

Natural Gum-Based Solid Dispersions of Naproxen: Comparative Evaluation of Guar Gum, Xanthan Gum and Gum Acacia for Improved Solubility and Dissolution

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Abstract:

Naproxen, a Biopharmaceutics Classification System (BCS) Class II non-steroidal anti-inflammatory drug (NSAID), shows dissolution-rate-limited absorption owing to its poor aqueous solubility. This study compared three hydrophilic natural gums – guar gum (GG), xanthan gum (XG) and gum acacia (GA) – as carriers for naproxen solid dispersions. Twenty-seven batches were prepared by crossing three carriers, three techniques (solvent evaporation, fusion and kneading) and three drug-to-polymer ratios (1:1, 1:2 and 1:3 w/w). Drug content was determined for all batches, and a representative eleven-batch panel was evaluated for equilibrium solubility (water and pH 6.8 phosphate buffer) and USP Apparatus II dissolution. The optimised batch was characterised by Fourier-transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) and stored for 90 days at 40 °C/75% relative humidity. Drug content ranged from 97.2% to 99.1%, and every dispersion evaluated improved solubility and dissolution relative to pure naproxen ($p < 0.001$). Guar gum prepared by solvent evaporation at 1:3 (GG-SE3) was best, releasing $94.82 \pm 3.1\%$ in 60 min against $28.6 \pm 1.8\%$ for the pure drug, with 4.6-fold higher buffer solubility (0.543 vs 0.118 mg/mL); XG-SE3 and GA-SE3 released 91.6% and 88.4%. FTIR band shifts indicated drug–polymer hydrogen bonding, and the DSC enthalpy of fusion fell from 128.6 J/g to < 5 J/g, consistent with a marked loss of crystallinity. After 90 days, changes in drug content, release and solubility were not significant ($p > 0.05$). Natural gums, particularly guar gum, are inexpensive, biocompatible carriers that markedly improve the in vitro dissolution of naproxen; in vivo and long-term stability studies are warranted.

Keywords: Naproxen; Solid Dispersion; Guar Gum; Xanthan Gum; Gum Acacia; Solubility; Dissolution Rate; BCS Class II; Accelerated Stability.

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Introduction

Oral delivery, solubility and the BCS: Oral administration is the most widely used route of drug delivery because of its convenience, low cost and high patient compliance [1]. A drug must dissolve in gastrointestinal fluid before it can be absorbed, so slow dissolution limits absorption regardless of how readily the dissolved molecule crosses the intestinal epithelium [2]. An estimated 40% or more of new chemical entities are poorly water soluble, which makes this dissolution bottleneck a central problem in formulation development [1,3,4]. For such compounds, dissolution rather than membrane permeation usually controls the rate and extent of oral absorption, and bioavailability can be low or variable [5]. The dependence of dissolution rate on surface area and solubility is described by the Noyes–Whitney relationship [6].

The BCS classifies drugs by aqueous solubility and intestinal permeability into four classes [2,7]. In Class II (low solubility, high permeability), dissolution is the rate-limiting step, so formulation strategies that accelerate dissolution can translate into improved bioavailability [2,7].

Naproxen: Naproxen, (S)-6-methoxy- α -methyl-2-naphthaleneacetic acid ($C_{14}H_{14}O_3$; molecular weight 230.26 g/mol), is a propionic-acid-derived NSAID that melts at 153–158 °C and has a pKa of about 4.15 and a log P of about 3.18 [8] (Table 1). Its intrinsic aqueous solubility is of the order of 15–25 mg/L at room temperature [8]. As a weak acid, its solubility is strongly pH dependent and is lowest in acidic media [9]. Naproxen is commonly regarded as a BCS Class II drug because of its low solubility in

acidic media combined with high permeability and near-complete oral absorption [10].

Table 1: Physicochemical and biopharmaceutical properties of naproxen [8,10].

Property	Description
Chemical name	(S)-6-methoxy- α -methyl-2-naphthaleneacetic acid
Molecular formula; weight	C ₁₄ H ₁₄ O ₃ ; 230.26 g/mol
Appearance	White to off-white crystalline powder
Melting point	153–158 °C
Aqueous solubility	About 15–25 mg/L at room temperature
pKa; log P	About 4.15; about 3.18
BCS class	Class II (low solubility, high permeability)
Plasma protein binding	About 99%
Elimination half-life	12–17 h
Oral bioavailability	About 95%

Naproxen inhibits cyclooxygenase-1 and -2 non-selectively and is used for arthritic conditions, musculoskeletal pain, dysmenorrhoea and acute gout [10]. It is highly protein bound (about 99%), has an elimination half-life of 12–17 h and an oral bioavailability of about 95% [10]. Its main adverse effects are gastrointestinal, ranging from dyspepsia to ulceration and haemorrhage, and arise largely from loss of prostaglandin-mediated mucosal protection [11,12]. Because NSAID-related gastrointestinal risk increases with exposure [11,12], formulation approaches that deliver a rapid and reproducible dissolution profile are of practical interest. In addition, because the free acid is least soluble in acidic gastric fluid and becomes more soluble as pH rises along the gastrointestinal tract [9], the site and rate of dissolution from a solid dosage form depend strongly on the medium, which further motivates carrier-based dissolution enhancement.

Solubility enhancement and solid dispersions:

Established approaches to poor solubility include particle-size reduction [13], nanosuspensions [14], salt formation for ionisable drugs [15] and cyclodextrin complexation [16]. Each has limitations, such as the need for specialised equipment, restriction to ionisable molecules, or added bulk and cost [1,13,16]. Solid dispersion, the dispersion of a drug in a hydrophilic carrier at the solid state, is among the most widely studied alternatives for BCS Class II drugs [17,18].

The concept originated with Sekiguchi and Obi, who showed that a eutectic mixture of sulfathiazole with a soluble carrier dissolved faster than the pure drug [19]. Chiou and Riegelman later defined the term and classified the systems [20]. Solid dispersions are now grouped into generations according to the physical state of the drug and the carrier, from eutectic mixtures to amorphous dispersions and surfactant-containing systems [21,22]. Dissolution enhancement arises from reduced particle size, improved wettability, partial or complete amorphisation, reduced aggregation and, in some

systems, supersaturation [17,18,23]. Amorphous drug has higher free energy than the crystal and dissolves faster, but it is thermodynamically metastable and may recrystallise on storage [24,25]. Drug-carrier interactions such as hydrogen bonding help to stabilise the amorphous state [26,27].

Solid dispersions are prepared mainly by solvent evaporation, fusion (melting) and kneading, among other techniques [21,22]. Solvent evaporation allows molecular-level mixing in a common solvent and avoids heating, but requires a solvent in which both components dissolve and its complete removal [17,21]. Fusion is solvent-free but demands that the components tolerate the processing temperature [17,22]. Kneading is simple and inexpensive and suits laboratory-scale screening [22]. Comparing the three methods with the same carriers therefore indicates which processing route best exploits a given carrier.

Natural gums as carriers: Synthetic carriers dominate marketed amorphous dispersions, which has stimulated interest in natural polymers that are biocompatible, biodegradable and inexpensive [28]. Modified gum karaya, for example, enhanced the dissolution of nimodipine from solid dispersions [29], and a *Ziziphus spina-christi* gum, used by co-grinding, solvent evaporation and kneading at 1:1, 1:2 and 1:3 drug-to-polymer ratios, improved the solubility of every drug tested, by up to about 51-fold for loratadine [30]. Three gums with different structures were selected for the present study.

Guar gum is a galactomannan from the endosperm of *Cyamopsis tetragonoloba*, with a β -(1→4)-mannose backbone carrying α -(1→6)-galactose branches at a mannose-to-galactose ratio of about 2:1 [31,32]. Its abundant hydroxyl groups give strong hydrogen-bonding capacity and rapid hydration and swelling [31,32]. Xanthan gum is an anionic heteropolysaccharide produced by *Xanthomonas campestris*, with a cellulosic backbone and trisaccharide side chains containing mannose and glucuronic acid, and it forms viscous solutions that are stable over wide pH and

temperature ranges [33,34]. Gum acacia (gum arabic) is a branched arabinogalactan–protein exudate of *Acacia senegal* and *Acacia seyal* that is compact in solution and dissolves at comparatively low viscosity [35,36]; it is widely used as an emulsifier and stabiliser [36,37]. Because their hydroxyl and carboxyl functionalities differ in density and accessibility, these gums can be expected to interact differently with naproxen.

Prior work, research gap and objectives: Naproxen dissolution has been improved by solid dispersion with polysaccharide and polymeric carriers, including chitosan [38] and sodium starch glycolate alone or with PEG 8000 [39]. In the literature reviewed here, however, we did not find a study that compared several natural gums for naproxen across multiple preparation methods and drug loadings under identical conditions. The aim of this work was therefore to formulate and compare solid dispersions of naproxen with guar gum, xanthan gum and gum acacia and to identify the carrier, method and ratio giving the greatest improvement in solubility and dissolution. The objectives were to (i) characterise naproxen and screen drug–polymer compatibility; (ii) prepare 27

batches by solvent evaporation, fusion and kneading at 1:1, 1:2 and 1:3 (w/w); (iii) evaluate drug content, solubility and in vitro dissolution; and (iv) characterise the optimised batch by FTIR and DSC and assess its accelerated stability.

Objectives: To systematically compare the influence of different natural polymeric carriers (guar gum, xanthan gum, and gum acacia), preparation techniques (solvent evaporation, fusion, and kneading), and drug-to-polymer ratios (1:1, 1:2, and 1:3) on the solubility and in vitro dissolution behaviour of naproxen solid dispersions. Furthermore, to evaluate the dissolution performance of the prepared formulations in comparison with pure naproxen and identify the optimised formulation based on its overall solubility enhancement, drug-release characteristics, and physicochemical compatibility.

Materials and Methods

Materials and Instruments: Naproxen was obtained as a gift sample, and the natural gums and reagents were purchased as listed in Table 2. All reagents were of analytical grade and used as received. The instruments used are listed in Table 3.

Table 2: Drug, polymers and reagents.

Material	Source / grade
Naproxen	Gift sample, Yarrow Chem Products, Mumbai
Guar gum	SD Fine Chem Ltd., Mumbai
Xanthan gum	HiMedia Laboratories Pvt. Ltd., Mumbai
Gum acacia	Nice Chemicals Pvt. Ltd., Kochi
Methanol	AR grade, Merck Life Science Pvt. Ltd., Mumbai
Ethanol (95%)	AR grade, Changshu Yangyuan Chemicals, China
Hydrochloric acid (conc.)	AR grade, Merck Life Science Pvt. Ltd., Mumbai
Potassium dihydrogen phosphate	AR grade, HiMedia Laboratories Pvt. Ltd., Mumbai
Sodium hydroxide	AR grade, Merck Life Science Pvt. Ltd., Mumbai
Silica gel (desiccant)	Thomas Baker (Chemicals) Pvt. Ltd., Mumbai

Table 3: Major instruments.

Instrument	Make / model
UV-visible spectrophotometer	Shimadzu UV-1900, Japan
Dissolution apparatus, USP Type II (paddle)	Labindia DS 8000, India
Analytical balance	Shimadzu AUX220, Japan
FTIR spectrophotometer	Shimadzu IR Affinity-1, Japan
Differential scanning calorimeter	Mettler Toledo DSC 822e, Switzerland
Digital pH meter	Systronics pH 361, India
Hot-air / vacuum oven	Narang Scientific Works, India
Magnetic stirrer with hot plate	Remi Equipment Pvt. Ltd., India
Stability chamber	Thermo Scientific SPX-180-SD, USA

Pre-formulation studies: Naproxen was examined for colour, form and odour, and its melting point was determined in triplicate by the capillary (Thiele tube) method and compared with the pharmacopoeial range of 153–158 °C [8,40]. A stock solution (100 µg/mL) in methanol was diluted with pH 6.8 phosphate buffer and 0.1 N HCl, spectra were recorded from 200 to 400 nm, and calibration curves were constructed over 2–20 µg/mL in each

medium. Equilibrium solubility was determined by agitating excess drug in 10 mL of distilled water, pH 6.8 phosphate buffer, 0.1 N HCl, methanol or ethanol at 37 ± 0.5 °C for 24 h, followed by filtration (Whatman No. 42), dilution and UV assay. For compatibility screening, 1:1 (w/w) physical mixtures of naproxen with each gum were prepared by trituration, and FTIR spectra of the drug,

polymers and mixtures were recorded (4000–400 cm^{-1} , KBr pellets).

Preparation of solid dispersions: Twenty-seven batches were prepared by fully crossing three carriers (GG, XG, GA), three methods (solvent evaporation, SE; fusion, MM; kneading, KM) and three drug-to-polymer ratios (1:1, 1:2, 1:3 w/w; 250 mg naproxen basis). Batches are coded by carrier, method and ratio; GG-SE3, for example, is the guar gum batch prepared by solvent evaporation at 1:3. These are standard solid dispersion techniques [21,22]. The three ratios span low to high carrier proportions, since carrier amount is a major determinant of dissolution enhancement [17,18]. In the solvent evaporation method, drug and gum were co-dissolved in a minimal volume of methanol with magnetic stirring at 300 rpm, the solvent was evaporated in a water bath at 50 °C, and the mass was dried under vacuum at 40 °C for 24 h. In the fusion method, the gum was heated 10–15 °C above its softening range in a porcelain dish, naproxen was dispersed into it with stirring, and the mass was quench-cooled in an ice bath. In the kneading method, drug and gum were first blended in a mortar for 10 min, then kneaded for 30 min with dropwise methanol (about 2–3 mL per gram of solids) to a paste, and the paste was dried at 40 °C for 24 h. All products were pulverised, passed through BSS sieve no. 60 and stored over silica gel in tightly closed containers. Pure naproxen was processed identically as the reference.

Evaluation: Drug content. An amount equivalent to 25 mg naproxen was dissolved in 10 mL methanol by sonication for 10 min, filtered (Whatman No. 42), diluted with pH 6.8 buffer and assayed at 262 nm in triplicate.

Solubility and dissolution. Preliminary drug content and solubility screening of all 27 batches showed that the 1:3 ratio consistently outperformed 1:1 and 1:2 irrespective of carrier or method. A representative eleven-batch panel was therefore carried forward, comprising the 1:3 batch of every carrier–method combination plus the full 1:1–1:3 solvent evaporation series for guar gum, the best preliminary performer: GG-SE1, GG-SE2, GG-SE3, GG-MM3, GG-KM3, XG-SE3, XG-MM3, XG-KM3, GA-SE3, GA-MM3 and GA-KM3. Equilibrium solubility in distilled water and pH 6.8 buffer was determined as in Section 2.2. Dissolution was performed in USP Apparatus II (paddle) with 900 mL pH 6.8 phosphate buffer at 37 ± 0.5 °C and 50 rpm, using an amount equivalent to 250 mg naproxen. Samples (5 mL) were withdrawn at 5, 10, 15, 20, 30, 45 and 60 min through a 0.45 μm filter, replaced with fresh pre-warmed medium and assayed at 262 nm. Cumulative drug release was calculated as (amount released $\div$ total drug content) $\times$ 100. The remaining sixteen batches were characterised for drug content only. The pH 6.8

phosphate buffer was chosen as the dissolution and solubility medium because the intestinal pH range is where a weak acid such as naproxen is increasingly ionised and dissolves [9], and each withdrawn volume was replaced with fresh medium so that the total volume remained constant.

Characterisation of the optimised batch. The best batch was analysed with pure naproxen, pure guar gum and the corresponding 1:3 physical mixture. FTIR spectra were recorded by the KBr technique (4000–400 cm^{-1} , 4 cm^{-1} resolution; about 2–3 mg of sample in 200 mg of dried KBr, compressed at 10 tonnes). For DSC, 3–5 mg samples were heated in sealed aluminium pans from 25 to 250 °C at 10 °C/min under nitrogen (50 mL/min) on an indium-calibrated instrument, and the onset, peak and enthalpy of the naproxen melting endotherm were compared as an index of crystallinity [38]. Powder X-ray diffraction was not performed in this study.

Stability and statistics: The optimised batch was packed in HDPE bottles sealed with aluminium foil and stored at 40 ± 2 °C/ $75 \pm 5\%$ RH, the accelerated condition of ICH Q1A(R2) [41]. This was a 90-day study, shorter than the six-month period described in the guideline. Samples were withdrawn at 0, 30, 60 and 90 days for appearance (colour, texture, flow, caking), drug content, dissolution and buffer solubility, and each time point was compared with day 0. All measurements were made in triplicate and expressed as mean $\pm$ SD. Carriers, methods and stability time points were compared by one-way ANOVA with Tukey's post-hoc test (GraphPad Prism 9.0); $p < 0.05$ was considered significant.

Results and Discussion

Pre-formulation characterization: Naproxen was a free-flowing, non-hygroscopic, white to off-white crystalline powder with a faint characteristic odour and a slightly bitter taste, and a melting point of 154–156 °C, within the reported 153–158 °C range and consistent with the identity and purity of the drug [8,40]. The λ_{max} was 262 nm in pH 6.8 phosphate buffer and 272 nm in 0.1 N HCl. Calibration curves were linear over 2–20 $\mu\text{g/mL}$ (phosphate buffer: $y = 0.0471x + 0.0032$, $R^2 = 0.9998$; 0.1 N HCl: $y = 0.0382x + 0.0041$, $R^2 = 0.9996$), supporting the analytical method. Naproxen was practically insoluble in water and 0.1 N HCl, only very slightly soluble in pH 6.8 buffer and freely soluble in methanol and ethanol (Table 4). The very low solubility in 0.1 N HCl and its higher value at pH 6.8 agree with the behaviour expected of a weak acid [9]. These values served as the baseline for all dispersions. The solubility of pure naproxen in pH 6.8 buffer, 0.118 mg/mL, is the reference against which all fold-increases in this paper are calculated, and the 4.6-fold figure for GG-SE3 should be read in that context.

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

Medium	Solubility (mg/mL)	Descriptive class
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
0.1 N 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

Drug-polymer compatibility and drug content:

Physical mixtures of naproxen with each gum retained the diagnostic naproxen bands – O–H stretch near 3001 cm^{-1} , C=O stretch near 1727 cm^{-1} , aromatic C=C near 1606 cm^{-1} , C–O–C near 1230 cm^{-1} and the naphthalene ring band near 820 cm^{-1} – with shifts of no more than 1–4 cm^{-1} . This indicates no chemical incompatibility between naproxen and the three gums at the physical-mixture stage, which is the usual purpose of such screening before formulation development [21,22]. Drug content of

all 27 batches ranged from 97.2 $\pm$ 0.93% to 99.1 $\pm$ 0.52% (Table 5), within the 95–105% acceptance range set for this study. Solvent evaporation batches, particularly at 1:3, gave the highest and most reproducible content, plausibly because co-dissolution distributes the drug more uniformly than fusion or kneading [21,22]; fusion batches were marginally lower, which may reflect minor thermal decomposition or volatilisation of naproxen during heating, and kneading batches were intermediate.

Table 5: Drug content (%) of all 27 batches (n = 3, mean $\pm$ SD).

Batch	Content	Batch	Content	Batch	Content
GG-SE1	98.4 $\pm$ 0.62	XG-SE1	97.8 $\pm$ 0.71	GA-SE1	98.1 $\pm$ 0.55
GG-SE2	98.9 $\pm$ 0.48	XG-SE2	98.2 $\pm$ 0.63	GA-SE2	98.6 $\pm$ 0.72
GG-SE3	99.1 $\pm$ 0.52	XG-SE3	98.7 $\pm$ 0.44	GA-SE3	99.0 $\pm$ 0.61
GG-MM1	97.6 $\pm$ 0.81	XG-MM1	97.2 $\pm$ 0.93	GA-MM1	97.4 $\pm$ 0.78
GG-MM2	98.2 $\pm$ 0.67	XG-MM2	97.8 $\pm$ 0.59	GA-MM2	97.9 $\pm$ 0.84
GG-MM3	98.6 $\pm$ 0.74	XG-MM3	98.1 $\pm$ 0.68	GA-MM3	98.4 $\pm$ 0.69
GG-KM1	97.8 $\pm$ 0.88	XG-KM1	97.5 $\pm$ 0.76	GA-KM1	97.7 $\pm$ 0.82
GG-KM2	98.3 $\pm$ 0.55	XG-KM2	97.9 $\pm$ 0.64	GA-KM2	98.1 $\pm$ 0.73
GG-KM3	98.7 $\pm$ 0.61	XG-KM3	98.4 $\pm$ 0.57	GA-KM3	98.5 $\pm$ 0.66

Solubility and dissolution: Every dispersion evaluated outperformed pure naproxen in equilibrium solubility and dissolution ($p < 0.001$). The best batch, GG-SE3, showed a 4.6-fold increase in pH 6.8 solubility (0.543 vs 0.118 mg/mL) and released 94.82 $\pm$ 3.1% of drug at 60 min compared with 28.6 $\pm$ 1.8% for pure naproxen, a 3.3-fold improvement (Tables 6–10). At the 1:3 ratio, the order of both solubility and release was guar gum > xanthan gum > gum acacia, and for each gum solvent evaporation outperformed fusion, which

outperformed kneading. For guar gum, buffer solubility rose from 0.298 mg/mL (1:1) to 0.382 mg/mL (1:2) and 0.543 mg/mL (1:3), with corresponding 60-min release of 76.8%, 88.2% and 94.82%. Within the guar gum 1:3 series, solubility fold-increases were 4.60 (SE), 3.57 (MM) and 3.37 (KM), and 60-min release was 94.82%, 84.6% and 79.2%. The corresponding releases were 91.6%, 80.8% and 76.4% for xanthan gum (Table 8) and 88.4%, 77.6% and 73.2% for gum acacia (Table 9).

Table 6: Equilibrium solubility of the eleven-batch panel at 37 °C (n = 3, mean $\pm$ SD).

Formulation	Water (mg/mL)	pH 6.8 buffer (mg/mL)	Fold rise (buffer)
Pure naproxen	0.024 $\pm$ 0.003	0.118 $\pm$ 0.008	1.00 (ref.)
GG-SE1	0.062 $\pm$ 0.005	0.298 $\pm$ 0.011	2.53
GG-SE2	0.091 $\pm$ 0.007	0.382 $\pm$ 0.014	3.24
GG-SE3	0.128 $\pm$ 0.009	0.543 $\pm$ 0.018	4.60
GG-MM3	0.102 $\pm$ 0.008	0.421 $\pm$ 0.015	3.57
GG-KM3	0.094 $\pm$ 0.007	0.398 $\pm$ 0.013	3.37
XG-SE3	0.104 $\pm$ 0.007	0.448 $\pm$ 0.016	3.80
XG-MM3	0.086 $\pm$ 0.006	0.374 $\pm$ 0.012	3.17
XG-KM3	0.079 $\pm$ 0.005	0.356 $\pm$ 0.011	3.02
GA-SE3	0.098 $\pm$ 0.008	0.423 $\pm$ 0.014	3.58
GA-MM3	0.082 $\pm$ 0.006	0.368 $\pm$ 0.012	3.12
GA-KM3	0.075 $\pm$ 0.005	0.344 $\pm$ 0.010	2.92

Table 7: Cumulative drug release (%) of guar gum batches in phosphate buffer pH 6.8 (n = 3, mean $\pm$ SD).

Time (min)	Pure naproxen	GG-SE1	GG-SE2	GG-SE3	GG-MM3
5	6.2 $\pm$ 0.8	18.4 $\pm$ 1.1	24.6 $\pm$ 1.4	31.2 $\pm$ 1.6	22.8 $\pm$ 1.3
10	9.8 $\pm$ 0.9	28.3 $\pm$ 1.4	36.4 $\pm$ 1.8	46.8 $\pm$ 2.1	34.6 $\pm$ 1.7
15	12.4 $\pm$ 1.1	36.8 $\pm$ 1.6	46.2 $\pm$ 2.0	58.4 $\pm$ 2.3	44.2 $\pm$ 1.9
20	15.6 $\pm$ 1.3	44.2 $\pm$ 1.9	55.6 $\pm$ 2.2	68.6 $\pm$ 2.5	52.8 $\pm$ 2.1
30	19.8 $\pm$ 1.5	56.4 $\pm$ 2.1	68.4 $\pm$ 2.5	80.2 $\pm$ 2.8	64.4 $\pm$ 2.3
45	24.2 $\pm$ 1.7	68.6 $\pm$ 2.3	80.8 $\pm$ 2.7	89.4 $\pm$ 3.0	76.2 $\pm$ 2.6
60	28.6 $\pm$ 1.8	76.8 $\pm$ 2.6	88.2 $\pm$ 2.9	94.82 $\pm$ 3.1	84.6 $\pm$ 2.8

GG-MM3 released 20.4 $\pm$ 1.2, 31.2 $\pm$ 1.5, 39.8 $\pm$ 1.8, 47.4 $\pm$ 2.0, 58.8 $\pm$ 2.2, 70.6 $\pm$ 2.4 and 79.2 $\pm$ 2.6% at 5, 10, 15, 20, 30, 45 and 60 min, respectively.

Table 8: Cumulative drug release (%) of xanthan gum batches in phosphate buffer pH 6.8 (n = 3, mean $\pm$ SD).

Time (min)	Pure naproxen	XG-SE3	XG-MM3	XG-KM3
5	6.2 $\pm$ 0.8	26.4 $\pm$ 1.5	19.6 $\pm$ 1.2	17.8 $\pm$ 1.1
10	9.8 $\pm$ 0.9	39.8 $\pm$ 1.8	31.2 $\pm$ 1.6	27.8 $\pm$ 1.4
15	12.4 $\pm$ 1.1	50.4 $\pm$ 2.0	40.2 $\pm$ 1.8	36.2 $\pm$ 1.7
20	15.6 $\pm$ 1.3	60.2 $\pm$ 2.3	49.4 $\pm$ 2.0	44.6 $\pm$ 1.9
30	19.8 $\pm$ 1.5	72.8 $\pm$ 2.5	61.2 $\pm$ 2.3	56.4 $\pm$ 2.2
45	24.2 $\pm$ 1.7	83.4 $\pm$ 2.7	72.6 $\pm$ 2.5	67.8 $\pm$ 2.3
60	28.6 $\pm$ 1.8	91.6 $\pm$ 2.9	80.8 $\pm$ 2.7	76.4 $\pm$ 2.5

Table 9: Cumulative drug release (%) of gum acacia batches in phosphate buffer pH 6.8 (n = 3, mean $\pm$ SD).

Time (min)	Pure naproxen	GA-SE3	GA-MM3	GA-KM3
5	6.2 $\pm$ 0.8	24.8 $\pm$ 1.4	18.4 $\pm$ 1.2	16.6 $\pm$ 1.0
10	9.8 $\pm$ 0.9	37.6 $\pm$ 1.7	29.8 $\pm$ 1.5	26.4 $\pm$ 1.3
15	12.4 $\pm$ 1.1	47.8 $\pm$ 1.9	38.4 $\pm$ 1.7	33.8 $\pm$ 1.5
20	15.6 $\pm$ 1.3	57.4 $\pm$ 2.1	46.8 $\pm$ 1.9	41.2 $\pm$ 1.7
30	19.8 $\pm$ 1.5	69.6 $\pm$ 2.4	58.8 $\pm$ 2.2	52.6 $\pm$ 2.0
45	24.2 $\pm$ 1.7	80.2 $\pm$ 2.6	69.4 $\pm$ 2.4	63.8 $\pm$ 2.2
60	28.6 $\pm$ 1.8	88.4 $\pm$ 2.8	77.6 $\pm$ 2.6	73.2 $\pm$ 2.3

Table 10: Best batch from each carrier compared with pure naproxen (all solvent evaporation, 1:3; n = 3, mean $\pm$ SD).

Carrier	Batch	Release at 60 min (%)	Solubility fold-rise (pH 6.8)	Drug content (%)
Guar gum	GG-SE3	94.82 $\pm$ 3.1	4.60	99.1 $\pm$ 0.52
Xanthan gum	XG-SE3	91.6 $\pm$ 2.9	3.80	98.7 $\pm$ 0.44
Gum acacia	GA-SE3	88.4 $\pm$ 2.8	3.58	99.0 $\pm$ 0.61
Pure naproxen	—	28.6 $\pm$ 1.8	1.00 (ref.)	—

Solubility and dissolution rankings were broadly parallel: the same three batches (GG-SE3, XG-SE3 and GA-SE3) ranked highest by both measures, and the 1:1, 1:2 and 1:3 guar gum series increased monotonically in both. The amount released from GG-SE3 at 60 min corresponds to about 237 mg of the 250 mg dose in 900 mL, an apparent concentration of about 0.26 mg/mL, which is more than twice the 0.118 mg/mL equilibrium solubility of the pure drug in the same buffer. Dispersions in hydrophilic carriers can generate such apparent supersaturation relative to the crystalline drug by improving wettability and reducing the energy

barrier to dissolution [17,23,26]. Whether this concentration is maintained or declines through recrystallisation was not examined beyond 60 min.

To compare whole profiles rather than single time points, dissolution efficiency over 60 min (DE₆₀) and the time for 50% release (t₅₀) were calculated from the mean profiles in Tables 7–9 by the trapezoidal rule and linear interpolation (Table 11). DE₆₀ was 18.1% for pure naproxen and 70.9% for GG-SE3, and the ranking of batches by DE₆₀ and t₅₀ matched the ranking by release at 60 min. Pure naproxen did not reach 50% release within 60 min, whereas GG-SE3 did so in about 11 min.

Table 11: Dissolution efficiency (DE₆₀) and time to 50% release (t₅₀), calculated from the mean profiles in Tables 7–9.

Batch	DE ₆₀ (%)	t ₅₀ (min)
Pure naproxen	18.1	> 60
GG-SE1	51.0	24.8
GG-SE2	61.4	17.0
GG-SE3	70.9	11.4
GG-MM3	58.1	18.4
GG-KM3	53.3	22.3
XG-SE3	64.7	14.8
XG-MM3	54.8	20.5
XG-KM3	50.6	24.6
GA-SE3	62.0	16.1
GA-MM3	52.4	22.7
GA-KM3	47.6	27.7

The gap between the dispersions and pure naproxen widened across the sampling period, indicating a sustained advantage rather than an early burst only (Tables 7–9).

Influence of carrier and method: The superiority of guar gum is plausibly linked to its high density of free hydroxyl groups along the galactomannan backbone, which can hydrogen-bond with the carboxylic acid group of naproxen and promote drug–polymer miscibility [26,31]. Xanthan gum, whose anionic backbone also offers hydrogen-bonding sites [33,34], gave intermediate performance, and the more compact, globular gum acacia [35,36] gave the lowest enhancement of the three. These explanations are interpretive and were not tested directly in this study. The advantage of solvent evaporation over fusion and kneading is consistent with the view that co-dissolution in a common solvent gives finer, closer-to-molecular mixing than melt- or paste-based routes [17,21,22]. The increase in performance with polymer loading agrees with the general observation that higher carrier proportions improve wettability and reduce drug aggregation [17,18]. Natural gums at high loadings can also form viscous layers that slow release [23], and the optimum should therefore be confirmed for each drug–gum system; within the ratios studied here, 1:3 remained the best. The three gums also differ in how they hydrate. Rapidly swelling gums form a hydrated layer around drug particles that improves wetting, but if the layer

becomes too viscous it can impede diffusion of drug away from the particle [23,31]. The monotonic improvement up to 1:3 observed here suggests that, for naproxen at this scale, the wetting and hydrogen-bonding benefits outweighed any viscosity penalty, although higher loadings were not tested. Improved dissolution of naproxen from other hydrophilic or polysaccharide carriers has been reported [38,39], and the present results indicate that low-cost natural gums can achieve comparable improvements, although direct comparison is limited by differences in method and test conditions.

Solid-state characterisation of GG-SE3: FTIR band positions are given in Table 12. In GG-SE3, the carbonyl band of naproxen shifted from 1727 to 1712 cm⁻¹ and the aromatic C=C band from 1606 to 1598 cm⁻¹, whereas the physical mixture showed bands essentially identical to those of the components (1726 and 1605 cm⁻¹). A shift of the C=O stretch to lower wavenumber is a recognised indicator of hydrogen bonding at the carbonyl oxygen [26,27]. The broad O–H region also changed, with the naproxen band near 3001 cm⁻¹ replaced by a broadened band at 3264 cm⁻¹; because guar gum itself absorbs strongly in this region (about 3340 cm⁻¹), this change reflects overlap and altered hydrogen bonding of both components and is less specific than the carbonyl shift. Together, the changes, which were absent from the physical mixture, indicate drug–polymer interaction arising during processing rather than on simple mixing.

Table 12: FTIR band positions (cm⁻¹) of naproxen, guar gum, their 1:3 physical mixture and GG-SE3.

Sample	O–H stretch	C=O	Aromatic C=C	Guar gum O–H
Pure naproxen	3001 (broad)	1727	1606	–
Pure guar gum	3340 (broad)	–	–	3340
Physical mixture (1:3)	3001, 3340	1726	1605	3338
GG-SE3	3264 (broadened)	1712	1598	3264

DSC data are given in Table 13. Pure naproxen showed a sharp melting endotherm (onset 153.2 °C, peak 156.4 °C, 128.6 J/g), consistent with a highly crystalline drug, and guar gum showed no melting

event. The 1:3 physical mixture retained a diluted but distinct endotherm (peak 155.6 °C, 32.4 J/g), whereas GG-SE3 showed only a faint residual signal (< 5 J/g) and no distinct melting peak.

Disappearance or marked reduction of the drug melting endotherm is widely used as evidence of reduced crystallinity or amorphisation in solid dispersions [24,38]. A reduced endotherm can, however, also arise from drug dissolution in the polymer during heating, and powder X-ray

diffraction was not carried out. The DSC and FTIR findings are therefore interpreted as consistent with, but not definitive proof of, a largely amorphous, hydrogen-bonded drug state. Such a state would be expected to raise apparent solubility and dissolution rate through loss of crystal-lattice energy [24,26,42].

Table 13: DSC data of naproxen, guar gum, their 1:3 physical mixture and GG-SE3.

Sample	Onset (°C)	Peak (°C)	Enthalpy of fusion (J/g)
Pure naproxen	153.2	156.4	128.6
Pure guar gum	No melting event	–	–
Physical mixture (1:3)	151.8	155.6	32.4
GG-SE3	No distinct peak	–	< 5 (residual)

Practical implications and comparison with the literature: Natural gums have been proposed as sustainable and biocompatible alternatives to synthetic carriers in amorphous solid dispersions [28], and modified gum karaya has improved the dissolution of nimodipine from solid dispersions [29]. Guar gum is a widely used, inexpensive material available in large quantities [31,32], and gum arabic has been extensively studied for biological effects and safety [37], which supports the pharmaceutical relevance of these carriers. Because gums are of natural origin, their composition and viscosity can vary between lots, so material specifications and batch consistency need to be controlled during development [28]. In this work the carrier effect was the same for all three methods, with guar gum giving the highest release and gum acacia the lowest, suggesting that carrier choice and processing route act together rather than

independently. Whether the ranking holds for other drugs, particularly those lacking a carboxylic acid group that can hydrogen-bond with hydroxylated polysaccharides, remains to be tested.

Accelerated stability of GG-SE3: After 90 days at 40 °C/75% RH, GG-SE3 showed only small, statistically non-significant changes ($p > 0.05$): drug content fell from 99.1% to 98.0%, 60-min release from 94.82% to 92.8% and buffer solubility from 0.543 to 0.512 mg/mL (Table 14). A slight off-white tinge appeared at day 90, with no caking or change in flow. Amorphous dispersions can recrystallise during storage, particularly under humidity [24,25], so these results are encouraging but limited. The 90-day period is shorter than the six-month accelerated study in ICH Q1A(R2), and long-term testing at 25 °C/60% RH remains necessary [41].

Table 14: Accelerated stability of GG-SE3 (40 ± 2 °C/75 ± 5% RH; n = 3, mean ± SD).

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, pH 6.8 (mg/mL)	0.543 ± 0.018	0.536 ± 0.019	0.524 ± 0.021	0.512 ± 0.022

Integrated interpretation: Three observations point to the same mechanism. First, the physical mixtures showed no enhancement signal in FTIR or DSC, whereas the solvent-evaporated dispersion showed both spectral shifts and loss of the melting endotherm, so enhancement was linked to processing and not to simple blending [26,27]. Second, the carrier hierarchy (guar gum > xanthan gum > gum acacia) and the method hierarchy (solvent evaporation > fusion > kneading) were consistent across solubility, release, dissolution efficiency and t_{50} , which argues against chance variation between individual batches. Third, enhancement increased with polymer proportion over the range studied, as expected when more carrier is available to wet and separate drug particles [17,18]. These findings agree in direction with the general view that hydrophilic carriers prepared by co-dissolution give the largest dissolution gains for BCS Class II drugs [17,21].

From a formulation standpoint, the data suggest that a three-part decision defines performance: the carrier determines how strongly the drug can interact with the matrix, the method determines how intimately the two are mixed, and the ratio determines how much matrix is available. Solvent evaporation with guar gum at 1:3 combined the most favourable value of each factor in this study. Its drawbacks, namely the need for methanol and its complete removal, should be weighed against the dissolution benefit in any development decision [17,21]. Because the pure-drug control may have been affected by non-sink conditions (Section 5), the size of the improvement should be regarded as an upper estimate, while the ranking of the dispersions relative to one another is not affected by that limitation.

Conclusion

Among 27 batches, guar gum prepared by solvent evaporation at a 1:3 drug-to-polymer ratio gave the greatest improvement in the solubility and in vitro dissolution of naproxen, with a 4.6-fold increase in pH 6.8 solubility and 94.82% release in 60 min against 28.6% for the pure drug. The ranking guar gum > xanthan gum > gum acacia and solvent evaporation > fusion > kneading was consistent across the panel. FTIR and DSC findings are consistent with drug-polymer hydrogen bonding and a marked loss of drug crystallinity, and the optimised batch retained most of its performance over 90 days of accelerated storage. These findings support natural gums, particularly guar gum, as low-cost and biocompatible carriers for improving the dissolution of naproxen.

Limitations and Future Scope: This was a laboratory-scale in vitro study. Powder X-ray diffraction was not performed; FTIR and DSC were run on the optimised batch only; solubility and dissolution were studied for eleven of the 27 batches; and stability was assessed under accelerated conditions for 90 days only. At the measured pH 6.8 solubility of 0.118 mg/mL, pure naproxen could dissolve only about 106 mg of the 250 mg dose in 900 mL, so the pure-drug control probably ran under non-sink conditions and may overstate the advantage of the dispersions. No in vivo data were generated. The following studies are suggested.

In vivo evaluation. Pharmacokinetic studies in an animal model should determine AUC, C_{max} and T_{max} for GG-SE3 relative to pure naproxen and a marketed product, because in vitro dissolution enhancement does not by itself guarantee improved bioavailability [2,18]. Pharmacodynamic confirmation of anti-inflammatory activity would add to this; improved analgesic activity of a naproxen solid dispersion has been reported in mice [39].

Solid-state and long-term stability studies. XRD and microscopy should confirm the physical state of the drug, and long-term testing at 25 °C/60% RH, with intermediate testing where required, should define the stability of the dispersion, since amorphous systems can recrystallise [24,25,41].

Dosage-form development and scale-up. The optimised dispersion could be developed into capsules or tablets, with attention to compressibility, disintegration and dissolution from the finished dosage form [17,21]. Scale-up by industrial methods such as spray drying or hot-melt extrusion would need to be assessed for natural gums [21,42].

Modified gums and other drugs. Chemically or physically modified gums may offer different swelling and dissolution behaviour [28,29], and the

multi-variable design used here could be applied to other poorly soluble NSAIDs [1,3].

Abbreviations: BCS, Biopharmaceutics Classification System; DSC, differential scanning calorimetry; FTIR, Fourier-transform infrared spectroscopy; GA, gum acacia; GG, guar gum; ICH, International Council for Harmonisation; KM, kneading method; MM, fusion (melt) method; NSAID, non-steroidal anti-inflammatory drug; RH, relative humidity; SE, solvent evaporation; XG, xanthan gum; XRD, X-ray diffraction.

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