Formulation and Evaluation of sodium alginate based wound healing films with Diclofenac sodium

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***Abstract*—In order to improve healing efficacy, the current study is to create and assess wound healing films based on sodium alginate that are combined with diclofenac sodium and additional bioactive substances. Sodium alginate, a naturally occurring biopolymer with moisture- retentive and biocompatible qualities, was mixed with hydroxypropyl methylcellulose (HPMC) to increase mechanical strength and film-forming capacity. To lessen discomfort and inflammation at the wound site, diclofenac sodium, a non-steroidal anti-inflammatory medicine (NSAID), was used. To stop infection and encourage healing, zinc oxide—known for its antibacterial and tissue-regeneration qualities—was added. Glycerin and polyethylene glycol (PEG) were employed as plasticisers to increase skin adhesion and flexibility. The films' physical characteristics, drug release behaviour, antibacterial activity, and capacity for wound healing were assessed after they were made using the solvent casting process. The formulation is a viable option for efficient wound care because of the synergistic effect of the bioactive components, which provided anti-inflammatory, antibacterial, and tissue- regenerative properties.**

***Index Terms*—Anti-bacterial, Anti-inflammatory, Tissue Regeneration, Solvent Casting, Bioadhesive,Skin Permeation, Topical Diclofenac, Fabrication.**

I. INTRODUCTION

For a number of reasons, including avoiding first-pass metabolism, lowering the risk of systemic side effects, and enabling direct distribution over the target locations, topical administration of medications
can be a viable substitute for oral delivery. Not only should topical formulations be simple and safe to apply, but they must also be able to penetrate the skin and reach the target locations in large enough quantities to have a therapeutic impact. In both acute and chronic painful diseases, topical analgesics are frequently used to treat pain by delivering non-steroidal anti-inflammatory medicines (NSAIDs) including acetylsalicylic acid, diclofenac, and ibuprofen straight to the site of damage**.**

They can be especially helpful a chronic condition was taking oral NSAIDs on a regular basis to manage painful flare-ups may be linked to systemic adverse events. This is especially true for older people who are more likely to experience adverse events.

According to several international standards, topical NSAIDs are advised before oral NSAIDs they have been shown to be just as effective and better tolerated than oral NSAIDs.

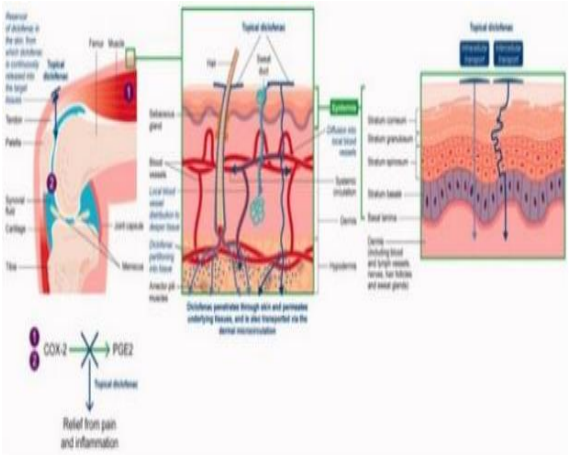
Topical NSAIDs must act at the right location of action in order to effectively treat pain. Both the activation of central pain-processing pathways and peripheral variables (e.g., damaged structures impinging on other local structures) seem to affect how pain is perceived. Furthermore, has an inflammatory component, as evidenced by the activation and production of local proinflammatory mediators like prostaglandins or cytokines.

Using diclofenac as a specific example, the current analysis examines the general factors that affect topical medication efficacy. Issues with skin penetration and tissue permeation, as well as the concentrations attained in and around the articular joint and in plasma in published research, are among the factors discussed. We selected diclofenac because, according to analysis, it is the most effective COX-2 inhibitor when compared to other widely used NSAIDS.

Topical medications' routes of action to target tissues:

The capacity of a topical medication to penetrate skin and reach the target tissues determines how well it works to reduce pain and inflammation. According to some theories, topical NSAIDs work locally at the structures surrounding superficial joints like the knee or hand as well as inside the joint itself.
They also need to accumulate to a concentration in those regions that is adequate to inhibit the COX enzymes**.**
Drugs taken orally must first enter the bloodstream and then be distributed to the peripheral tissues. Instead, topical medications work pharmacologically by penetrating the stratum corneum and entering the skin's lower layers, .

Figure 1. Penetration of topical diclofenac through the skin and permeation through the deeper layers to the inflamed joint.



II. MATERIALS AND METHODS

Materials Used in Wound Healing Films
- Binders
- Microcrystalline cellulose
- Hydroxypropyl Methyl Cellulose
Role: Improves texture and stability
- Lubricants
- Polyethylene glycol
- Polyalkyline glycol
Role: Accelerates wound healing by forming a protective barrier
- Protective Agents
- Zinc oxide
- Petrolatum
Role: Soothing, calming, and enhancing healing
- Humectants
- Glycerine
- Sorbitol
Role: Maintains moisture levels
- Film Forming Agents-
Sodium alginate
Role: Improves adhesion between surface and film

Methods:
Casting or preparation techniques that directly affect the film properties are necessary for the fabrication of PFs [47]. These methods are distinct and customized for particular polymers and use cases [48].
1. salt leaching,
2. spin coating,
3. microfluidic spinning,
4.3D printing, and
5.solvent casting**.**
Salt Leaching Method:
By preparing a polymer solution, adding a pore former,
pouring the mixture onto Petri dishes, and washing it with deionized water to leach out the salt crystals, the salt leaching method—which is based on the fact that inorganic salts are insoluble in organic solvents that dissolve biodegradable
Advantage:
It has high porosity. Disadvantage:
Limitation of using water soluble materials.
1. Spin Coating Method:
By spreading homogenous polymer layers on a spinning plate, the spin coating technique creates thin coatings that range in thickness from 1 to 10 µm. Solvent evaporation is aided by the rotation, and the ultimate thickness can be controlled by varying the speed.
Advantage:
Versatality in modifying the thickness of final permeable film.
Disadvantage:
Low material efficiency**.**
2. Microfluidic Spinning Method:
The concept of microscale fluid dynamics underlies microfluidic spinning, in which core and sheath flows combine to form a coaxial flow inside a specially designed microchannel. Solvent exchange, ionic or chemical crosslinking, and UV radiation all contribute to the solidification of the polymer dispersion.
Advantage:

the capacity to manipulate individual strands to create three-dimensional fibrous structures. Disadvantage:
High cost and high energy consumption**.**

4.3-D Printing Method:

the capacity to manipulate individual strands to create three-dimensional fibrous structures. Advantage:
manufacturing reproducibly flexible matrices with preset pore diameters

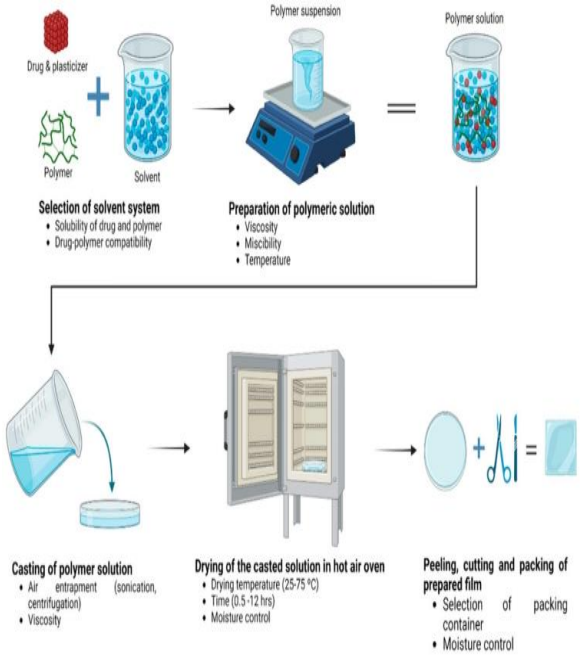
Disadvantage:

Highly expensive.

5.Solvent Casting Method:

The most straightforward technique for creating hydrogel is solvent casting. Based on the inversion approach of a mixed polymer solution, it addresses the issue of partial solute dissolution leading to faulty pore architectures. [36]

Because of its relaxed and reasonably inexpensive process, the solvent casting method is a dependable, preferred, and widely utilized technique [54]. In the solvent casting method, a polymer and plasticizer are dissolved, the solution is spread out on a substrate, and the solvent is removed. This results in the intercalation of plasticizer molecules and the molecular orientation of the polymer chains, which forms a film [55]. This process involves dissolving the polymer or polymers and plasticizer in a volatile solvent, such as water, ethanol, acetone, or a mixture of solvents. If a medication is added, it can be dissolved or suspended in the mixture, then poured into a mold and allowed to dry.



Aim:

To develop and evaluate alginate-based wound healing films incorporating diclofenac sodium for enhanced anti-inflammatory activity and improved wound healing efficacy.

Objectives:

1. Formulation Development:

To formulate wound healing films using sodium alginate as the primary polymer matrix and diclofenac sodium as the active pharmaceutical ingredient (API).

2. Characterization of Films:

To evaluate the physicochemical properties of the films, including thickness, tensile strength, folding endurance, moisture content, and swelling behavior.

3. Drug Loading and Release Studies:To determine the drug content uniformity and study the in vitro drug release profile of diclofenac sodium from the alginate-based films.

4. Anti-inflammatory and Healing Assessment:

To assess the anti-inflammatory activity and wound healing potential of the films using suitable in vitro and/or in vivo models.

5. Biocompatibility and Safety Evaluation:

To evaluate the biocompatibility and skin irritation potential of the formulated films through cytotoxicity or dermal compatibility studies.

6. Stability Studies:

To conduct stability testing of the films under various environmental conditions as per ICH guidelines to ensure product consistency and shelf life.

III. EXPERIMENTAL WORK

Standard Graph of Diclofenac Sodium:

Preparation Of Stock Solution:

Take 100mg of diclofenac sodium in 100ml of methanol

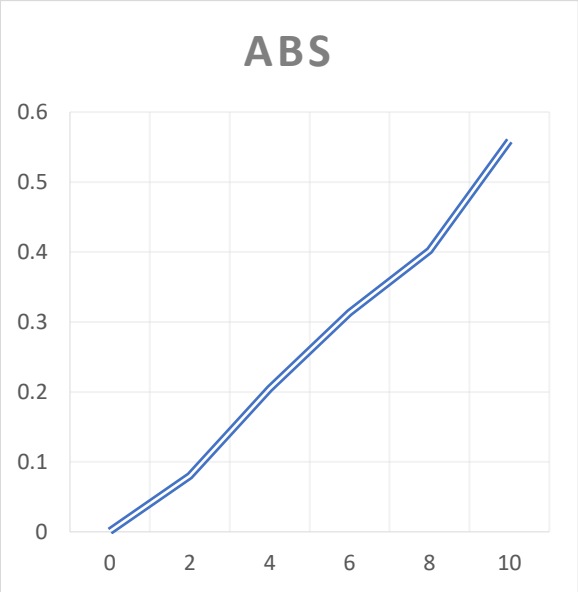
Absorbance maxima:

From above stock solution take 2.5 ml and dilute to 25ml with water.

Prepare a series of working standard solutions (eg.10,20,30,40,50µg/ml) by diluting the stock solution with the solvent

Measure the absorbance of each working standard solution at a specific wavelength of 276nm for diclofenac sodium.

Concentration(µg/ml)	Absorbance at 276nm
0	0.001
20	0.080
40	0.205
60	0.313
80	0.402
100	0.559



Preparation of wound healing films (transdermal films) of Diclofenac Sodium using solvent casting technique:

1. Weigh the required amount of diclofenac sodium and polymer.
2. Dissolve the polymer in the solvent under stirring until a clear solution is obtained.
3. Add Diclofenac Sodium to the polymer solution and stir until completely dissolved.
4. Add plasticizer to improve film flexibility.
5. Pour the film-forming solution onto the casting surface.
6. Spread the solution evenly to form a thin layer, using a glass rod.
7. Allow the solvent to evaporate slowly at room temperature or under controlled temperature and humidity conditions.
8. Once the solvent was evaporated, place the film in a hot air oven or at room temperature for 24hrs.
9. Dry the film at a temperature range of 40-50 degrees for several hours to remove any residual solvent.

Formulation table of diclofenac sodium transdermal films

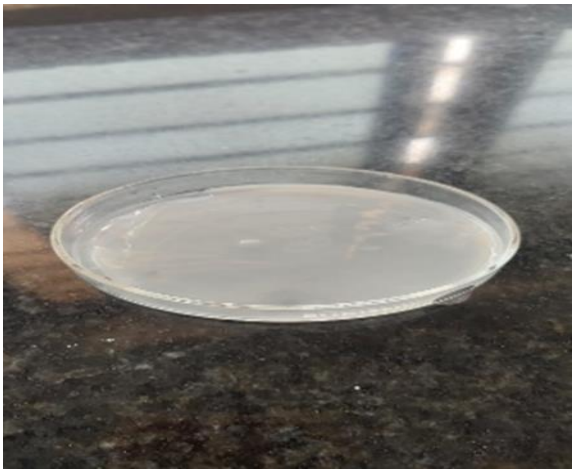
Ingredients	F1	F2	F3	F4	F4
Diclofenac sodium	600mg	600mg	600mg	600 mg	600mg
Sodium Alginate	1500mg	1500mg	1500mg	1500mg	1500mg
HPMC	500mg	-	1000mg	500mg	1000mg
Zinc oxide	-	-	500mg	-	500mg
Glycerine	2ml	2ml	4ml	4ml	4ml
Poly Ethylene Glycol	1ml	1ml	1ml	1ml	1ml
Water	50ml	50ml	30ml	50ml	30ml
carbopol	-	1000mg	-	-	-

FORMULATION-1

FORMULATION-2

FORMULATION-3

FORMULATION-4



IV. EVALUATIONS OF TRANSDERMAL FILMS

1.Thickness:

1. To ensure homogeneity, cut several samples from various regions of the transdermal film.

2.Take several measurements of the thickness using a dial gauge, digital calliper, or micrometre screwgauge.

3.Verify the consistency by contrasting the resulting values with the permissible range. To guarantee homogeneity, the mean thickness and standard deviation are computed.

FORMULA: MSR+(CSR×LC)±Zero error

Where, MSR=mean scale reading

CSR=Circular scale reading

LC=Least count

2.Folding Endurance:

1.A consistent transdermal film is made and sliced into a suitable-sized strip, such as (2cm×2cm).

2. Until the film breaks or exhibits obvious cracks, it is folded at the same spot repeatedly.

3.The folding endurance value of a film is the number of folds it can sustain before breaking.

4.Better mechanical strength and flexibility are indicated by higher folding endurance, which increases the film's suitability for use without breaking when handled or used**.**

Formula: no.of folds/thickness of the film

- The pH should ideally be within the skin's normal range (4.5–6.5) to avoid irritation.

3.weight variation:

1. Each individual film is weighed using a precision balance.

2.The average weight of all samples is determined.

3.The individual weights are compared to the mean weight.

The percentage deviation is calculated using:

Percentage Deviation= (Individual Weight−Mean Weight/Mean Weight)×100

- Acceptance Criteria – The weight variation should fall within acceptable limits (commonly ±5% for films of standard size).

4.Swelling index:

1.The transdermal film is preweighed

2.The film is kept at room temperature in a petri dish with an appropriate media (such as phosphate buffer pH 7.4).

3.The film is taken off, wiped to eliminate extra surface moisture, and weighed at pre-arranged intervals.

Calculation of Swelling Index:

Swelling Index (%)=(Wt−W0)/W0×100

where W_0 is the initial weight and W_t is the weight at time t.

5. Dissolution profile:

Dissolution Evaluation Test Procedure for Transdermal Wound Healing Films

The dissolution evaluation test is a critical step in the development and quality control of transdermal wound healing films. This test assesses the release rate of the active ingredient from the film into a dissolution medium, simulating the conditions at the wound site.

Dissolution Test Procedure

1. Apparatus: Use a dissolution apparatus, such as a USP Type 1 basket or Type 7 (reciprocating holder), depending on the film's characteristics.
2. Dissolution Medium: Select a suitable dissolution medium, such as phosphate buffer (pH 7.4).

Preparation of phosphate buffer(7.4)

➢ Materials

1. Potassium dihydrogen orthophosphate (KH2PO4): 6.8 g
2. Sodium hydroxide (NaOH): 1.5 g
3. Distilled water: 1000 mL

➢ Preparation

1. Dissolve KH2PO4: Dissolve 6.8 g of KH2PO4 in 800 mL of distilled water.
2. Add NaOH: Add 1.5 g of NaOH to the solution and stir until dissolved.
3. Adjust pH: Adjust the pH to 7.4 using NaOH or HCl.
4. Make up volume: Make up the volume to 1000 mL with distilled water.

parameters

- Temperature: Maintain the dissolution medium at a temperature of 32°C ± 0.5°C to simulate the skin temperature.
- Film Sample: Cut the transdermal film into a suitable size (i.e.,2×2cm) and shape for the dissolution apparatus.
- Test Conditions: Set the dissolution test conditions, including the basket speed (e.g., 75 rpm) and the sampling intervals (e.g.,5, 15, 30, 60,90,120 minutes).
- Sampling: Collect samples from the dissolution medium at the specified intervals and analyze them for the active ingredient using a suitable analytical method (e.g., HPLC, UV-Vis spectroscopy).

❖ UV Analysis of Dissolution Evaluation Test for Diclofenac Transdermal Wound Healing Films

➢ Parameters

1. Wavelength: 276 nm (maximum absorption wavelength of diclofenac)
2. Solvent: Methanol or phosphate buffer (pH 7.4)
3. Concentration: 10-50 µg/mL (depending on the film's diclofenac content)
4. Path length: 1 cm
5. Detector: UV-Vis detector (photodiode array or variable wavelength detector)

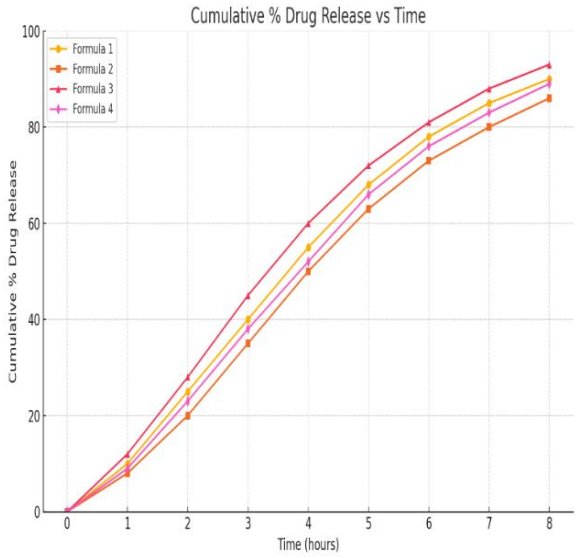
➢ Procedure

1. Sample preparation: Collect samples from the dissolution medium at specified intervals (e.g.,5, 15, 30, 60 , 90, 120minutes).
2. Dilution: Dilute the samples with methanol or phosphate buffer (pH 7.4) to a suitable concentration.
3. UV analysis: Measure the absorbance of the samples at 276 nm using a UV-Vis spectrophotometer.
4. Calibration: Calibrate the instrument using a standard solution of diclofenac.

➢ Calculation 1. Absorbance: Measure the absorbance of the samples and calculate the concentration of diclofenac using the calibration curve.

2. Cumulative release: Calculate the cumulative release of diclofenac from the film over time.

Dissolution profiles of wound healing transdermal films prepared with Diclofenac sodium and sodium alginate



Here's the dissolution profile comparing the four formulations of your diclofenac-loaded wound healing transdermal films. Each line shows how much of the

drug is released over time — based on typical release behavior for these types of polymer blends

V. RESULTS AND DISCUSSION

Evaluation parameters

Evaluation parameters	F-1	F-2	F-3	F-4
Weight variation	13.46%	7.27%	10.34%	10.34%
Thickness	0.198mm	0.220mm	0.240mm	0.250mm
Folding endurance	100	900	565.5	384.6
Swelling index	200%	150.91%	144.83%	196.55%

Dissolution Profile:

Invitro dissolution of designed wound healing transdermal films prepared with Diclofenac sodium

Time in minutes	F-1 %Drug release	F-2 %Drug release	F-3 %Drug release	F-4 %Drug release
0	0	0	0	0
5	15	12.5	18.26	10
15	28	25	32.5	21.2
30	44.2	40	48.3	36.8
60	57.1	50	58.2	45.9
90	55.7	55	62.1	52.6
120	64.2	60	65	55.4

Discussion

Weight variation:

The weight variation values for the transdermal wound healing film formulations range from 7.27% to 13.46%. Our formulation (Formula 4) has a weight variation of 10.34%, which is within the acceptable range.

The weight variation values suggest differences in the uniformity of the films. A lower weight variation, like Formula 2, may indicate better uniformity and consistency, while a higher value, like Formula 1, may indicate more variability in film weight.

Thickness:

The thickness values for the transdermal wound healing film formulations range from 0.198 mm to 0.250 mm. Our formulation (Formula 4) has a thickness of 0.250 mm, which is the highest among the four formulations.

The varying thickness values may impact the films' flexibility, durability, and overall performance. A thicker film like Formula 4 may provide better mechanical strength, but may also affect drug release and absorption

Folding endurance:

The folding endurance values for the transdermal wound healing film formulations vary significantly, ranging from 100 to 900. Our formulation (Formula 4) has a folding endurance of 384.6, which is moderate compared to the other formulations.

The wide range of folding endurance values suggests differences in film flexibility and durability. A higher folding endurance, like Formula 2, may indicate better resistance to cracking and breaking, while a lower value, like Formula 1, may indicate a more brittle film.

Swelling index:

The swelling index values for the transdermal wound healing film formulations range from 144.83 to 200. Our formulation (Formula 4) has a swelling index of 196.55, which is close to the highest value.

The swelling index values suggest differences in the films' ability to absorb and retain wound exudate. A higher swelling index, like Formula 1 and Formula 4, may indicate better performance in promoting wound healing by maintaining a moist environment.

Dissolution:

Acceptance criteria

Dissolution rate: The dissolution rate should meet the specified requirements (e.g., ≥ 80% released within 2 hours).

- Observations

1. Initial Release: All formulations show an initial burst release of the drug, with F-4 showing the lowest release at 5 minutes (10%).
2. Release Rate: The release rate of F-4 is slower compared to the other formulations, with a more gradual increase in drug release over time.
3. Cumulative Release: F-4 shows a cumulative release of 55.4% at 120 minutes, which is lower compared to F-1 (64.2%), F-2 (60%), and F-3 (65%).

- Discussion

The dissolution profile of F-4 is more favorable due to its:

1. Sustained Release: F-4 shows a sustained release of the drug over a longer period, which can provide a prolonged therapeutic effect.
2. Lower Initial Burst: The lower initial burst release of F-4 reduces the risk of an excessive initial dose, which can be beneficial for wound healing.
3. More Consistent Release: The release rate of F-4 is more consistent over time, which can provide a more predictable therapeutic effect.

Comparative Study of Formulations F1-F4

- HPMC Comparison

1. F1 and F3: Both formulations contain 500mg of HPMC, which suggests that HPMC is a common excipient in these formulations.
2. F4: This formulation contains 1000mg of HPMC, which is twice the amount used in F1 and F3. This may indicate that F4 requires a higher concentration of HPMC to achieve the desired properties.
3. F2: This formulation does not contain HPMC, which suggests that it may use alternative excipients to achieve the desired properties.

- Carbopol Comparison

1. F2: This formulation contains 1000mg of Carbopol, which is a significant amount. Carbopol is a thickening agent and may be used to enhance the viscosity of the formulation.
2. F1, F3, and F4: These formulations do not contain Carbopol, which suggests that they may use alternative thickening agents or have different viscosity requirements.

Favouring Formulation 4 with HPMC

1. Higher HPMC content: F4 contains a higher amount of HPMC (1000mg) compared to F1 and F3 (500mg). This may provide a more sustained release of the drug and improve the formulation's viscosity.
2. Improved stability: The higher HPMC content in F4 may also improve the stability of the formulation by reducing the risk of phase separation.
3. Enhanced bioavailability: The use of HPMC in F4 may enhance the bioavailability of the drug by increasing its solubility and permeability.

VI. CONCLUSION

A potential strategy in controlled drug release systems is the creation of hydrogels based on alginate for the delivery of diclofenac sodium. These hydrogels are appropriate delivery systems for non-steroidal anti-inflammatory medications (NSAIDs) due to their superior biocompatibility, swelling behaviour, and sustained release properties. In addition to improving the drug's stability, the encapsulation of diclofenac sodium in the alginate matrix reduces the possibility of adverse effects that come with traditional delivery. All things considered, this study supports alginate hydrogels' potential as a secure and effective drug delivery system, opening the door for other therapeutic uses and investigation into customised drug release mechanisms.

Based on the comparative study, Formulation 4 (F4) with HPMC is favoured due to its:

1. Higher HPMC content: Providing a more sustained release of the drug and improving the formulation's viscosity.
2. Improved stability: Reducing the risk of phase separation and improving the overall stability of the formulation.
3. Enhanced bioavailability: Increasing the solubility and permeability of the drug, leading to improved bioavailability.

The absence of Carbopol in F4 suggests that HPMC is the preferred excipient for achieving the desired properties in this formulation.

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