneous hydrogel solution was obtained, which was then used for the preparation of the drug-loaded hydrogel patch.

2.3 characterization of patch

1. Organoleptic Test Results

The prepared patches were evaluated for their organoleptic properties such as color, odor, and overall appearance. The formulations showed uniform texture and smooth surface without any visible defects. The results indicated good aesthetic and physical acceptability for topical application.

2. Drug Content Estimation of Patches

Drug content was determined by dissolving a known area of patch in a suitable solvent followed by spectrophotometric analysis. The results confirmed uniform distribution of bromelain within the polymer matrix. The drug content was found to be within acceptable limits.

3. Folding Endurance

Folding endurance was assessed by repeatedly folding the patch at the same point until it cracked or broke. The number of folds required to break the patch was recorded. The results indicated good flexibility and handling properties.

4. Tensile Strength

Tensile strength was measured using a tensile strength apparatus by applying force until the patch broke. The formulation showed adequate mechanical strength suitable for application

and handling. This ensured durability of the patch during use.

5. Thickness

The thickness of the patches was measured at different points using a Thickness tester. Uniform thickness was observed across all formulations. This uniformity ensures consistency in drug delivery.

6. pH Determination

The pH of the patches was measured using a calibrated digital pH meter. The patches showed a skin-compatible pH, indicating suitability for topical application. This minimizes the risk of skin irritation.

7. Swelling Index

The swelling index was determined by measuring the weight gain of the patch after immersion in buffer solution. The patches showed good swelling behavior, indicating proper hydration ability. This property supports controlled drug release.

8. Weight Uniformity

Individual patches were weighed to assess weight variation among formulations. The results showed minimal variation, confirming uniform preparation. This ensures dose consistency in each patch.

9. Moisture Content

Moisture content was evaluated by drying the patches and measuring weight loss. The formulations showed acceptable moisture levels ensuring stability. Proper moisture control helps in preventing microbial growth and degradation.

10. Drug Release Study

In vitro drug release was performed using a suitable dissolution medium over a specified time period. At predetermined intervals, samples were withdrawn and analyzed spectrophotometrically by measuring absorbance. The absorbance values were converted into drug concentration using to determine the percentage drug release. The results indicated a sustained and controlled release of bromelain from the patches.

11. In Vitro Evaluation of Anti-inflammatory Activity

The anti-inflammatory activity of bromelain was evaluated using the inhibition of albumin denaturation assay. Bromelain solutions of different concentrations were incubated with albumin solution under controlled conditions. The degree of protein denaturation was measured spectrophotometrically and compared with control. The results demonstrated significant anti-inflammatory potential of bromelain.

3. Results & Discussion

3.1. Table 2 : physiochemical evaluation of bromelain

Parameter	observation
Physical appearance	White amorphus powder
Nature	Hygroscopic
Solubility in water	Freely soluble
Flow properties	Free flowing in dry form
odour	Faint characteristic odour

Table 3:Solubility of bromelain in different media

Medium	Observation	Solubility Interpretation
Distilled water	Clear solution obtained after gentle stirring	Freely soluble
Phosphate buffer pH 5.5	Clear solution	Freely soluble
Phosphate buffer pH 6.8	Clear solution	Freely soluble
Phosphate buffer pH 7.4	Clear solution	Soluble
HPMC solution (2% w/v)	Clear and uniform solution	Soluble
PVA solution (10% w/v)	Slight turbidity after standing	Moderately soluble
ethanol	opalence observed	Moderately soluble

3.3 drug polymer interaction studies

The following are the FTIR graphs indicating there is no incompatibility between bromelain HPMC and other excipients.

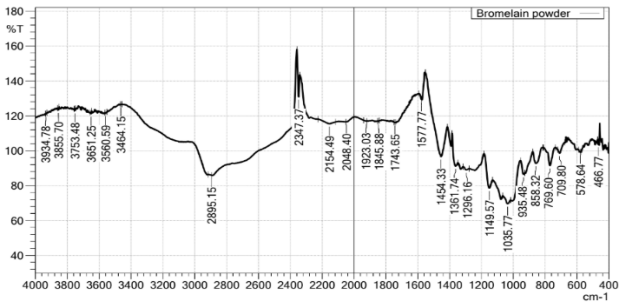

Fig 2: Bromelain + HPMC

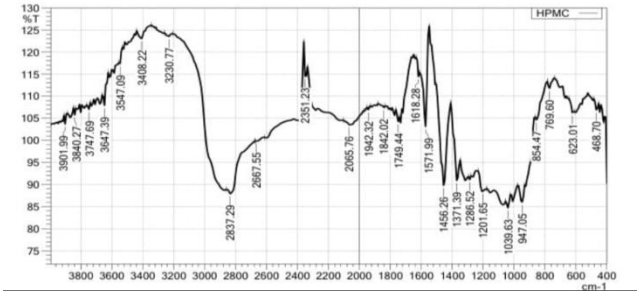

Fig 3:Bromelain+PVA+HPMC+DMSO+PEG400

3.4 construction of calibration curve of bromelain:

Standard Stock Solution I (1 mg/ml): 100 mg of accurately weighed Bromelain was transferred into a 100 ml volumetric flask. The drug was dissolved and the volume was made up to the mark using pH 6.2 Phosphate Buffer. Standard Stock Solution II (100 µg/ml): 10 ml of Stock Solution I was pipetted into another 100 ml volumetric flask and diluted to the mark with pH 6.2 Phosphate Buffer.

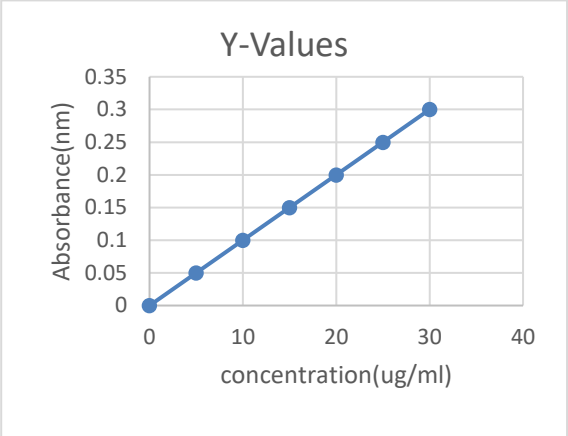

Fig 4 : caliberation curve

3.5. *table 4: evaluation of patch*

Evaluation Parameter	Control Patch	F1 (Bromelain Patch)
Color	Transparent	Whitish (slightly opaque)
Odor	Odorless	Odorless
Texture	Smooth	Smooth
Flexibility	Highly flexible	Flexible
Surface Appearance	Clear, glossy, uniform film	Uniform, slightly matte surface
Homogeneity	Uniform	Uniform distribution

3.6 Drug content estimation of bromelain hydrogel patches:

The percentage drug content in the prepared transdermal patches was found to be in the range of 9.80% to 10.12% w/w with slight variation, This level of drug loading is suitable for topical anti-inflammatory therapy

.3.7 Folding indurance:

The bromelain hydrogel patch showed satisfactory Avg. folding endurance of 251.3 folds, indicating good flexibility and resistance to repeated mechanical stress

3.8 *Tensile streangth:*

The average tensile strength of the prepared hydrogel patches was found to be 1.81 N/cm², indicating satisfactory mechanical strength and flexibility.

3.9 *Thickness measurement:*

The thickness of hydrogel patches (F1, F2, F3) was measured at three different The thickness was found to be in the range of 1.29–1.31 mm, indicating uniformity in formulation."

3.10 pH:

The pH of the bromelain hydrogel patch was found to be 6.58 ± 0.01, which is within the normal skin pH range of 4.5 to 6.5. This shows that the formulation is suitable for skin application and is unlikely to cause irritation. The very small standard deviation indicates that the results are consistent and reliable. This pH also helps in maintaining the stability and activity of bromelain in the hydrogel.

3.11 *Swelling index*

The swelling index of the bromelain hydrogel patch increased progressively with time and reached near-equilibrium at around 120 minutes.

The bromelain-based hydrogel patch showed good swelling behavior with effective water

3.12 *Weight uniformity*

The prepared hydrogel patches (F1, F2, F3) showed good weight uniformity

All formulations fall within the acceptable range of 1.5 g – 2.0 g, indicating consistent casting and uniform distribution of polymer matrix.

3.13 *Moisture content*

The prepared hydrogel patches (F1, F2, F3) showed moisture content in the range of 72.50% to 77.14%, which lies within the acceptable range of 70–80%.

3.14 drug release study of bromelain hydrogel patch

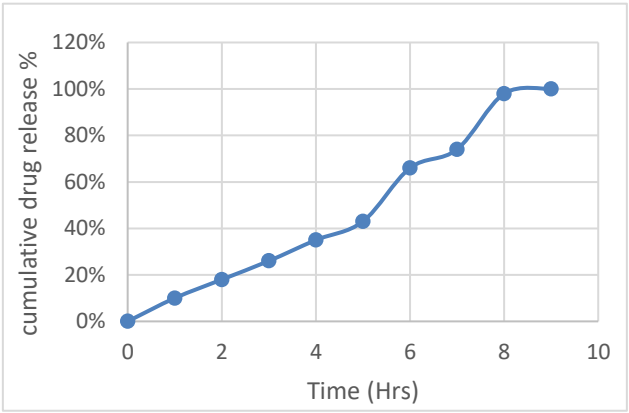

Fig:5 Release of drug from hydrogel patch over time

3.12 in-virto evaluation of anti-inflammatory activity

Material Required :

Bromelain (2400 GDU) powder ,Diclofenac sodium (standard) ,Egg albumin , Phosphate buffer (pH 6.4– 6.5) , Distilled water ,Test tubes ,Pipettes ,Water bath, Incubator

Instrument used :

UV-Visible, Spectrophotometer used for measuring absorbance of sample

Procedure :

Different concentrations of bromelain and standard diclofenac sodium were prepared and added to albumin solution to evaluate their anti-inflammatory activity by inhibition of protein denaturation. A control was maintained without any drug. All solutions were prepared using distilled water and phosphate buffer (pH 6.4–6.5)

Solution 1 : Standard diclofenac solution

Solution 2 : 1gm of albumin is dissolve in 100 ml water

Solution 3 : 10mg of bromelain is dissolved in 10gm of phosphate buffer

preparation of reaction mixture :

Different concentrations of bromelain and a standard drug (diclofenac sodium) were added to albumin solution to study their ability to inhibit protein denaturation. A control without drug was maintained for comparison.

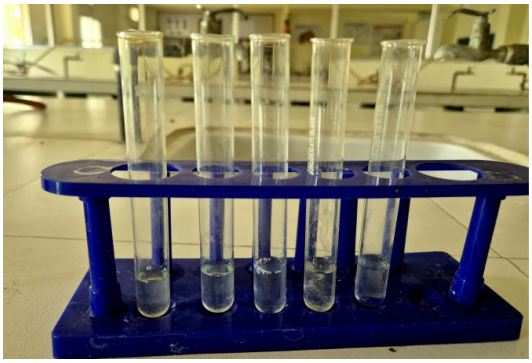

fig :6 test sample test tubes 1 to 5

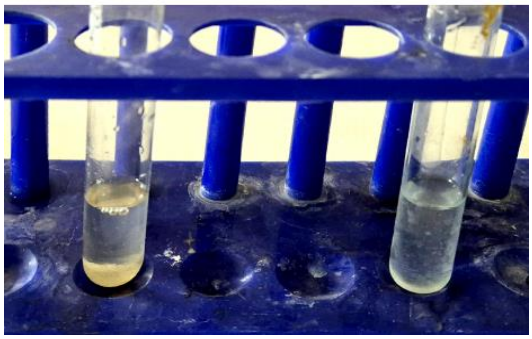

fig:7 standard (left) & control(right) (6 &7)

table 5 : composition of reaction mixture

S.N	Test tube	Albumin (ml)	Bromelain(ml)	Diclofenac(ml)	Buffer (ml)	Total vol.
1	Test 1	0.5	0.50	-	2.00	3ml
2	Test 2	0.5	0.25	-	2.25	3ml
3	Test 3	0.5	0.125	-	2.375	3ml
4	Test 4	0.5	0.0625	-	2.4375	3ml
5	Test 5	0.5	0.03125	-	2.46875	3ml
6	standard	0.5	-	0.5	2.0	3ml
7	control	0.5	-	-	2.5	3ml

:

1l reaction mixtures were adjusted to pH 6.5 using phosphate buffer to provide suitable conditions for the reaction.

Incubation

The test tubes were incubated at 37°C for 15–20 minutes to allow proper interaction between albumin and bromelain/standard drug.

This step ensures that the test sample and standard drug bind or interact with the protein (albumin) before denaturation occurs, which is necessary to observe their protective (anti-inflammatory)effect

Induction of denaturation:

After incubation, the samples were heated at 70°C for 5 minutes in a water bath to induce denaturation of albumin. The test tubes were removed and allowed to cool to room temperature.

Measurement of Absorbance:

The turbidity formed due to protein denaturation was measured as absorbance using a UV-Visible spectrophotometer at 660 nm The absorbance of each sample is measured at a specific wavelength (commonly around 660 nm) against a blank solution. The control sample, which contains denatured protein without any test drug, shows maximum absorbance due to maximum turbidity. In the presence of anti-inflammatory agents such as bromelain, the denaturation of protein is inhibited, resulting in lower turbidity and hence lower absorbance values.

Table:6 Absorbance and Percentage Inhibition of Protein Denaturation by Bromelain

Tube type	**Absorbance**	**Percentage inhibition**
Control	0.260	-
Standard	0.091	65%
Test 1 (highest conc.)	0.080	69%
Test 2	0.090	65%
Test 3	0.105	60%
Test 4	0.120	54%
Test 5 (lowest bromelain conc.)	0.140	46%

Percentage Denaturation:

$$= \frac{\text{Absorbance of control} - \text{Absorbace of sample}}{\text{Absorbance of control}}$$

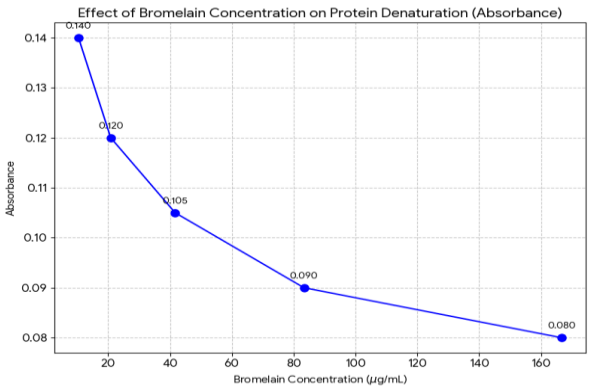

Fig 8 :effect of bomelain concentation on protein denaturation

Bromelain showed concentration-dependent anti-inflammatory activity, reaching 69% inhibition at its highest concentration—outperforming the standard drug (65%).

3.conclusion:

The present study successfully formulated and evaluated a bromelain-loaded hydrogel patch showing optimal physicochemical, mechanical, and swelling properties. In vitro evaluations demonstrated sustained drug release and significant concentration-dependent anti-inflammatory activity, outperforming the standard drug at higher concentrations. Overall, the hydrogel patch serves as a promising topical drug delivery system for localized anti-inflammatory therapy and wound management, though further studies are warranted to confirm clinical efficacy and safety..

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