



ENGINEERING A PHYSICALLY CROSSLINKED N-ACETYLCYSTEINE LOADED BIOPOLYMERIC HYDROGEL AS A SUSTAINED TOPICAL DELIVERY PLATFORM FOR LAMELLAR ICHTHYOSIS

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ABSTRACT

Lamellar ichthyosis is a rare inherited disorder of cornification marked by hyperkeratosis, scaling and impaired barrier function. This work aimed to develop a 5% w/w N-acetylcysteine (NAC) loaded sustained-release topical hydrogel prepared by ionic gelation, using chitosan and guar gum as polymers and sodium tripolyphosphate (STPP) as a physical cross-linker. Nine formulations (F1–F9) with increasing chitosan (0.01–0.08 g) and STPP (0.005–0.025 g) per 10 g batch were evaluated for appearance, pH, viscosity, spreadability, extrudability, washability, swelling, drug content, entrapment efficiency and *in vitro* release. Infrared spectroscopy showed no incompatibility between NAC and the excipients. All batches were smooth, homogeneous gels (pH 5.72–6.10; viscosity 4,200–6,510 mPa·s). Higher polymer and cross-linker levels lowered spreadability (8.6 to 4.9 g·cm/s), extrudability (95 to 80%) and 8 h drug release (83.5 to 68.0%). F5 (0.05 g chitosan, 0.02 g guar gum, 0.015 g STPP) was selected as optimum, with pH 6.01, viscosity 5,480 mPa·s, spreadability 6.9 g·cm/s, extrudability 90%, maximum swelling (140% at 5 h), drug content 94.1% and entrapment efficiency 94.92%. F5 released 75.0% of NAC in 8 h against 94.2% from a plain gel, and its release fitted the Higuchi model ($R^2 = 0.9995$) with a Korsmeyer–Peppas exponent of 0.866, indicating diffusion with polymer relaxation. Scanning electron microscopy showed a porous, interconnected network. The cross-linked F5 hydrogel is a promising sustained-release topical platform for NAC that merits *ex vivo*, stability and clinical evaluation.

KEYWORDS: N-acetylcysteine; hydrogel; ionic gelation; chitosan; sustained release; lamellar ichthyosis.

INTRODUCTION

Lamellar ichthyosis (LI) is a rare autosomal recessive disorder of cornification, most often linked to transglutaminase-1 mutations, in which defective cornified envelope formation produces thick plate-like scales, hyperkeratosis and a compromised epidermal barrier.^[1] Treatment is largely symptomatic, based on emollients, keratolytics and retinoids of moderate effectiveness.^[2] Topical delivery to lesional skin is attractive because it localises drug action and limits systemic exposure, yet the stratum corneum and

thickened scale restrict drug penetration and retention.^[3] Conventional preparations also need frequent reapplication because of their limited residence on the skin.

N-acetylcysteine (NAC) is a thiol-containing cysteine derivative and glutathione precursor with antioxidant and anti-inflammatory activity, and topical NAC has been used in disorders of abnormal keratinisation, including reports of 10% NAC cream reducing hyperkeratosis and improving barrier function in LI.^[4,5] Its topical use is

nevertheless limited by chemical instability, poor skin substantivity and rapid release from aqueous vehicles. Incorporation into a hydrogel provides a hydrated

environment suited to dry, scaly skin and prolongs residence at the application site.^[6]

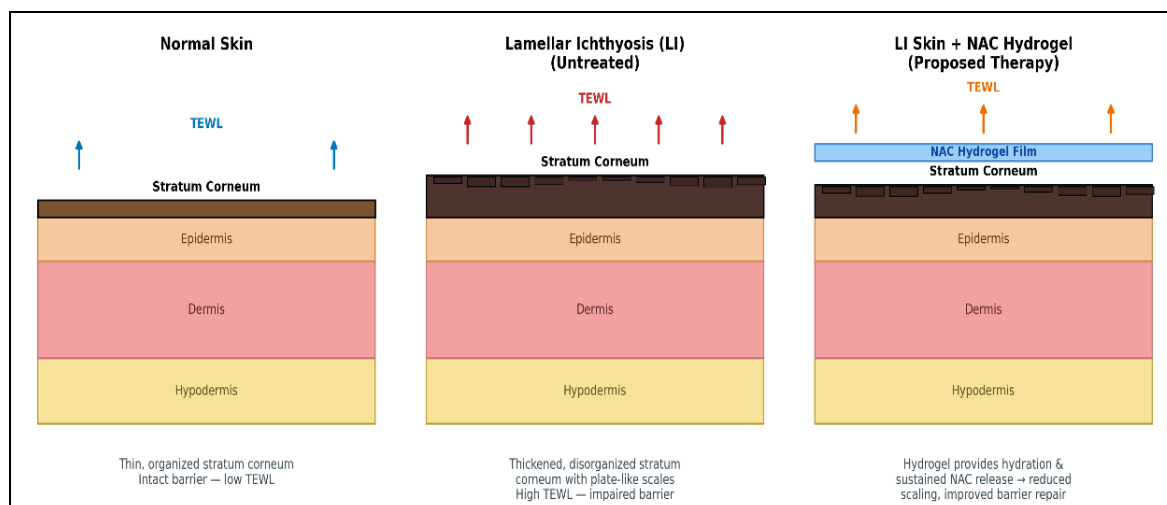


Figure 1: Epidermal barrier status in normal skin, Untreated *Lamellar ichthyosis*, Proposed NAC hydrogel therapy.

Hydrogels are hydrophilic three-dimensional polymer networks that hold large amounts of water, are soft and biocompatible, and regulate drug diffusion through their cross-link density.^[7,8] Physically cross-linked networks formed through ionic interactions avoid toxic covalent cross-linkers and form under mild conditions.^[9] Chitosan, a cationic polysaccharide, forms ionic networks with polyanions such as sodium tripolyphosphate (STPP),^[10] while guar gum, a

galactomannan, contributes viscosity and water retention. A bipolymeric physically cross-linked NAC hydrogel has been described for wound dressing.^[11] The present study formulated a 5% w/w NAC-loaded chitosan–guar gum hydrogel cross-linked with STPP by ionic gelation, characterised nine compositions, selected an optimised formulation on physicochemical and release behaviour, analysed its release kinetics and compared its release with a plain, non-cross-linked gel.

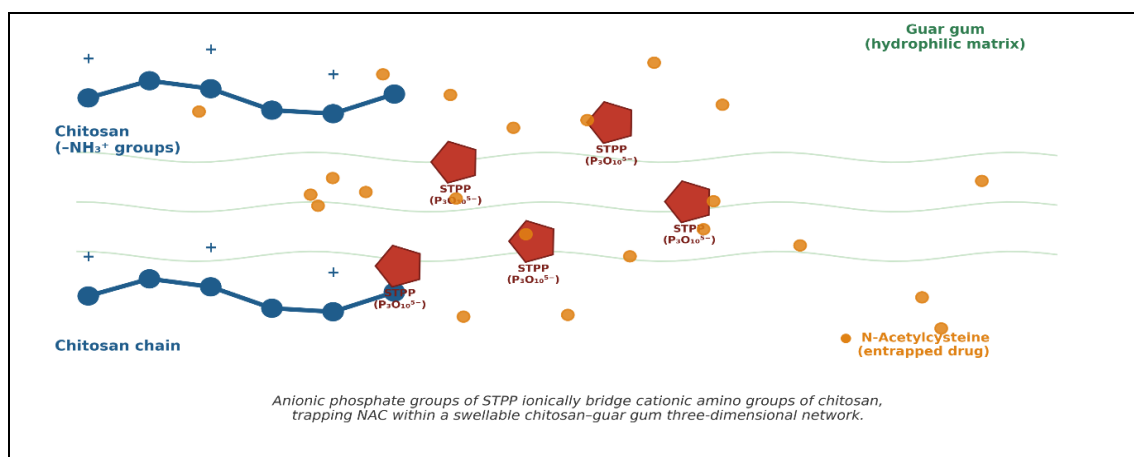


Figure 2: Mechanism of Ionic-mediated Physically Cross-linked NAC Loaded Hydrogel.

MATERIALS AND METHODS

Materials

N-Acetylcysteine (Jay Jalaram Lifesciences Pvt. Ltd.), chitosan, guar gum and acetic acid (Johns Chemicals) and sodium tripolyphosphate (Sri Chemicals) were used; distilled water was the solvent. Equipment comprised a magnetic stirrer hot plate (Lab India Analytical), electronic balance (A&D, Japan), ultrasonicator (Vabronic, Mumbai), digital pH meter (MC Dalal, Chennai), centrifuge (Eppendorf), Brookfield viscometer

(AMETEK), UV–visible spectrophotometer UV-1700 (Shimadzu, Japan), FTIR spectrophotometer (Shimadzu, Japan) and scanning electron microscope (ZEISS).

Preformulation, UV analysis and FTIR drug–excipient compatibility

Colour, odour and form of NAC were compared with the certificate of analysis. The melting point was determined by the open capillary method, the n-octanol/water partition coefficient by the shake-flask method with

spectrophotometric assay of the aqueous phase,^[12] and the pH of a freshly prepared aqueous solution with a pH meter calibrated at pH 4.0, 7.0 and 9.2. A 10 µg/mL NAC solution in 0.1 N NaOH was scanned from 200 to 400 nm to locate λ_{max} , and a calibration curve was prepared from 2–10 µg/mL solutions at that wavelength.^[13] For drug–excipient compatibility, FTIR spectra (4000–400 cm⁻¹, KBr pellets) of NAC, chitosan, guar gum, STPP and their physical mixture in the formulation ratio were compared.

Preparation of hydrogels

Hydrogels were prepared by ionic gelation at 25 ± 2 °C (Table 1). Chitosan was dispersed in 1% w/v acetic acid and stirred (400–500 rpm, 45–60 min) until clear. Guar

gum was hydrated in water at 55–60 °C for 30 min and cooled to 25 °C, then blended slowly into the chitosan solution (500–800 rpm, 30 min). NAC, dissolved in a small volume of water, was mixed in (500–600 rpm, 15–20 min). STPP solution was added dropwise over 10–15 min (300–500 rpm), causing ionic cross-linking between protonated chitosan amino groups and STPP phosphate groups. After gentle homogenisation (300–400 rpm, 10–15 min) the weight was adjusted to 10 g with water, and the gels were deaerated for 30–60 min and stored in airtight containers at 25 ± 2 °C protected from light. Each 10 g batch held 0.5 g NAC (50 mg/g; 5% w/w). The plain gel contained 0.50 g NAC, 0.20 g chitosan, 0.05 g guar gum and 0.10 mL of 1% w/v acetic acid in 10 g, without STPP.

Table 1: Formulation design of NAC-loaded topical hydrogel.

Code	NAC (g)	Chitosan (g)	Guar gum (g)	STPP (g)	1% w/v acetic acid (mL)
F1	0.50	0.01	0.02	0.005	0.10
F2	0.50	0.02	0.02	0.005	0.10
F3	0.50	0.03	0.02	0.010	0.10
F4	0.50	0.04	0.02	0.010	0.10
F5	0.50	0.05	0.02	0.015	0.10
F6	0.50	0.06	0.02	0.015	0.10
F7	0.50	0.07	0.02	0.020	0.10
F8	0.50	0.08	0.02	0.020	0.10
F9	0.50	0.08	0.02	0.025	0.10

NAC: *N*-acetylcysteine; STPP: sodium tripolyphosphate.

Evaluation of hydrogels

Colour, appearance, homogeneity, texture, phase separation and lumps were assessed visually, and F5 was viewed by light microscopy (10×).^[14] The pH was measured on a 1% w/v aqueous dispersion and viscosity with a Brookfield viscometer at 25 ± 1 °C. Washability was judged by rinsing 0.5 g of gel with distilled water after 5–10 min contact. Spreadability was measured by the parallel-plate method (10 g load, 5 min) and calculated as $S = M \times L/T$, where *M* is the applied weight (g), *L* the distance moved (cm) and *T* the time (s). Extrudability was expressed as (weight extruded/initial weight) × 100. Swelling index = $[(W_t - W_0)/W_0] \times 100$ was determined in phosphate buffer (pH 7.4) at 30 min and 1–5 h.^[15] For drug content, 2 g of gel was extracted with buffer under stirring for 30–60 min, filtered, diluted and assayed at λ_{max} against the calibration curve. Entrapment efficiency was determined by dispersing 1 g of gel in 10 mL of phosphate buffer (pH 7.4), centrifuging (5000 rpm, 10–15 min), filtering the supernatant (0.45 µm) and assaying free NAC: EE (%) = $[(\text{NAC added} - \text{free NAC})/\text{NAC added}] \times 100$.^[16]

In vitro release, kinetics, SEM and FTIR

Release was studied across a pre-soaked cellophane membrane mounted between donor and receptor compartments; the receptor held 100 mL of phosphate buffer (pH 7.4) at 37 ± 0.5 °C, stirred at 50–100 rpm. Aliquots (2 mL) were withdrawn at 30, 60, 120, 180,

240, 300, 360, 420 and 480 min, replaced with fresh buffer, and assayed spectrophotometrically. Data for F5 were fitted to zero-order, first-order, Higuchi, Korsmeyer–Peppas and Hixson–Crowell models,^[17] and the plain gel was tested identically. Dried F5 was gold-coated and examined by SEM, and its FTIR spectrum (KBr, 4000–400 cm⁻¹) was recorded.

RESULTS AND DISCUSSION

Preformulation and analytical characterisation

NAC was a white crystalline powder with a slightly acetic odour complying with the certificate of analysis. Its melting point was 109 °C, its partition coefficient 0.4 and the pH of its aqueous solution 2.4. The low partition coefficient shows a predominantly hydrophilic drug that disperses uniformly in an aqueous gel and is readily released from it, whereas the acidic pH, due to the carboxylic acid group, explains why the final gel pH was controlled for skin compatibility. NAC showed λ_{max} at 235 nm (Figure 3a), and the calibration curve in 0.1 N NaOH (2–10 µg/mL) was linear ($y = 0.0144x - 0.0036$; $R^2 = 0.9961$; Figure 3b), so the method obeys Beer's law over this range.

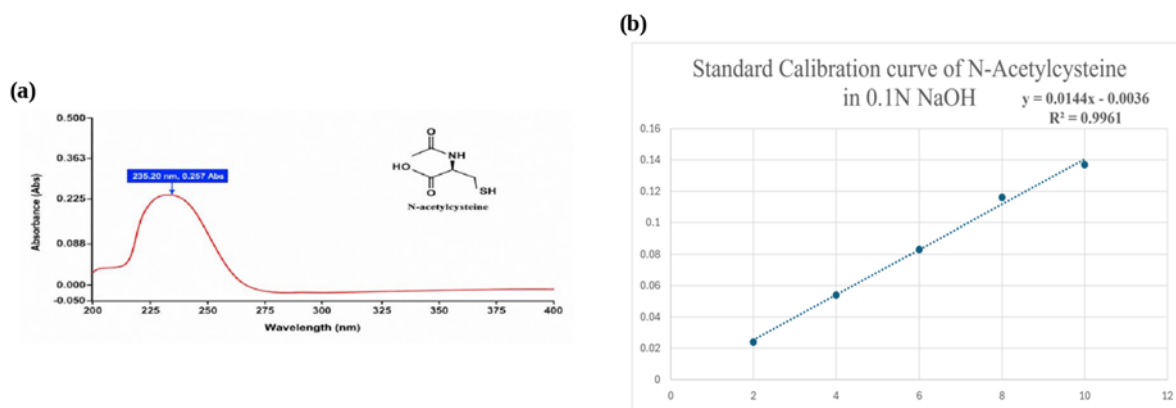


Figure 3: Ultraviolet spectrum (a) and calibration curve (b) of N-acetylcysteine.

Drug–excipient compatibility (FTIR)

The spectra of NAC, chitosan, guar gum and STPP showed their expected functional groups (Figure 2a–d, Table 2). NAC displayed O–H/N–H stretching at 3419 cm^{-1} , amide C=O/N–H at 1628 cm^{-1} and C–S bands at 821 , 623 and 565 cm^{-1} ; chitosan and guar gum showed hydroxyl, C–H and C–O–C bands of polysaccharides;

STPP showed P=O and P–O–P bands. In the physical mixture (Figure 4e) the NAC thiol band at 2549 cm^{-1} and amide bands at 1651 and 1539 cm^{-1} persisted with no disappearance or significant shift of principal peaks, indicating that NAC is compatible with chitosan, guar gum and STPP.

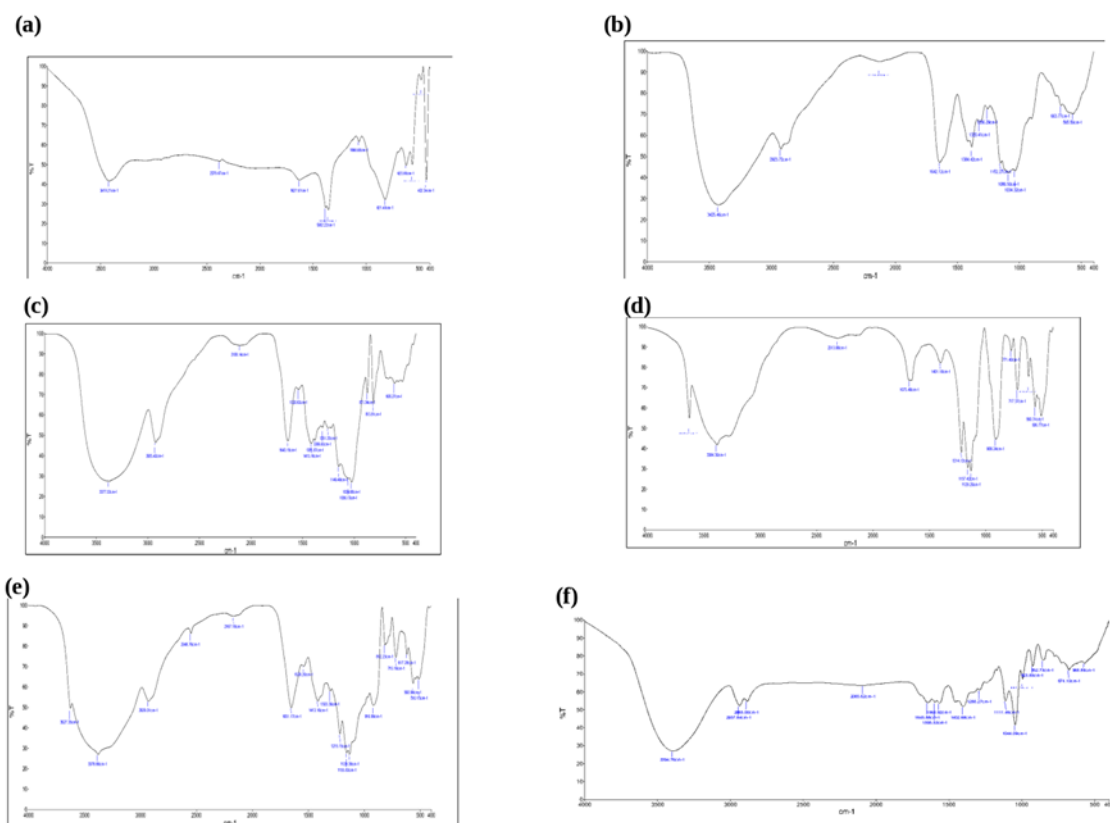


Figure 4: FTIR spectra of N-acetylcysteine (a), chitosan (b), guar gum (c), sodium tripolyphosphate (d), physical mixture (e) and optimised formulation F5 (f).

Table 2: Characteristic FTIR peaks (cm⁻¹) of NAC, excipients and physical mixture.

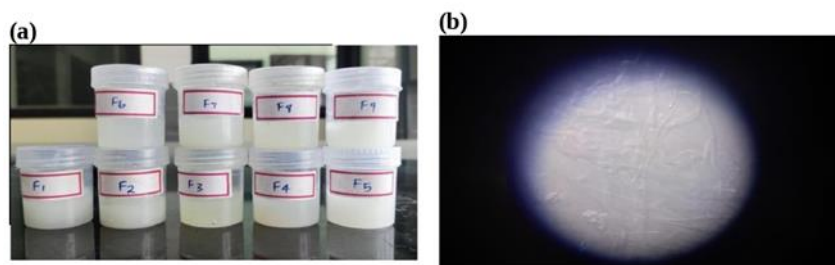
Sample	Peak (assignment)
NAC	3419 (O–H/N–H str.); 1628 (amide C=O/N–H bend); 1382 (CH ₃ bend); 1356 (C–N); 1067 (C–O/C–N)
Chitosan	3425 (O–H/N–H); 2924 (C–H); 1642 (amide I); 1152 (C–O–C); 1034 (C–O)
Guar gum	3378 (O–H); 2925 (C–H); 1643 (H–O–H bend); 1149 (C–O–C); 1025 (C–O)
STPP	3384 (O–H); 1675 (H–O–H bend); 1214 (P=O); 1157 (P–O–P asym.); 909 (P–O–P)
Physical mixture	3379 (O–H/N–H); 2928 (C–H); 2549 (S–H); 1651 (amide I); 1539 (amide II)

str.: stretching; bend: bending; asym.: asymmetric.

Physicochemical evaluation of hydrogels

All nine formulations were slightly yellowish, smooth and free of phase separation and lumps (Figure 5a). Homogeneity was very good to excellent for F3–F6 (excellent for F5) and fair for F9, while F1 was low in viscosity and F8–F9 were thick and dense. Light microscopy of F5 showed a uniform matrix without

visible aggregates (Figure 5b), consistent with successful physical cross-linking. The pH rose slightly from 5.72 (F1) to 6.10 (F9) (Table 3), within the mildly acidic skin range (5.5–6.5), because more chitosan and STPP partly neutralise the acetic acid; such values should minimise irritation.

**Figure 5: Physical characterisation of hydrogels: F1–F9 formulations (a), light microscopy of F5 at 10× (b).**

Viscosity increased steadily from 4,200 mPa·s (F1) to 6,510 mPa·s (F9), and spreadability and extrudability fell in parallel, from 8.6 to 4.9 g·cm/s and from 95 to 80% (Table 3). Higher chitosan concentration increases chain entanglement, and more STPP adds ionic junctions, so the network resists flow, which improves retention but

impairs spreading and expulsion from the tube.^[10] Washability was good for F1–F5 but only moderate, with slight polymeric residue, for F6–F9. F5 (5,480 mPa·s, 6.9 g·cm/s, 90%) gave the best balance of consistency, spreadability and ease of application.

Table 3: Physicochemical evaluation of F1–F9 hydrogels.

Code	pH	Viscosity (mPa·s)	Spreadability (g·cm/s)	Extrudability (%)	Washability	Swelling at 5 h (%)	Drug content (%)	EE (%)
F1	5.72	4,200	8.6	95	Good	105	88.5	86.40
F2	5.78	4,520	8.2	94	Good	110	90.2	88.75
F3	5.84	4,810	7.8	92	Good	120	92.0	90.20
F4	5.88	5,120	7.3	91	Good	130	93.1	92.10
F5	6.01	5,480	6.9	90	Good	140	94.1	94.92
F6	6.02	5,720	6.4	88	Moderate	135	91.4	91.35
F7	6.05	5,980	5.9	85	Moderate	125	90.8	90.80
F8	6.08	6,240	5.4	82	Moderate	120	89.6	89.65
F9	6.10	6,510	4.9	80	Moderate	110	88.9	88.90

EE: entrapment efficiency. Viscosity in mPa·s (1 mPa·s = 1 cP).

Swelling rose with time for all batches and was greatest for F5 (140% at 5 h), then declined from F6 to F9 (135 to 110%) (Figure 6). Swelling is governed by cross-link density; moderate cross-linking lets water penetrate and expand the network, whereas the denser, more rigid networks of F6–F9 restrict water uptake.^[9]

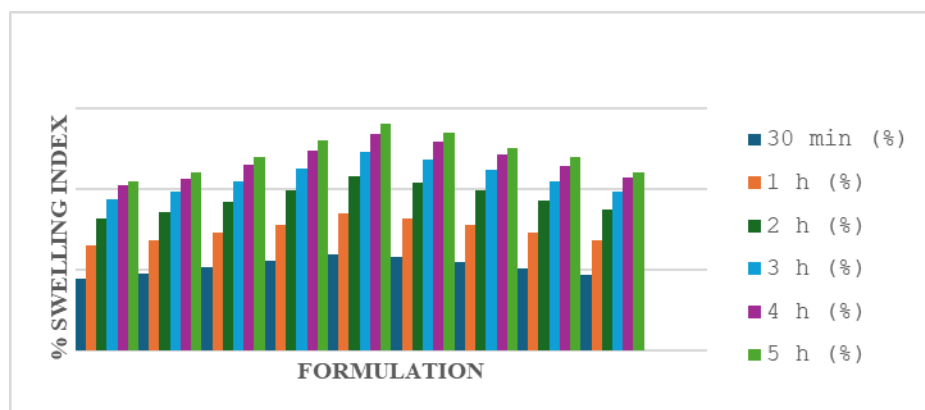


Figure 6: swelling index of F1–F9 hydrogels from 30 min to 5 h (a).

Drug content and entrapment efficiency

Drug content ranged from 88.5 to 94.1% and entrapment efficiency from 86.40 to 94.92%, both peaking at F5 (Table 3, Figure 7). Up to F5, more chitosan with matched STPP improves incorporation and retention of

NAC within the network. Beyond F5, the denser network probably hinders extraction of NAC into the medium, so apparent drug content and entrapment fall slightly (F6–F9: 88.9–91.4% and 88.90–91.35%, respectively).

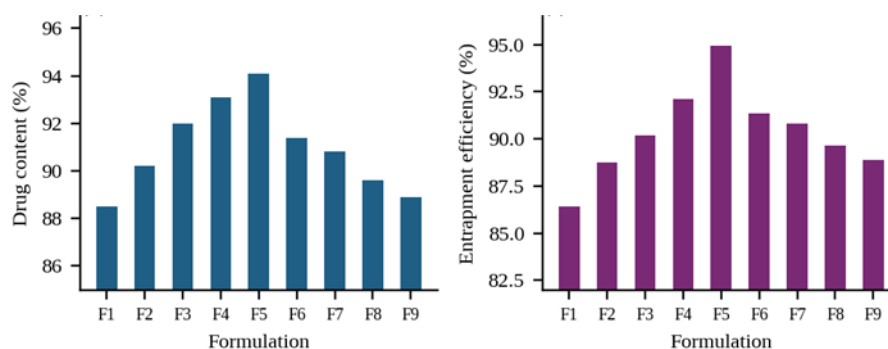


Figure 7: Drug content (a) and Entrapment efficiency (b) of F1–F9 hydrogel.

In vitro drug release and kinetics

All formulations released NAC gradually over 8 h (Table 4, Figure 8). At 30 min release ranged from 8.7 to 13.5%, and at 480 min from 68.0% (F9) to 83.5% (F1); F5 released 75.0%. Release decreased progressively with

increasing chitosan and STPP, because a denser, more viscous and more highly cross-linked matrix offers greater diffusional resistance. F5 showed intermediate, controlled release and, having the best physicochemical profile, was chosen as the optimised formulation.

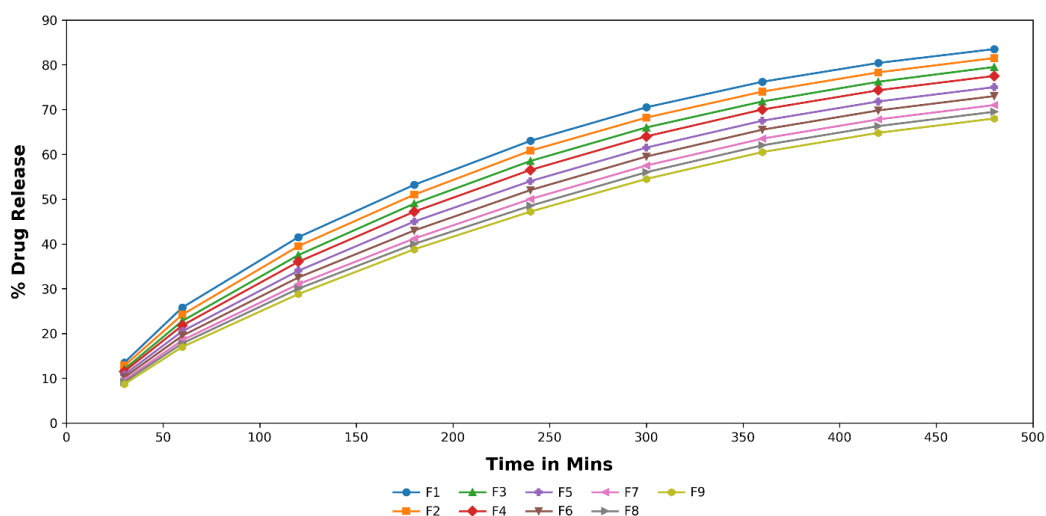


Figure 8: *In vitro* release profiles of F1–F9 hydrogels.

Table 4: Cumulative in vitro NAC release (%) from F1–F9 hydrogels.

Code	30 min	60 min	120 min	180 min	240 min	300 min	360 min	420 min	480 min
F1	13.5	25.8	41.5	53.2	63.0	70.5	76.2	80.4	83.5
F2	12.8	24.2	39.5	51.0	60.8	68.2	74.0	78.3	81.5
F3	12.0	22.8	37.5	49.0	58.5	66.0	71.8	76.2	79.5
F4	11.5	21.8	36.0	47.2	56.5	64.0	70.0	74.3	77.5
F5	10.8	20.5	34.0	45.0	54.0	61.5	67.5	71.8	75.0
F6	10.2	19.5	32.5	43.0	52.0	59.5	65.5	69.8	73.0
F7	9.6	18.5	31.0	41.2	50.0	57.5	63.5	67.8	71.0
F8	9.2	17.8	30.0	40.0	48.5	56.0	62.0	66.3	69.5
F9	8.7	17.0	28.8	38.8	47.2	54.5	60.5	64.8	68.0

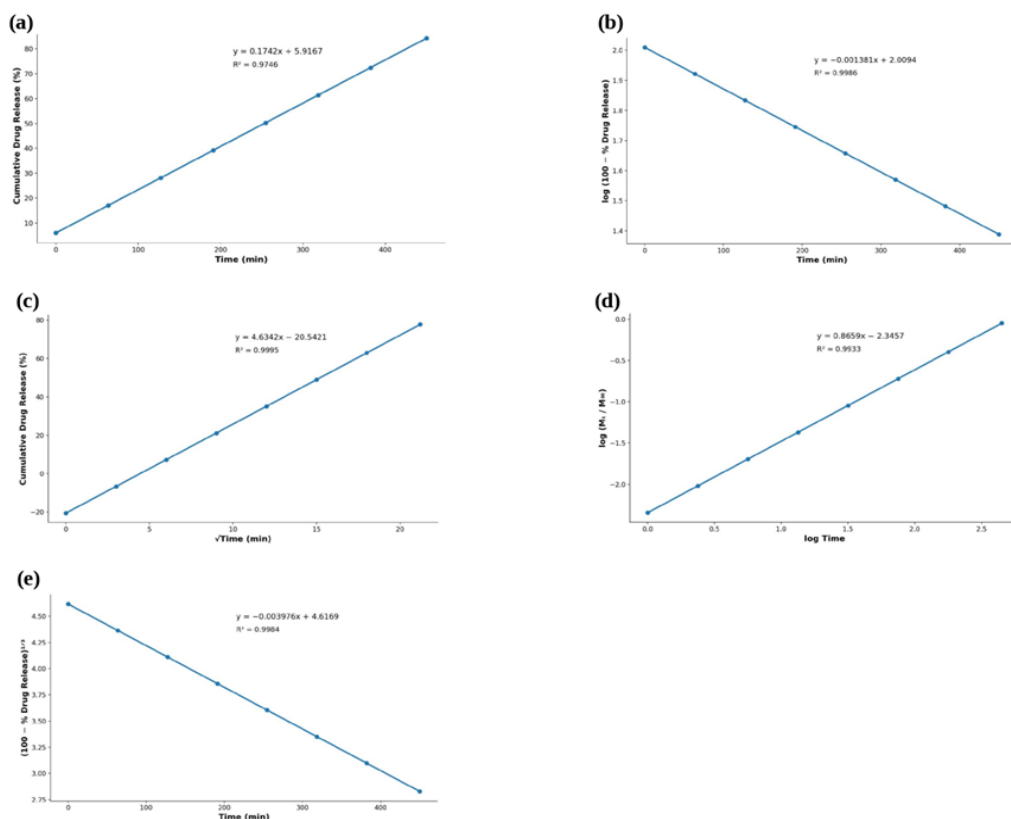
The release of F5 was best described by the Higuchi model ($R^2 = 0.9995$), followed by first-order (0.9986), Hixson–Crowell (0.9984), Korsmeyer–Peppas (0.9933) and zero-order (0.9746) models (Table 5, Figure 9). The high Higuchi correlation shows diffusion-controlled release through the hydrated matrix. The Korsmeyer–Peppas exponent ($n = 0.866$; $0.5 < n < 1$) indicates

anomalous (non-Fickian) transport, in which diffusion is accompanied by polymer relaxation or swelling.^[18] Because several models correlate strongly, the mechanism is best judged from the combination of Higuchi fit and n value rather than R^2 alone.

Table 5: Release kinetics of the optimised F5 hydrogel.

Model	Linear equation	R^2
Zero-order	$y = 0.1742x + 5.9167$	0.9746
First-order	$y = -0.001381x + 2.0094$	0.9986
Higuchi	$y = 4.6342x - 20.5421$	0.9995
Korsmeyer–Peppas	$y = 0.8659x - 2.3457$	0.9933
Hixson–Crowell	$y = -0.003976x + 4.6169$	0.9984

Higuchi gave the highest R^2 ; $n = 0.8659$ (Korsmeyer–Peppas).

**Figure 9: Release kinetics of F5: zero-order (a), first-order (b), Higuchi (c), Korsmeyer–Peppas (d) and Hixson–Crowell (e) plots.**

Surface morphology (SEM) of the optimised formulation

SEM of F5 at increasing magnification showed a rough, heterogeneous surface with interconnected polymeric regions and pores, typical of a three-dimensional physically cross-linked network (Figure 10). Such

porosity lets the aqueous medium enter, supporting swelling and diffusion of NAC. Irregular particulate and crystalline domains within the matrix are likely NAC deposited during drying, although SEM alone cannot prove molecular-level entrapment.

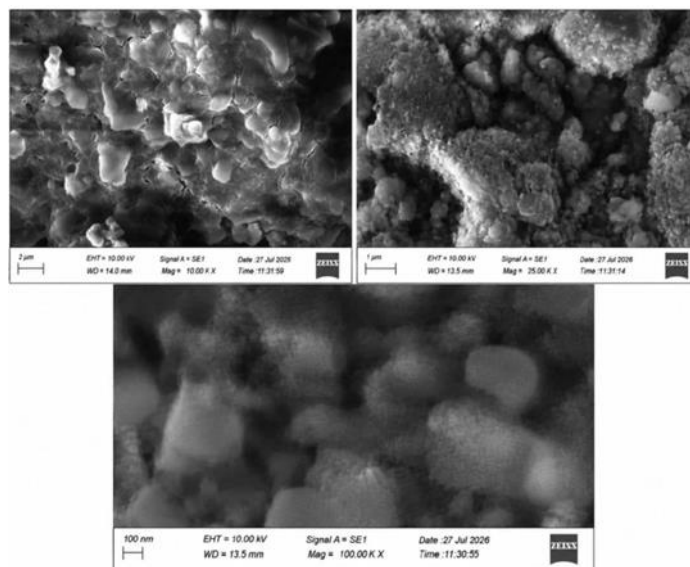


Figure 10: SEM images of the optimised F5 hydrogel at increasing magnification.

FTIR of the optimised formulation

The F5 spectrum (Figure 4f) showed a broad O–H/N–H band at 3395 cm^{-1} , C–H bands at 2938 and 2885 cm^{-1} , amide/carbonyl and N–H bands at 1646 , 1596 and 1564 cm^{-1} , and C–O/C–O–C and phosphate P–O bands at 1111 and 1044 cm^{-1} and near 569 cm^{-1} . The persistence of characteristic bands without unexpected new peaks, together with the phosphate bands, indicates that the network forms mainly through ionic interaction and hydrogen bonding rather than new covalent bonds, and that NAC remains compatible in the final formulation.

Comparison with Plain topical gel

The plain gel released NAC faster, reaching 15.2% at 30 min and 94.2% at 480 min, against 10.8% and 75.0% for F5 (Figure 11). The gap widened with time to 19.2 percentage points at 8 h, showing that the STPP cross-linked network of F5 retards NAC release and sustains it over the study period. The plain topical gel differed from F5 in polymer content as well as in lacking STPP (0.20 g chitosan and 0.05 g guar gum versus 0.05 g and 0.02 g), so the difference reflects overall matrix composition, and cross-linking is its probable principal contributor.

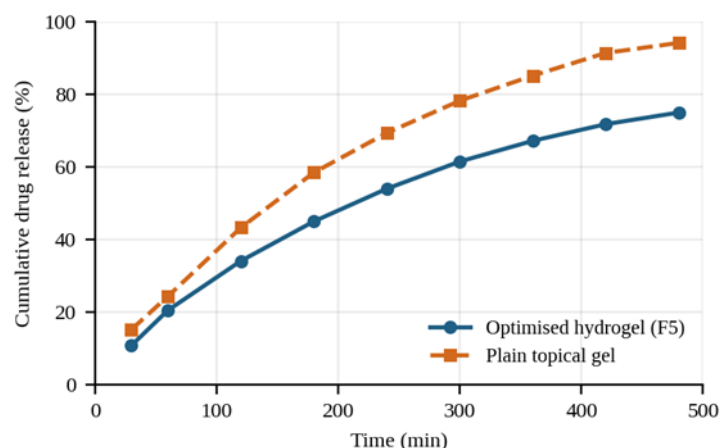


Figure 11: Comparative in vitro release of the optimised F5 hydrogel with plain topical gel.

CONCLUSION

A 5% w/w NAC-loaded chitosan–guar gum hydrogel cross-linked with STPP was successfully prepared by

ionic gelation. Polymer and cross-linker levels controlled viscosity, spreadability, extrudability, swelling, entrapment and drug release. Formulation F5 (0.05 g

chitosan, 0.02 g guar gum, 0.015 g STPP per 10 g) combined a skin-compatible pH (6.01), good spreadability and extrudability, maximum swelling, 94.92% entrapment efficiency and sustained release (75.0% in 8 h versus 94.2% for plain topical gel) by a diffusion-dominated, anomalous mechanism. F5 is a promising topical delivery system for NAC in lamellar ichthyosis; *ex vivo* permeation, stability, irritation and clinical studies are recommended.

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Conflict of Interest: The authors declare no conflict of interest.

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