

Formulation and Comparative Evaluation of Various Natural Polymer-Based Solid Dispersions of Naproxen for Enhanced Solubility and Dissolution

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ABSTRACT

Background: Naproxen, a propionic-acid-derived non-steroidal anti-inflammatory drug (NSAID), is classified under Biopharmaceutics Classification System (BCS) Class II, meaning it is highly permeable across the intestinal membrane but poorly soluble in aqueous media, so its rate-limiting step for oral absorption is dissolution rather than membrane transport. This solubility bottleneck contributes to slow and variable release from conventional dosage forms, which in clinical practice can encourage higher or more frequent dosing and, in turn, a greater burden of NSAID-related gastrointestinal adverse effects.

Objective: The present investigation was undertaken to formulate solid dispersions of naproxen using three hydrophilic natural polysaccharide gums guar gum (GG), xanthan gum (XG) and gum acacia (GA) and to comparatively evaluate their capacity to enhance aqueous solubility and in-vitro dissolution relative to one another and to the unprocessed drug.

Methods: Twenty-seven formulation batches were generated by fully crossing the three carriers, three preparation techniques (solvent evaporation, fusion/melt, and kneading) and three drug-to-polymer ratios (1:1, 1:2 and 1:3 w/w). Pre-formulation studies organoleptic evaluation, melting-point verification, equilibrium solubility profiling and FTIR-based drug-polymer compatibility screening preceded formulation. Eleven batch was assessed for drug content, equilibrium solubility (in water and pH 6.8 phosphate buffer) and USP Apparatus II dissolution behaviour; the best-performing batch was further characterised in-house by FTIR and differential scanning calorimetry (DSC), compared against powder X-ray diffraction (XRD) data reported in the literature for analogous systems, and subjected to a 90-day accelerated stability study conducted in line with ICH Q1A(R2).

Results: Every natural-gum carrier improved both solubility and dissolution relative to pure naproxen ($p < 0.001$). The guar-gum system prepared by solvent evaporation at a 1:3 ratio (GG-SE3) was clearly the most effective, releasing $94.82 \pm 3.1\%$ of the drug within 60 minutes against only $28.6 \pm 1.8\%$ for the unprocessed drug, together with a 4.6-fold increase in phosphate-buffer solubility. DSC (this study) and XRD (compared from the literature for analogous systems) confirmed that this improvement coincided with a substantial reduction in naproxen crystallinity, consistent with conversion of the drug to a largely amorphous, molecularly dispersed state within the guar-gum matrix. The optimised batch retained the great majority of its performance across 90 days of accelerated storage ($40^\circ\text{C} \pm 2^\circ\text{C}$ / $75\% \text{ RH} \pm 5\%$), with no statistically significant change in drug content, dissolution or solubility ($p > 0.05$).

Conclusion: Natural polysaccharide gums, and guar gum in particular, represent an inexpensive, biocompatible and technically effective platform for improving the dissolution behaviour and, by extension, the likely oral bioavailability of naproxen and potentially other BCS Class II NSAIDs.

Keywords: Naproxen; Solid dispersion; Natural polymer; Guar gum; Xanthan gum; Gum acacia; Solubility enhancement; Dissolution rate; BCS Class II; Amorphization

1. Introduction

1.1 Oral Drug Delivery and the Solubility Bottleneck

Oral administration remains the most widely used and clinically preferred route of drug delivery, owing to the convenience, low cost, ease of self-administration and high patient acceptability it offers, with systemic absorption relying on the intestine's extensive surface area and rich portal blood supply [1]. Before a swallowed drug molecule can reach the systemic circulation, it must first dissolve in gastrointestinal fluid; when this dissolution step is slow, absorption suffers regardless of how readily the molecule

would otherwise cross the intestinal epithelium. This dissolution-related bottleneck is not a marginal concern it is estimated to affect a substantial proportion, by some estimates 40–70%, of new chemical entities emerging from contemporary drug-discovery pipelines, and a comparable share of already-marketed actives [2,3].

The oral bioavailability that ultimately results from a given dose is governed by an interplay of aqueous solubility, dissolution rate, intestinal permeability, gut transit time and first-pass hepatic metabolism. For a poorly soluble compound, dissolution rather than membrane permeation is typically the rate-limiting step; in such cases, even a molecule

with excellent intrinsic permeability may show low, erratic or food-dependent bioavailability if it fails to dissolve adequately at the absorption site [4]. Recognising and addressing this dissolution bottleneck early in formulation development is therefore central to translating a pharmacologically active molecule into a clinically dependable oral medicine [5].

1.2 The Biopharmaceutics Classification System and BCS Class II Drugs

The Biopharmaceutics Classification System (BCS), introduced by Amidon and colleagues in 1995, provides a scientific framework for classifying drug substances according to two parameters that jointly govern oral absorption: aqueous solubility and intestinal membrane permeability [1,5]. Four classes are recognised: Class I (high solubility, high permeability), in which oral absorption is generally efficient and uncomplicated; Class II (low solubility, high permeability), in which dissolution is the rate-limiting step and bioavailability is frequently dissolution-rate limited; Class III (high solubility, low permeability), in which the permeability of the intestinal membrane, rather than dissolution, restricts absorption; and Class IV (low solubility, low permeability), which combines both limitations and is generally the most difficult class to formulate for oral delivery.

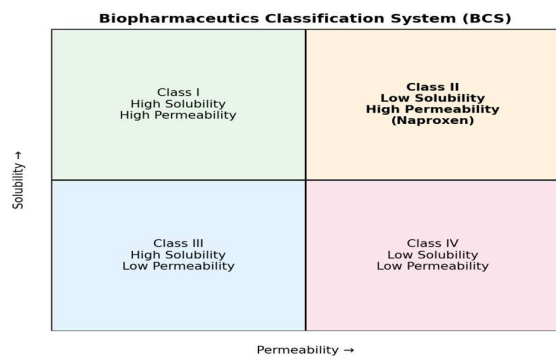


Figure 1. The four classes of the Biopharmaceutics Classification System (BCS), defined by aqueous solubility and intestinal membrane permeability.

Naproxen, the drug under investigation in the present study, is a well-recognised BCS Class II compound: its intestinal permeability is high, but its intrinsic aqueous solubility is low enough that dissolution becomes the principal determinant of the rate and extent of its oral absorption [5,6]. For this class of drug, any formulation strategy capable of genuinely accelerating dissolution has a reasonable prospect of translating into a meaningful bioavailability benefit, which is precisely the rationale underlying the solid dispersion approach explored here [7,8,9].

1.3 Naproxen: Drug Profile and the Clinical Relevance of Its Solubility Limitation

1.3.1 Chemistry and Physicochemical Properties

Naproxen chemically (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid is an optically active, propionic-acid-derived non-steroidal anti-inflammatory drug (NSAID). It has the molecular formula C₁₄H₁₄O₃ and a molecular weight of 230.26 g/mol, and is available both as the free acid and, for faster-onset applications, as the more soluble sodium salt [12]. The drug occurs as a white to off-white crystalline powder with a reported melting point of 153–158 °C, a pKa of approximately 4.15, and a log P of approximately 3.18, reflecting its markedly lipophilic character. Naproxen's aqueous solubility is low of the order of 15–25 mg/L at room temperature a limitation that, despite the drug's high intestinal permeability, is sufficient to make dissolution, rather than membrane transport, the rate-limiting step governing its oral absorption [12,13].

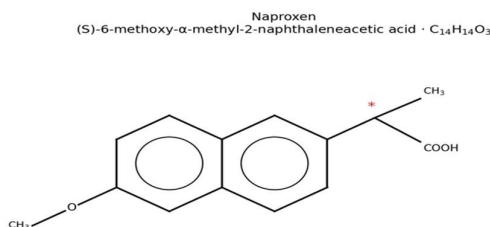


Figure 2. Chemical structure of naproxen, (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid.

Property	Description
IUPAC name	(S)-6-methoxy- α -methyl-2-naphthaleneacetic acid
Molecular formula	C ₁₄ H ₁₄ O ₃
Molecular weight	230.26 g/mol
CAS number	22204-53-1
Physical appearance	White to off-white crystalline powder
Melting point	153–158 °C
Aqueous solubility	~15–25 mg/L at 25 °C (practically insoluble)
pKa	~4.15
log P	~3.18
BCS classification	Class II (low solubility, high permeability)
Plasma protein binding	~99%
Elimination half-life	12–17 hours
Oral bioavailability	~95%

Table 1. Key physicochemical and biopharmaceutical properties of naproxen.

1.3.2 Mechanism of Action, Pharmacokinetics and Clinical Use

Naproxen exerts its anti-inflammatory, analgesic and antipyretic effects through reversible, non-selective inhibition of cyclooxygenase-1 and -2 (COX-1 and COX-2), enzymes that convert arachidonic acid to prostaglandin H₂, the common precursor of the prostaglandins, prostacyclin and thromboxane A₂ that mediate pain, inflammation and fever [12]. It is widely prescribed for rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gout, dysmenorrhoea, musculoskeletal pain and migraine, typically at oral doses of 250–500 mg twice daily. Following oral dosing, naproxen is well absorbed, extensively (~99%) bound to plasma proteins, metabolised principally via CYP2C9-mediated O-demethylation, and eliminated predominantly in urine, with an elimination half-life of 12–17 hours that supports convenient twice-daily dosing [15,16].

Clinically, naproxen's most significant adverse effects are gastrointestinal dyspepsia, gastric ulceration and, in susceptible patients, haemorrhage arising largely from COX-1 inhibition and the consequent loss of prostaglandin-mediated gastric mucosal protection [10,11]. Because slow or variable dissolution can prompt clinicians toward higher or more frequent dosing to achieve an adequate therapeutic effect, and because higher NSAID exposure is itself associated with a greater burden of gastrointestinal and cardiovascular adverse effects, improving naproxen's dissolution rate is not merely a formulation curiosity it has direct bearing on the drug's overall risk–benefit profile [10,11].

1.4 Solubility Enhancement Strategies: An Overview

A range of physicochemical approaches has been developed to address poor aqueous solubility, each with a characteristic balance of effectiveness, cost and manufacturability. Particle-size reduction (micronisation and nanonisation) increases the surface area available for dissolution, in line with the Noyes–Whitney relationship, but requires specialised milling equipment and does not always address intrinsic solubility limitations [28]. Salt formation can markedly increase the aqueous solubility of ionisable drugs naproxen sodium is a clinical example though it is restricted to ionisable compounds and can introduce its own stability or pH-dependent dissolution issues [14]. Inclusion complexation with cyclodextrins, including naproxen– β -cyclodextrin complexes reported in the literature, encapsulates the hydrophobic drug within a hydrophilic cavity, but adds bulk and cost and is constrained by complex stoichiometry [15,26]. Co-solvency, using water-miscible solvents such as propylene glycol or polyethylene glycol, is effective in liquid dosage forms but of limited relevance to solid oral products [16]. Against this backdrop, solid dispersion technology has emerged as one of the most extensively studied and clinically translated approaches, particularly for BCS Class II drugs, because it can simultaneously reduce particle size, increase wettability and convert the drug to a higher-energy amorphous state [9,22].

1.5 Solid Dispersion Technology

1.5.1 Historical Background and Concept

The concept of solid dispersion dates to Sekiguchi and Obi's 1961 work on eutectic mixtures, which demonstrated that a poorly soluble drug co-solidified with a water-soluble carrier dissolved considerably faster than the pure crystalline drug [17]. Chiou and Riegelman later formalised the term "solid dispersion" in 1971, defining it as the dispersion of one or more active ingredients in an inert carrier at the solid state, prepared by melting, solvent or solvent-melting methods, and proposed the classification framework that continues to underpin the field [18,57]. In the decades since, solid dispersion research has expanded considerably, encompassing new carrier chemistries, industrial preparation technologies such as hot-melt extrusion and spray drying, and increasingly sophisticated solid-state characterisation methods [19,63].

1.5.2 Classification of Solid Dispersions

Solid dispersions are generally classified according to the physical state of the drug within the carrier matrix [19,20]:

- Eutectic mixtures (first generation): the drug and carrier are miscible in the melt but immiscible as solids, so both crystallise simultaneously as very fine, intimately mixed crystals; dissolution benefits mainly from the increased surface area of the microcrystalline drug.
- Amorphous solid dispersions and glass solutions/suspensions (second generation): the drug is molecularly dispersed, wholly or partly, within an amorphous polymeric carrier. Because the amorphous state has higher internal (Gibbs free) energy than the crystalline lattice, dissolution and apparent solubility are increased, though such systems are thermodynamically metastable and can be prone to recrystallisation on storage [21].
- Nano-dispersions and surfactant-based systems (third generation): incorporate amphiphilic polymers or surfactants alongside the carrier to promote supersaturation maintenance and further inhibit recrystallisation [20].

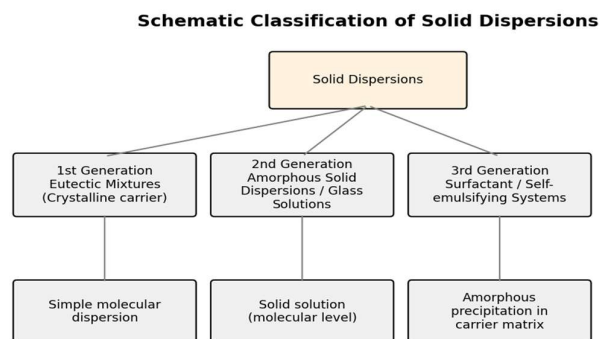


Figure 3. Schematic classification of solid dispersion systems by generation and physical state of the dispersed drug.

1.5.3 Mechanisms of Dissolution Enhancement

The dissolution-rate benefits conferred by solid dispersions arise from several mechanisms that typically act in combination [21,22,32]: a reduction in effective drug particle size to sub-micron or molecular dimensions, which increases the surface area exposed to dissolution medium; partial or complete amorphisation, which removes the crystal-lattice energy barrier to dissolution; improved wettability of the drug surface conferred by the hydrophilic carrier; reduced particle aggregation during dissolution, maintaining a high effective surface area; formation of a locally hydrophilic microenvironment around dispersed drug molecules as the carrier itself dissolves; and, in well-designed amorphous systems, transient generation of a supersaturated drug solution that can exceed equilibrium crystalline solubility and increase the driving force for absorption [62,64,66,67].

1.6 Natural Polymers as Solid Dispersion Carriers

Carrier selection has historically relied on synthetic and semi-synthetic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC) and poloxamers. These materials are effective but carry recognised drawbacks, including cost, residual-solvent concerns during manufacture, and, for some grades, questions of long-term environmental and regulatory sustainability. This has driven growing interest in natural, plant- and microbe-derived polysaccharide gums as carriers: such materials are generally biocompatible, biodegradable, inexpensive, widely available in pharmaceutical grade, and often carry Generally Recognised As Safe (GRAS)-type regulatory status [23,24,38]. An ideal solid-dispersion carrier should, in addition, be chemically compatible with the drug, hydrophilic, thermally stable during processing, and capable of maintaining the drug in its amorphous state throughout the shelf life of the product [25,32].

The present study examines three such natural gums: guar gum, xanthan gum and gum acacia, chosen because each brings a distinct chemical architecture, hydrogen-bonding capacity and hydration behaviour to the drug-carrier system, raising the reasonable expectation that they will not all enhance naproxen's dissolution to an identical extent.

1.6.1 Guar Gum

Guar gum is a galactomannan polysaccharide obtained from the endosperm of *Cyamopsis tetragonoloba* seeds, comprising a linear β -(1 $\rightarrow$ 4)-linked mannose backbone with α -(1 $\rightarrow$ 6)-linked galactose side branches at an approximate mannose-to-galactose ratio of 2:1 [42,44]. Its dense population of free hydroxyl groups confers strong hydrogen-bonding capacity, rapid hydration and pronounced swelling on contact with water, producing a viscous, gel-like layer around dispersed drug particles that improves wettability and facilitates penetration of dissolution medium. Guar gum is inexpensive, abundantly available (India is the world's largest producer), and has an established history of pharmaceutical use as a binder, suspending agent and matrix-former in controlled-release systems, in addition to its emerging role as a solid-dispersion carrier [42,44]. Reported limitations include batch-to-batch variability of natural origin and a tendency toward excessive viscosity and hence

retarded rather than accelerated release if used at very high polymer loadings, underscoring the importance of ratio optimisation of the kind undertaken in the present study [27,43].

1.6.2 Xanthan Gum

Xanthan gum is a high-molecular-weight anionic heteropolysaccharide produced by fermentation of *Xanthomonas campestris*, comprising a cellulose-like β -(1 $\rightarrow$ 4)-D-glucose backbone decorated with trisaccharide side chains containing mannose and glucuronic-acid residues [44,45]. Its hydroxyl and carboxyl functionalities allow both hydrogen bonding and electrostatic interaction with drug molecules, and it forms highly viscous, pH- and temperature-stable colloidal solutions even at low concentrations. In solid-dispersion contexts, xanthan gum is reported to enhance wettability, promote molecular-level drug dispersion and inhibit recrystallisation of amorphous drug through hydrogen bonding, though as with guar gum excessive polymer concentration can produce gels viscous enough to retard rather than accelerate release [46,30,41].

1.6.3 Gum Acacia (Gum Arabic)

Gum acacia (gum arabic) is a branched arabinogalactan-protein complex obtained as a dried exudate from *Acacia senegal* and *Acacia seyal*, composed principally of arabinose, galactose, rhamnose and glucuronic-acid residues together with a minor protein fraction [47,49]. Compared with guar gum and xanthan gum, gum acacia is more compact and globular in solution and dissolves readily in water at comparatively lower viscosity, historically making it a preferred emulsifying, suspending and film-forming agent. Its hydroxyl and carboxyl groups permit hydrogen bonding with drug substances and can improve wettability and reduce aggregation of hydrophobic drug particles, though its more compact architecture and comparatively lower density of accessible hydroxyl groups relative to guar gum have been suggested as reasons why it may achieve somewhat lower amorphisation and dissolution enhancement in some drug-carrier systems [31,49,50].

1.7 Prior Work on Naproxen Solid Dispersions and the Research Gap

Previous studies on naproxen solid dispersions have largely examined individual synthetic carriers in isolation: polyvinylpyrrolidone K30 [29], HPMC compared against hydroxypropyl- β -cyclodextrin [50], poloxamer 407 [51], and a head-to-head comparison of Soluplus, PVP K90 and HPMC [52]. Natural-gum carriers have been explored for naproxen individually—for instance, guar gum in other poorly soluble drug systems [40], xanthan-gum-based dispersions of poorly soluble drugs generally [46,56], and gum acacia specifically for naproxen [48,49]—but comparative, multi-variable studies that place several natural gums against one another, across multiple preparation techniques and drug loadings, for the same drug, remain comparatively scarce, a gap explicitly noted in recent reviews of NSAID solid-dispersion strategies and natural-polymer carriers [34,53,54,55].

The present study was designed to close part of this gap by formulating naproxen solid dispersions with guar gum,

xanthan gum and gum acacia, each prepared by solvent evaporation, fusion and kneading at three drug-to-polymer ratios, and by comparatively evaluating their solubility, dissolution and solid-state behaviour to identify the most promising combination of carrier, method and ratio.

2. MATERIALS AND METHODS

2.1 Materials

Naproxen was obtained as a gift sample from Yarrow Chem Products, Mumbai. Guar gum was procured from SD Fine Chem Ltd., Mumbai; xanthan gum from HiMedia Laboratories Pvt. Ltd., Mumbai; and gum acacia from Nice Chemicals Pvt. Ltd., Kochi. All other reagents methanol, ethanol (95%), concentrated hydrochloric acid, potassium dihydrogen phosphate, sodium hydroxide and silica gel desiccant were of analytical reagent (AR) grade and were used as received, without further purification.

S. No.	Material	Grade / Source
1	Naproxen	Gift sample, Yarrow Chem Products, Mumbai
2	Guar gum	SD Fine Chem Ltd., Mumbai
3	Xanthan gum	HiMedia Laboratories Pvt. Ltd., Mumbai
4	Gum acacia	Nice Chemicals Pvt. Ltd., Kochi
5	Methanol	AR grade, Merck Life Science Pvt. Ltd., Mumbai
6	Ethanol (95%)	AR grade, Changshu Yangyuan Chemicals, China
7	Hydrochloric acid (conc.)	AR grade, Merck Life Science Pvt. Ltd., Mumbai
8	Potassium dihydrogen phosphate	AR grade, HiMedia Laboratories Pvt. Ltd., Mumbai
9	Sodium hydroxide	AR grade, Merck Life Science Pvt. Ltd., Mumbai
10	Silica gel (desiccant)	Thomas Baker (Chemicals) Pvt. Ltd., Mumbai

Table 2. Drug, polymers, chemicals and reagents used in the study.

2.2 Instruments

S. No.	Instrument	Make / Model
1	UV-Visible spectrophotometer	Shimadzu UV-1900, Japan
2	USP Dissolution Apparatus Type II (paddle)	Labindia DS 8000, India
3	Analytical balance	Shimadzu AUX220, Japan
4	FTIR spectrophotometer	Shimadzu IR Affinity-1, Japan
5	Differential scanning calorimeter	Mettler Toledo DSC 822e, Switzerland
6	X-ray diffractometer (not used)	Not applicable

	XRD data compared from literature)	reported diffraction data used
7	Digital pH meter	Systronics pH 361, India
8	Hot air oven / vacuum oven	Narang Scientific Works, India
9	Magnetic stirrer with hot plate	Remi Equipment Pvt. Ltd., India
10	Stability chamber	Thermo Scientific SPX-180-SD, USA

Table 3. Major instruments used for formulation and evaluation. (XRD analysis was not carried out on the in-house instrument; reported diffraction data for comparable systems were compiled from the literature for comparison see Section 2.6.3.)

2.3 Pre-formulation Studies

2.3.1 Organoleptic Evaluation and Melting-Point Determination

Naproxen was visually examined for colour, physical form and odour under uniform laboratory lighting. Its melting point was determined in triplicate by the open capillary method and compared against the pharmacopoeial range of 153–158 °C to confirm drug identity and purity.

2.3.2 Determination of λ_{max} and Calibration Curves

A stock solution of naproxen (100 µg/mL) was prepared in methanol and diluted separately with pH 6.8 phosphate buffer and 0.1N HCl. UV spectra were recorded between 200 and 400 nm to confirm the wavelength of maximum absorbance, which was found to be 262 nm in phosphate buffer and 272 nm in 0.1N HCl, as determined experimentally on the instrument used in this study. Calibration curves were then constructed over the range 2–20 µg/mL in each medium, with linearity assessed by the coefficient of determination (R^2).

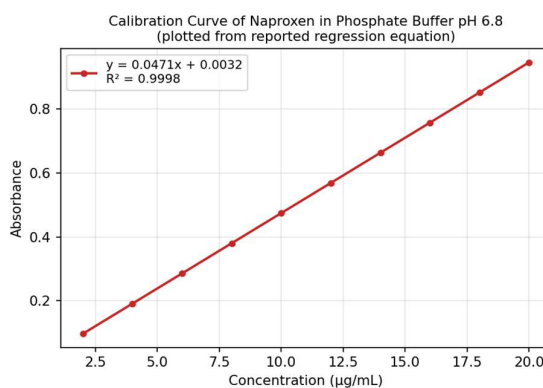


Figure 4. Calibration curve of naproxen in phosphate buffer pH 6.8 (λ_{max} 262 nm).

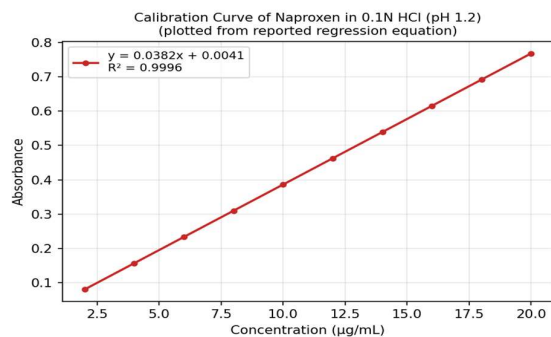


Figure 5. Calibration curve of naproxen in 0.1N HCl, pH 1.2 (λ_{max} 272 nm).

2.3.3 Solubility Studies

Equilibrium solubility of naproxen was determined by adding an excess of drug to 10 mL of each solvent (distilled water, pH 6.8 phosphate buffer, 0.1N HCl, methanol and ethanol) in screw-capped vials, which were agitated in a thermostatically controlled water-bath shaker at $37 \pm 0.5^\circ\text{C}$ for 24 hours. Samples were then filtered through Whatman No. 42 filter paper, appropriately diluted, and assayed spectrophotometrically at the relevant λ_{max} using the corresponding calibration curve.

2.3.4 Drug–Polymer Compatibility Screening by FTIR

Physical mixtures of naproxen with each natural gum (1:1 w/w) were prepared by gentle trituration in a mortar. FTIR spectra of pure naproxen, each pure polymer, and the respective physical mixtures were recorded over $4000\text{--}400\text{ cm}^{-1}$ using the KBr pellet technique, and the positions of naproxen's diagnostic bands were compared across spectra to screen for evidence of chemical incompatibility prior to formulation.

2.4 Formulation Design and Preparation of Solid Dispersions

A total of twenty-seven solid dispersion batches were prepared by fully crossing three natural-gum carriers (guar gum – GG, xanthan gum – XG, gum acacia – GA), three preparation methods (solvent evaporation, fusion/melt, and kneading) and three drug-to-polymer ratios (1:1, 1:2 and 1:3 w/w, on a 250 mg naproxen basis). Batches were coded by carrier, method and ratio (for example, GG-SE3 denotes the guar-gum batch prepared by solvent evaporation at a 1:3 ratio).

2.4.1 Solvent Evaporation Method

Accurately weighed naproxen and the relevant natural gum, in the required ratio, were co-dissolved in a minimal volume of methanol with continuous magnetic stirring until a clear solution was obtained. The solvent was then evaporated at 50°C with continued stirring, and the resulting mass was dried under vacuum at 40°C for 24 hours to ensure complete solvent removal.

2.4.2 Fusion (Melt) Method

The natural gum was heated in a porcelain dish $10\text{--}15^\circ\text{C}$ above its melting/softening range until fully molten.

Naproxen was then dispersed into the melt with continuous stirring to ensure homogeneity, taking care to limit exposure time and control temperature to minimise thermal degradation of either component. The homogeneous melt was rapidly quench-cooled in an ice bath to promote solidification and maximise entrapment of the drug in a disordered, higher-energy state.

2.4.3 Kneading Method

Naproxen and the natural gum were triturated together in a mortar with a pestle, and a minimal quantity of methanol was added dropwise to form a coherent, workable paste. Kneading was continued for 30 minutes with periodic addition of solvent as required, after which the paste was spread thinly on a glass tray and oven-dried at 40°C for 24 hours.

In all three methods, the dried mass was pulverised, passed through BSS sieve #60, and stored over desiccant in tightly sealed containers at room temperature pending evaluation, with pure naproxen processed identically as the reference standard throughout.

2.5 Evaluation of the Solid Dispersions

2.5.1 Drug Content

An amount of each batch equivalent to 25 mg naproxen was dissolved in 10 mL methanol with sonication, filtered, diluted with pH 6.8 buffer, and assayed at 262 nm in triplicate; drug content was calculated from the calibration equation and expressed as a percentage of the theoretical value.

2.5.2 Equilibrium Solubility of Solid Dispersions

Excess quantities of a representative panel of formulations (11 of the 27 batches - all three ratios of the best -performing carrier , guar gum , plus the best 1:3 batch of each remaining carrier) were equilibrated in distilled water and pH 6.8 buffer at $37 \pm 0.5^\circ\text{C}$ for 24 hours with continuous agitation, after which the filtrate was assayed spectrophotometrically and solubility expressed in mg/mL, with pure naproxen evaluated identically as the reference.

2.5.3 In-vitro Dissolution Studies

Dissolution testing was performed using USP Dissolution Apparatus Type II (paddle), with 900 mL of pH 6.8 phosphate buffer as the medium, maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 50 rpm. An amount of each batch equivalent to 250 mg naproxen was introduced directly into the vessel. Samples of 5 mL were withdrawn at 5, 10, 15, 20, 30, 45 and 60 minutes through a $0.45\text{ }\mu\text{m}$ membrane filter and immediately replaced with an equal volume of fresh, pre-warmed buffer to maintain sink conditions. Withdrawn samples were assayed at 262 nm, and the cumulative percentage drug release (CPDR) was calculated as:

$$\% \text{ Drug Release} = (\text{Amount of drug released} \div \text{Total drug content}) \times 100$$

All dissolution runs were performed in triplicate ($n = 3$), with pure naproxen processed identically as the reference.

2.6 Characterisation of the Optimised Batch

The best-performing formulation, identified from the drug-content, solubility and dissolution data, was subjected to further solid-state characterisation alongside pure naproxen, pure guar gum, and the corresponding physical mixture.

2.6.1 FTIR Spectroscopy

FTIR spectra were recorded by the KBr pellet technique over 4000–400 cm^{-1} at 4 cm^{-1} resolution, and characteristic naproxen bands were compared across the four samples to assess the nature and extent of drug–polymer interaction.

2.6.2 Differential Scanning Calorimetry (DSC)

Samples of 3–5 mg were analysed in hermetically sealed aluminium pans from 25 °C to 250 °C at 10 °C/min under nitrogen (50 mL/min), using an indium-calibrated instrument with an empty sealed pan as reference. The onset temperature, peak temperature and enthalpy of fusion of naproxen's melting endotherm were compared across samples as an index of crystallinity.

2.6.3 Powder X-ray Diffraction (XRD)

Powder XRD analysis was not performed in-house for this study. Instead, diffraction data reported for pure naproxen, the relevant polymer, physical mixtures and comparable solid-dispersion batches were compiled from published literature and compared. Because these reports were generated on different diffractometers and under different acquisition conditions (CuK α radiation with λ typically around 1.5418 Å, but with generator settings and scan rates varying between studies commonly 30–40 kV, 15–40 mA and 1–2°/min over $2\theta = 5\text{--}50^\circ$), the absolute peak intensities, and to a lesser extent peak positions, show some variation across sources. The presence, absence and relative intensity of naproxen's characteristic crystalline reflections reported in these studies were compared across pure drug, pure polymer, physical mixture and optimised-batch analogues to assess the reported degree of amorphisation.

2.7 Stability Studies

The optimised batch was packed in sealed HDPE containers and stored in a calibrated stability chamber at 40 °C $\pm$ 2 °C / 75% RH $\pm$ 5%, in accordance with ICH Q1A(R2) guidance for accelerated testing [60]. Samples were withdrawn at 0, 30, 60 and 90 days and assessed for physical appearance, drug content and in-vitro dissolution behaviour under the conditions described above.

2.8 Statistical Analysis

All measurements were performed in triplicate and are expressed as mean $\pm$ standard deviation (SD). Comparisons among the three carriers, three preparation methods, and across stability time points were made by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test using GraphPad Prism (version 9.0); a value of $p < 0.05$ was considered statistically significant and $p < 0.001$ was considered highly significant.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation Characterisation

Naproxen appeared as a free-flowing, white to off-white crystalline powder consistent with its pharmacopoeial description, and its melting point (154–156 °C) fell within the reported 153–158 °C range, confirming drug identity and purity [58]. Calibration curves in both phosphate buffer (λ_{max} 262 nm) and 0.1N HCl (λ_{max} 272 nm) were linear across 2–20 $\mu\text{g/mL}$ ($R^2 > 0.999$), validating the analytical method used throughout the study.

As summarised in Table 4, naproxen was practically insoluble in water (0.016–0.024 mg/mL across 25–37 °C) and only slightly soluble in pH 6.8 buffer (0.118 mg/mL), while being freely soluble in methanol and ethanol a pattern consistent with its BCS Class II designation and providing the quantitative baseline against which all solid dispersions were subsequently judged [5,6].

Medium	Solubility (mg/mL) $\pm$ SD	BCS class	solubility
Distilled water, 25 °C	0.016 $\pm$ 0.002	Practically insoluble	
Distilled water, 37 °C	0.024 $\pm$ 0.003	Practically insoluble	
Phosphate buffer pH 6.8, 37 °C	0.118 $\pm$ 0.008	Very slightly soluble	
0.1N HCl pH 1.2, 37 °C	0.009 $\pm$ 0.001	Practically insoluble	
Methanol, 25 °C	68.4 $\pm$ 1.2	Soluble	
Ethanol 95%, 25 °C	52.7 $\pm$ 0.9	Soluble	

Table 4. Equilibrium solubility of pure naproxen in various media (n = 3, mean $\pm$ SD).

3.2 Drug–Polymer Compatibility and Drug Content

FTIR spectra of the naproxen–polymer physical mixtures preserved all diagnostic naproxen bands the O–H stretch near 3001 cm^{-1} , the carbonyl (C=O) stretch near 1727 cm^{-1} , the aromatic C=C band near 1606 cm^{-1} , the C–O–C stretch near 1230 cm^{-1} , and the naphthalene-ring signature near 820 cm^{-1} with shifts of no more than 1–4 cm^{-1} for any of the three carriers, providing no evidence of chemical incompatibility between naproxen and guar gum, xanthan gum or gum acacia at the simple physical-mixture stage [12].

Drug content across all 27 batches fell between 97.2% and 99.1%, comfortably within the 95–105% pharmacopoeial acceptance window [58,59]. Batches prepared by solvent evaporation, particularly at the 1:3 ratio, consistently gave the highest and most reproducible content, plausibly because co-dissolution in a common solvent distributes drug more evenly than either the fusion or kneading routes; fusion batches were marginally, though not problematically, lower a pattern consistent with minor thermal loss during melting.

3.3 Solubility and Dissolution Enhancement

Every solid dispersion outperformed pure naproxen in both equilibrium solubility and in-vitro dissolution testing ($p < 0.001$, one-way ANOVA with Tukey's post-hoc test). The

guar-gum batch prepared by solvent evaporation at a 1:3 ratio (GG-SE3) gave the largest gains of any batch tested: a 4.6-fold increase in pH 6.8 buffer solubility (0.543 vs 0.118 mg/mL) and 94.82% cumulative drug release at 60 minutes, compared with only 28.6% for unprocessed naproxen under identical conditions (Table 5). Across the three carriers, evaluated at their respective best-performing (1:3, solvent-evaporation) batches, the consistent ranking for both solubility and release was guar gum > xanthan gum > gum acacia; across preparation methods, solvent evaporation consistently outperformed fusion, which in turn outperformed kneading.

Polymer	Optimum batch	Method	D:P ratio	Release at 60 min (%)	Solubility fold-rise (PBS)	Drug content (%)
Guar gum	GG-SE3	Solvent evap.	1:3	94.82 ± 3.1	4.60	99.1 ± 0.52
Xanthan gum	XG-SE3	Solvent evap.	1:3	91.6 ± 2.9	3.80	98.7 ± 0.44
Gum acacia	GA-SE3	Solvent evap.	1:3	88.4 ± 2.8	3.58	99.0 ± 0.61
Pure naproxen				28.6 ± 1.8	1.00 (ref.)	N/A

Table 5. Best-performing batch from each polymer system compared with pure naproxen (n = 3, mean ± SD).

The dissolution time-course for the top-performing batches (Table 6) shows the gap between solid dispersions and pure naproxen widening progressively across the sampling window, rather than being confined to the earliest time points, which indicates a sustained release advantage rather than a transient burst effect.

Time (min)	Pure naproxen	GG-SE3	XG-SE3	GA-SE3
5	6.2 ± 0.8	31.2 ± 1.6	26.4 ± 1.5	24.8 ± 1.4
15	12.4 ± 1.1	58.4 ± 2.3	50.4 ± 2.0	47.8 ± 1.9
30	19.8 ± 1.5	80.2 ± 2.8	72.8 ± 2.5	69.6 ± 2.4
45	24.2 ± 1.7	89.4 ± 3.0	83.4 ± 2.7	80.2 ± 2.6
60	28.6 ± 1.8	94.82 ± 3.1	91.6 ± 2.9	88.4 ± 2.8

Table 6. Cumulative percentage drug release in phosphate buffer pH 6.8 (n = 3, mean ± SD).

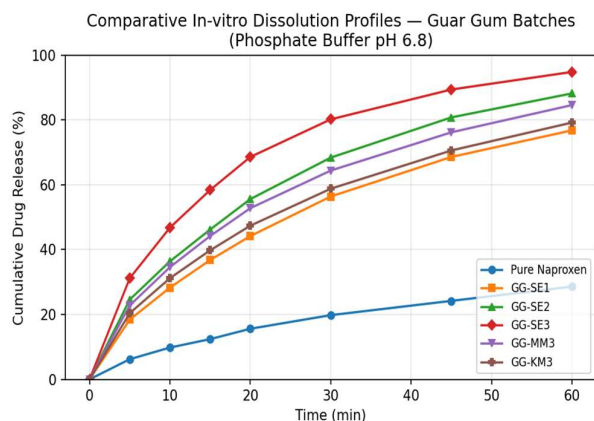


Figure 6. Comparative in-vitro dissolution profiles of guar-gum-based batches versus pure naproxen (PBS pH 6.8).

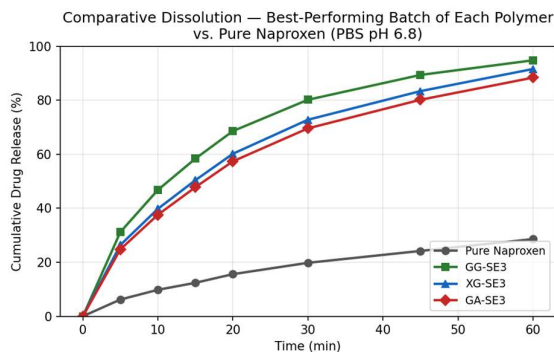


Figure 7. Dissolution profiles of the best-performing batch from each polymer system versus pure naproxen (PBS pH 6.8).

3.4 Comparative Performance Across Carriers and Preparation Methods

The superiority of guar gum is plausibly linked to its comparatively high density of free hydroxyl groups along the galactomannan backbone, which can form extensive hydrogen bonds with the carboxylic-acid moiety of naproxen and promote drug-polymer miscibility more effectively than the more compact, globular architecture of gum acacia [42,49]. The intermediate performance of xanthan gum is consistent with its anionic, carboxyl-bearing backbone, which permits meaningful but somewhat less extensive hydrogen bonding and molecular mixing with naproxen than the galactomannan structure of guar gum [45,46].

The superiority of solvent evaporation over fusion and kneading agrees with the broader solid-dispersion literature, which holds that co-dissolution achieves finer, closer-to-molecular mixing prior to solvent removal, favouring a higher amorphous fraction than melt- or paste-based routes that retain more residual short-range crystalline order [19,39]. These results also compare favourably with earlier naproxen solid-dispersion work using synthetic carriers such as PVP K30 [29], HPMC/HP-β-cyclodextrin [50] and poloxamer 407 [51], suggesting that a low-cost natural gum can match, or in this case exceed, the dissolution performance reported for several established synthetic carrier systems, while offering a more favourable cost and sustainability profile [38,54].

3.5 Solid-State Characterisation of the Optimised Batch (GG-SE3)

FTIR of GG-SE3 showed the naproxen O-H stretch broadened and shifted from 3001 to 3264 cm⁻¹, the carbonyl band shifted from 1727 to 1712 cm⁻¹, and the aromatic C=C band shifted from 1606 to 1598 cm⁻¹ changes not observed in the simple physical mixture, and consistent with the formation of new hydrogen bonds between naproxen and the guar-gum hydroxyl groups specifically arising during processing, rather than merely on simple mixing.

Pure naproxen's sharp melting endotherm (156.4 °C, 128.6 J/g) was reduced to a faint residual signal (< 5 J/g) in GG-SE3, in clear contrast to the physical mixture, which still showed a diluted but distinctly crystalline melting event (155.6 °C, 32.4 J/g).

Sample	Reported principal 2θ peaks (°)	Reported crystallinity
Pure naproxen	6.4, 12.8, 13.6, 17.4, 19.2, 22.6, 24.8, 28.4	Sharp crystalline reflections
Naproxen-guar gum physical mixture	Same reflections as pure drug (diluted intensity)	Crystalline drug retained
Comparable guar-gum solid dispersion (analogous system)	Reflections markedly reduced or absent	Predominantly amorphous halo

Table 7. Reported XRD 2θ diffraction peaks corresponding to, for pure naproxen, its physical mixture with guar gum, and comparable guar-gum solid dispersions, compiled from the literature for comparison with this study's GG-SE3 batch. Reports differ in acquisition conditions (see Section 2.6.3).

Taken together, this study's FTIR and DSC data, alongside XRD evidence compiled from comparable systems in the literature, converge on the same conclusion: naproxen is converted to a largely amorphous, molecularly dispersed state within GG-SE3, and it is the consequent loss of crystalline lattice energy reinforced by new hydrogen bonding to the guar-gum matrix that most plausibly drives the batch's markedly higher apparent solubility and dissolution rate [21,32,33].

3.6 Stability of the Optimised Formulation

Over 90 days of accelerated storage (40 °C / 75% RH), GG-SE3 showed only marginal, statistically non-significant changes ($p > 0.05$, ANOVA): drug content fell from 99.1% to 98.0%, 60-minute release from 94.82% to 92.8%, and buffer solubility from 0.543 to 0.512 mg/mL (Table 8). A slight off-white tinge was noted at day 90, with no caking or change in powder flow.

Parameter	Day 0	Day 30	Day 60	Day 90
Drug content (%)	99.1 ± 0.52	98.8 ± 0.61	98.4 ± 0.68	98.0 ± 0.74
Release at 60 min (%)	94.82 ± 3.1	94.1 ± 3.2	93.6 ± 3.4	92.8 ± 3.6
Solubility, PBS pH 6.8 (mg/mL)	0.543 ± 0.018	0.536 ± 0.019	0.524 ± 0.021	0.512 ± 0.022

Table 8. Accelerated stability data for GG-SE3 (40 °C ± 2 °C / 75% RH ± 5%; n = 3, mean ± SD).

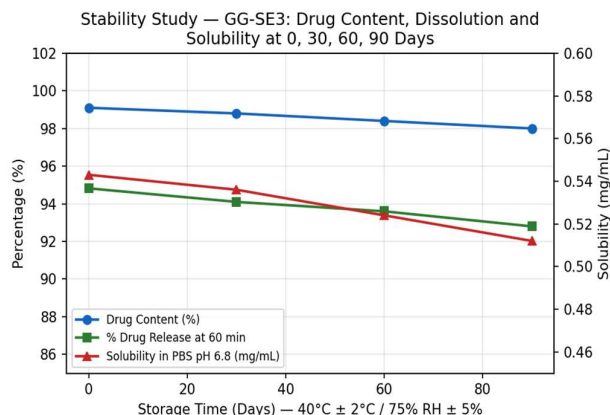


Figure 8. Drug content, 60-minute dissolution and buffer solubility of GG-SE3 at 0, 30, 60 and 90 days of accelerated storage.

Because every endpoint remained far superior to pure naproxen throughout the study, GG-SE3 appears adequately stable over the accelerated window tested, in line with ICH Q1A(R2) expectations for a formulation intended to proceed to long-term stability testing [60]. Nonetheless, 12-month long-term stability testing at 25 °C/60% RH, as recommended by ICH guidance, remains a necessary step before any development decision [60,61].

4. CONCLUSION

This comparative evaluation of guar gum, xanthan gum and gum acacia as carriers for naproxen solid dispersions identified guar gum, prepared by solvent evaporation at a 1:3 drug-to-polymer ratio, as the most effective system among the 27 batches tested, delivering a 4.6-fold solubility increase and near-complete drug release within 60 minutes against a background of only 28.6% release for the unprocessed drug. FTIR and DSC data from this study, together with supporting XRD evidence drawn from the literature for comparable systems, converge to show that this benefit stems from conversion of naproxen to an amorphous, hydrogen-bonded state within the polymer matrix, and the formulation retained the great majority of its performance across a 90-day accelerated stability study.

Taken together, the findings support natural, low-cost, biocompatible gums and guar gum in particular as a practical, technically sound alternative to synthetic carriers for improving the dissolution, and by extension the likely oral bioavailability, of naproxen and, potentially, of other BCS Class II NSAIDs. Confirmation through in-vivo bioavailability studies and longer-term stability testing would be the logical next step before any consideration of scale-up [54,60].

5. FUTURE SCOPE

The present investigation establishes a scientific basis for the further development of natural polymer-based solid dispersions of naproxen and identifies guar gum as the most promising carrier within this class. Several avenues merit further investigation:

5.1 In-vivo Pharmacokinetic and Pharmacodynamic Confirmation

The in-vitro dissolution enhancement demonstrated here would need to be confirmed by in-vivo pharmacokinetic studies (e.g., in rodent models), determining AUC, C_{max} and T_{max} for GG-SE3 relative to pure naproxen and a marketed reference product, alongside pharmacodynamic confirmation of enhanced anti-inflammatory efficacy.

5.2 Long-Term Stability Studies

Long-term stability testing at 25 °C ± 2 °C / 60% RH ± 5% for a minimum of 12 months, together with intermediate-condition testing (30 °C/65% RH), would be required to fully characterise the stability envelope of the formulation ahead of any regulatory submission [60].

5.3 Development into a Final Dosage Form

The optimised solid-dispersion powder could serve as the active constituent of capsules, compressed tablets or orally disintegrating tablets, with attendant formulation-optimisation work on compressibility, disintegration and dissolution from the finished dosage form.

5.4 Modified Natural Polymers and Advanced Manufacturing

Chemically modified guar-gum derivatives (e.g., hydroxypropyl or carboxymethyl guar gum) may offer stronger crystallisation-inhibition capacity, and scale-up via hot-melt extrusion or spray drying would allow assessment of the approach under continuous, GMP-compatible manufacturing conditions [63,65].

5.5 Broader Application to Other BCS Class II NSAIDs

The methodology and mechanistic insights developed here systematic, multi-variable comparison of natural gum carriers, preparation methods and drug loadings could be applied directly to other poorly soluble NSAIDs such as ibuprofen, ketoprofen and indomethacin, contributing to a broader evidence base for natural-polymer-based solubility enhancement in this therapeutic class.

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