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Sequential addition synthesis of guar gum based ternary hydrogels with kinetic asymmetry in drug release

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Currently, biomedical engineering is placing significant emphasis on hydrogels due to their exceptional capabilities in drug delivery, tissue regeneration, tissue adhesion, blood clot prevention, contrast imaging, safeguarding tissues or organs during radiotherapy, and enhancing the biocompatibility of medical implants. This study explores a temperature-controlled sequential addition method to synthesize pH responsive guar gum-sodium alginate hydrogels with PVA as third component. Obtained hydrogels have been observed with kinetic asymmetry in drug release at specific pH. The sequential addition method has augmented thermal stability of products by allowing for distinct crosslinking patterns in the hydrogels produced. Kinetic assymetry of in-vitro drug release has been observed, specifically depending upon drug hydrogel interaction as hydrogen bonding. The blends that were prepared with higher sodium alginate (NaA) contents demonstrated 1st order drug release kinetics due to highest swelling and fast ionic dissociation leads to fast drug release, whereas samples with higher guargum (GG) ratio in compositions presented zero order kinetics due to compact structure and sustained swelling. The maximum drug release achieved within 12 h was 92% in intestine at 7.4 (colon pH), which was subsequently characterized by non-Fickian diffusion due to polymer relaxation.

Keywords Controlled release, Diffusion, pH stimulated hydrogels, Drug delivery, Processing optimization

Three-dimensional networks of hydrophilic polymers, or hydrogels, have become very flexible platforms for tissue engineering and drug delivery. An ideal hydrogel must be simple to administer, easy to remove, mechanically strong, biocompatible, protected from accidental release, easy to fabricate, capable of acquiring high drug loading, inert and comfortable for patients[1–4]. A variety of biological applications[5–7] including but not limited to cardiology[8–10], tissue engineering[11,12], cancer treatment[13–15], pain relieving[16–18] and wound healing[19,20], use hydrogels. Biomedical hydrogels are pH-dependent. Wounds and tumor areas are found acidic and high in temperature[1]. Skin pH normally ranges 5.0–6.0, increase of which can causes inflammation, irritation and acne while decrease in pH can cause structural disorders.

pH responsive hydrogels are either cationic[15] or anionic[21] polymers, which upon stimulus, change shape and volume according to physiological conditions[15,21,22]. Typically, polymeric hydrogels exhibit either zero-order or first-order drug delivery. Zero-order drug delivery systems are appropriate for medicines with short biological half-lives or narrow therapeutic windows, whereas first-order drug delivery systems are good for burst release of medicine in emergency.

Natural polymers are considered best for hydrogels as per their biocompatibility, biodegradability, easy availability and high purity[23–25], particularly guar gum (GG) in drug transport[26], bone implants[27] and tissue replacements[28]. GG, a naturally occurring polysaccharide, has attracted much interest as a potential hydrogel ingredient because of its ability to release medicinal compounds over an extended period of time. Whereas sodium alginate based pH sensitive hydrogels work oppositely with controlled release[2]. This difference in drug release behavior of hydrogels, can be attributed to swelling and crosllinking density. Poly vinyl alcohol (PVA) is a widely used semicrystline synthetic polymer which along with their colpolymers lso control drug delivery

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of both hydrophilic and hydrophobic drugs[3]. They are colloidal dispersion and produce three diamensional crosllinking and swelling structres. Due to their good biocompatibility, water absorption capacity and low toxicity used as super absorbent espessially in biomedicines[4]. PVA hydrogels hve macropores fro any type solute diffusion and retain high water content as well as table at room temperature[5]. PVA has been used as crosslinking by measuring the durbity of PVA samples along with crystallization PVA concentration and gelation time[6]. On the other hand, to improve the targeted drug delivery at specific pH, it is also used with other components to prepare pH sensistive hydrogel dor methotrexate drug by M. Akhlaq with his coworkers[7]. CS/ PVA hydrogel released Bovine Serum Albumin drug 86% in 7.4 pH phosphate buffer and release a trace amount in acidic pH[8]. Natrual polymers have disadvantages also as they have low mechanical strength, larger mechanical distribution and limited drug-loading capacity then natural polymers. As they are biodegradable, their degradation products may be toxic and may cause alergic reactions[9]. These short coming can be overcome by adding crosslinking agents and via composite hydrogel formations as natural and synthestic polymers[10].

pH responsive hydrogels upon stimulus, change shape and volume according to physiological conditions[11,12], i.e. cationic hydrogels (Chitosan and poly (ethylene imine)) swell in acidic medium[13,14], and deliver drug in stomach i.e. pH 1.2[15]; whereas, anionic hydrogels (Carboxymethyl chitosan) swell in basic medium and deliver drug in intestine i.e. pH 7.4[16]. Sodium alginate as anionic copolymer and guar gum as non-ionic presents pH dependent drug release[17,18]. These hydrogels contained acidic or basic pendent groups and form complex with corresponding opposite charged bioactive components.

Multiple studies have examined GG and NaA based traditional hydrogels and found that they maintain an unaltered drug release kinetics[19,20], which hampers their broad use. This article introduces a new method for creating ternary hydrogels using GG, NaA and PVA. This method involves adding ingredients in a specific order, resulting in hydrogels that release drugs at different rates. Hydrogels displaying customizable drug release patterns and a noticeable asymmetry in release kinetics were produced by adjusting the synthesis conditions. Hydrogels usually exhibit a remarkably low thermal stability, which is an important factor to resist polymeric network damage during pH mediated swelling. pH responsive swelling augments drug release, through polymeric network disintegtration causing reduced control over drug release kinetics[11,15].

Literature states that crosslinking patterns play a crucial role in determining hydrogel properties, leading to distinct behaviors and functions even with the same composition[24]. Accordingly, numerous studies have explored different approaches to control crosslinking patterns in polymeric hydrogels for 3D printing[25] and biomedical applications[26]. Extending this concept, current research has developed NaA-PVA-GG hydrogels as drug carrier through sequential addition method, where a specific sequence of ingredient addition was employed. This sequential addition method enabled precise control over monomeric connectivity, influencing hydrogel's structure and properties. Designed hydrogels, despite of excellent thermal stability, have high swelling ratio (Table 1). A procedural change has helped to design special connections resulting in specific hydrogels with augmented thermal stability (44% wt. loss at 500 °C). This thermal stability has not compromised hydrogel's swelling capacity, hence leading to a significant release of drugs. This study shows that sequential addition method has developed strong inter-connectivity within polymer but interaction of surface functionalities with drug has enhanced drug release rate. The present study has verified that the properties of the hydrogels may be chemically manipulated by altering their method, resulting in specific outcomes under controlled settings. Comparison of present work with literature work is shown in Table 1. Current study differs from previous studies in both sample preparation method as well as composition. To the best of our knowledge all studies have reported simultaneous mixing of these three ingredients, whereas, in contrast, current research is being reported for sequential addition of ingredients, enabling targeted interactions between specific functional groups.

Materials and methods

Materials

GG (Analytical grade, M wt.535.14 Sigma Aldrich, 0.8–1.0 g/mol), Starch (BDH), NaA (1.0 g/cm^3, M wt. 216, Sigma Aldrich), PVA (1.19 g/cm^3, 87–90% hydrolyzed, Sigma Aldrich). Monosodium phosphate monohydrate (99% pure, Sigma Aldrich), Disodium phosphate heptahydrate (extra pure, Sigma Aldrich), Ortho phosphoric acid (85% Merck), Sodium hydroxide pellets (99%, 2.13 g/cm^3, Merck,) Hydrochloric acid (37%, 1.19 g/mL, Merck,) were bought and used as received without additional purification. Ibuprofen drug was obtained from Abbott Pharmaceutical, Pakistan. All types of solution preparations were done in distilled water.

Materials	Method	Drug	Characterization			References
			Drug loading (%)/Release (%)	Thermal stability (°C)/% wt.loss	Swelling (%)	
GG, PVA, NaA, gellan gum, xanthan gum	Ionic gelation method	Diclofenac sodium	90/50 (pH 6.8)	322/NR	NR	[21]
GG, PVA, NaA	Solution casting method	verapamil HCl	82/94 (pH 7.4)	283/77	2040	[22]
GG, PVA, Chitosan		No drug	NR/NR	NR/NR	810	[23]
GG, PVA, NaA	Sequential Addition (Solution casting) method	Ibuprofen	NR/92 (pH 7.4)	500/45	2000	*

Table 1. Comparative literature review and present work. *Present work.

Sample	Sample ID	NaA (g)	GG (g)	PVA (g)
Hydrogel	AGP1	0	0.5	0.1
	AGP2	0.1	0.4	0.1
	AGP3	0.2	0.3	0.1
	AGP4	0.3	0.2	0.1
	AGP5	0.4	0.1	0.1
	AGP6	0.5	0	0.1
Sample	**Sample ID**	**Hydrogel (0.2 g)**		**Ibuprofen**
Drug-loaded hydrogels	AGPD2	AGP2		0.54 mg
	AGPD3	AGP3		0.54 mg
	AGPD4	AGP4		0.54 mg
	AGPD5	AGP5		0.54 mg
	AGPD6	AGP6		0.54 mg

Table 2. Sample formulations.

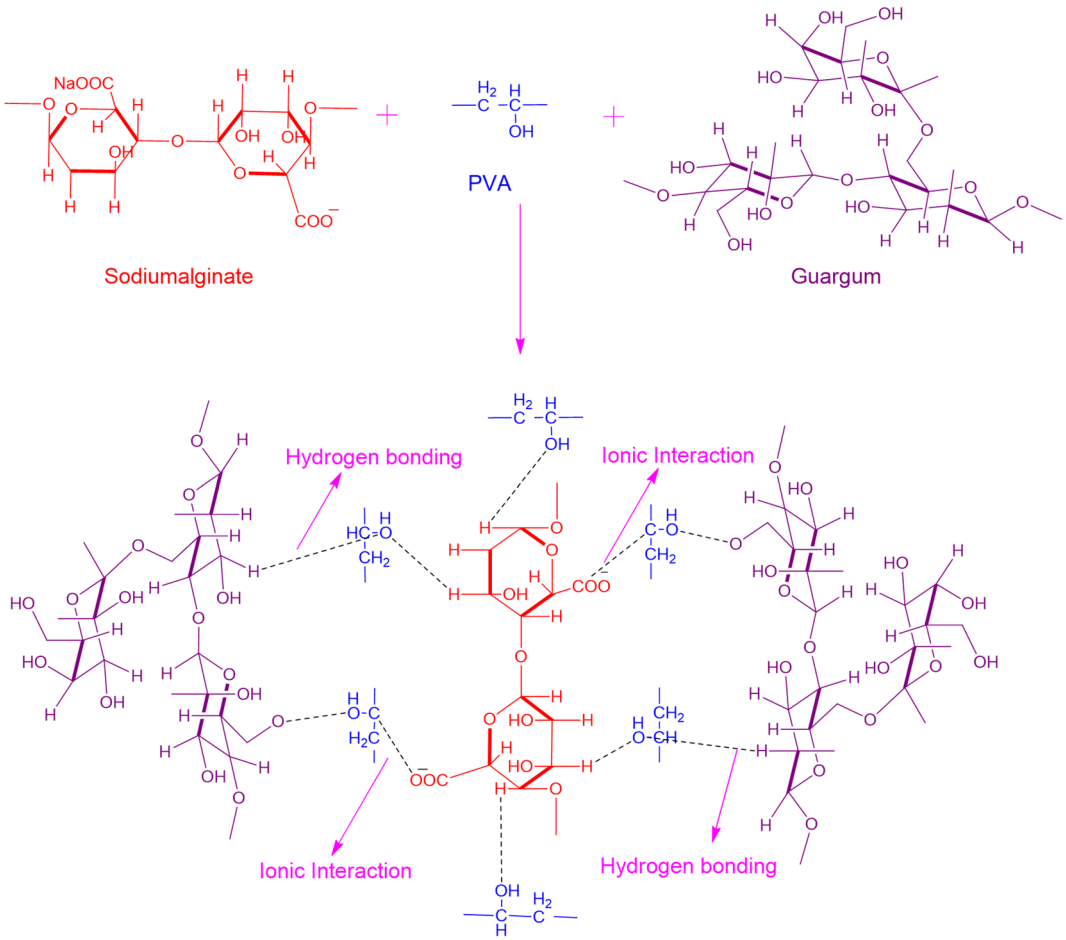


Fig. 1. NaA-PVA-GG blended hydrogel.

Methods

Synthesis of hydrogel films

Hydrogels were prepared as per formulations given in Table 2. Separate solutions of GG (50 °C, 700 rpm), NaA (50 °C, 500 rpm) and PVA (90 °C, 500 rpm) were prepared in distilled water. Aqueous solubility of these polymers are 8.59 mg/ml, 14.83 mg/ml and 8.6 mg/ml respectively. Following sequential addition method (proposed mechanism in Fig. 1), NaA was added dropwise into PVA solution while mixing at 90 °C for 60 min. Then GG solution was added dropwise into the mixture, and stirred at 50 °C, 1100 rpm for 6 h. Thick gel collected in petri

dish was allowed to set in air for 24 h, heated at 40 °C in a drying oven for 3 h followed by washing twice with distilled water and again heated at 40 °C for 4 h, to obtain thin optically transparent layers of hydrogels.

Characterization

Prepared samples were characterized by using following techniques: Surface chemistry of prepared samples was checked by using Shimadzu FTIR-ATR spectrometer from 4000 to 400 cm^{-1}. Thermal stability of prepared samples was studied by thermogravimetric analysis (TGA) moreover curing conversion was studied by differential scanning calorimetry (DSC). The studies were performed in Al crucible under nitrogen atmosphere from 25 to 500 °C with 10 °C/min heat rate. The produced samples were morphological analyzed to examine their structural properties using a scanning electron microscope (SEM, ZEISS EVO, Carl Zeiss).

To determine degradation at 37 °C in PBS media, accurately weighed dried hydrogel was placed in beaker containing PBS and incubated. The hydrogel were taken out, weighed after specific intervals and dried in oven to put into PBS to determine accurate degradation rate.

$$\%\text{Degradation} = (Wi - W_t/W_t \times 100) \tag{1}$$

where W_t scaffold weight at "t" and *W*i initial weight scaffold.

Hydrogel stability was determined by immersing 15 small square strip of samples in aquoeus phosphate buffer system at 7.4 pH and incubated at 37 °C. The strips were removed at 1 min interval, gently wiped with napkin and change in their shape was observed.

For gel contents, weighed quantity of samples was immersed in 10 mL DCM for 24 h. After 24 h, sample was removed from DCM and weighed again. The decrease in weight showed the unreacted macromolecules while those macromolecules that were polymerized remained intact. The gel content of hydrogel was also determined by using water. In this weighed amount of hydrogel was dipped in water and placed for 24 h at 60 °C. After this time swollen sample is removed from water and residual gel fraction is dried in ovan at 40 °C till constant weight[27]. Equation (1) was used to calculate the percentage of crosslinked material:

$$\%\text{GC} = (W_2/W_1 \times 100) \tag{2}$$

W_1 = weight of sample before immersing in DCM, W_2 = weight of sample after 24 h of immersing in DCM.

Swelling ratio of hydrogels was checked in PBS of pH 1.2 and 7.4 at 37 ℃ by using Eq. (2).

$$Sc = (W' - W)/W \tag{3}$$

Sc = swelling capacity, W = weight of hydrogel before swelling, W' = weight of hydrogel after swelling. For drug loading study, ibuprofen solution by dissolving 0.54 mg ibuprofen in 1 ml ethanol followed by solution iin 50 mL DI water was prepared. Hydrogel samples (0.2 g) were soaked in ibuprofen solution at 40–50 °C for 24 h with constant stirring. Loaded samples (AGPD1-AGPD6) were washed and dried at 40 °C for 3 h.

Drug loading efficiency was determined by UV–Vis's spectrophotometer. Loaded hydrogels (5 mg) were shaken (100 rpm) in 50 mL buffer solution for 24 h followed by centrifugation (2000 rpm) for 15 min. The solution was filtered, and the filtrate was analyzed by UV–Vis's spectrometer at the λ_{max} value to quantify the encapsulated drug by using Eq. (3).

$$\text{DL } \% = \text{M}_\text{D}/\text{M}_\text{HG} \times 100 \tag{4}$$

DL = loaded drug, M_D = mass of the drug in the hydrogel, M_{HG} = mass of hydrogel.

Drug release profile of hydrogels was studied by using dialysis membrane. The membrane was cut into 4 cm size and filled with 7.4 pH PBS (5 mL). Loaded hydrogels (0.1 g) were placed in the filled tube, tied at both ends, after shaking immersed in same buffer solution (20 mL) and kept on shaker at 100 rpm. After regular time intervals (2 h) till 24 h, 3 mL of solution was drawn and analyzed by UV–Vis spectroscopy to determine the amount of drug released (DR), calculated by Eq. (4). The same protocol was applied pH 1.2 samples, but analysis was carried out after every 15 min till 3 h.

$$\text{DR } \% = \text{D}_\text{t}/\text{D}_\text{l} \times 100 \tag{5}$$

Dt = amount of drug released at time interval t and Dl = amount of loaded drug.

Drug release kinetics were determined by applying kinetic models as zero order rate Eq. (5) which describe that drug release rate is independent of its concentration[28].

$$\text{C}_\text{o} - \text{C}_\text{t} = \text{K}_\text{o}\text{t} \tag{6}$$

C_o is the initial concentration of drug, C_t is the concentration of drug in solution at time t, K_o is the rate constant and t is time.

First order Eq. (6) describes the system, where drug release rate is concentration dependent.

$$\text{Log C} = \text{Log C}_\text{o} - \text{Kt}/2.303 \tag{7}$$

where K is the first-order constant, and Co Is the initial concentration of the drug.

Korsmeyer et al. derived an Eq. (7) to determine the drug release mechanism from a polymeric system. To find out the mechanism of drug release, % release data was fitted to the Korsmeyer Peppas model[29].

$$M_t/M_o = K\, t^n \quad (8)$$

M_t/M_o is the fraction of drug released at t, k is the rate constant and n is the release exponent. In this model n value characterize the drug release mechanism, as $n \geq 0.45$, corresponds to the Fickian diffusion method, $0.45 < n < 0.89$ to non-Fickian transport, $n = 0.89$ to Case II (relaxational) transport or zero order, and $n > 0.89$ to super case II transport[30]. It is evident that when n has a value of one, the drug release is independent of concentration and time, corresponding to zero-order release. Equation (7) is termed the power law model, with n equivalent to the diffusional exponent (e.g. for planar systems, $n = 0.5$ describes Fickian behavior indicating diffusion controlled drug release; $n = 1.0$ describes zero-order or case II transport; with $n - 1$ corresponding to the order of release).

Results and discussion

pH responsive tertiary blends of NaA and GG, synthesized through sequential addition method in solution casting approach, with PVA as a physical cross-linker, have been evaluated for significant changes in attributes like swelling, thermal stability, and drug release rate. Experiments demonstrating the proposed reaction found that NaA and GG adhere to one another via H bonds (Fig. 1).

FTIR analysis

Identification of functional groups in prepared hydrogel films was done by FTIR (Fig. 2a).

Peaks of mannose units and 1,4-glycosidic linkage (C–O–C stretching) have been observed at 678 cm^{-1}[31] and at 1055 cm^{-1}[31] respectively. which remained intact and stated polymeric stability throughout hydrogel formation. Prominent peaks have been observed at 1550–1650 cm^{-1} corresponding to asymmetric stretching of carboxylate group[31]. A slight shifting in hydroxyl peaks (at 3680–3730 cm^{-1}) have been detected due to hydrogen bonding[32] that counter confirmed the formation of linking between biopolymers.

Ibuprofen loaded samples (AGPD1-AGPD6) have also been analyzed through FTIR. Ibuprofen have shown stretching peaks of $-CH_3$ at 2917 cm^{-1}[32] and of CH_2 at 1415 cm^{-1}[31]. Prominent peaks at 2957 cm^{-1} and 791 cm^{-1}

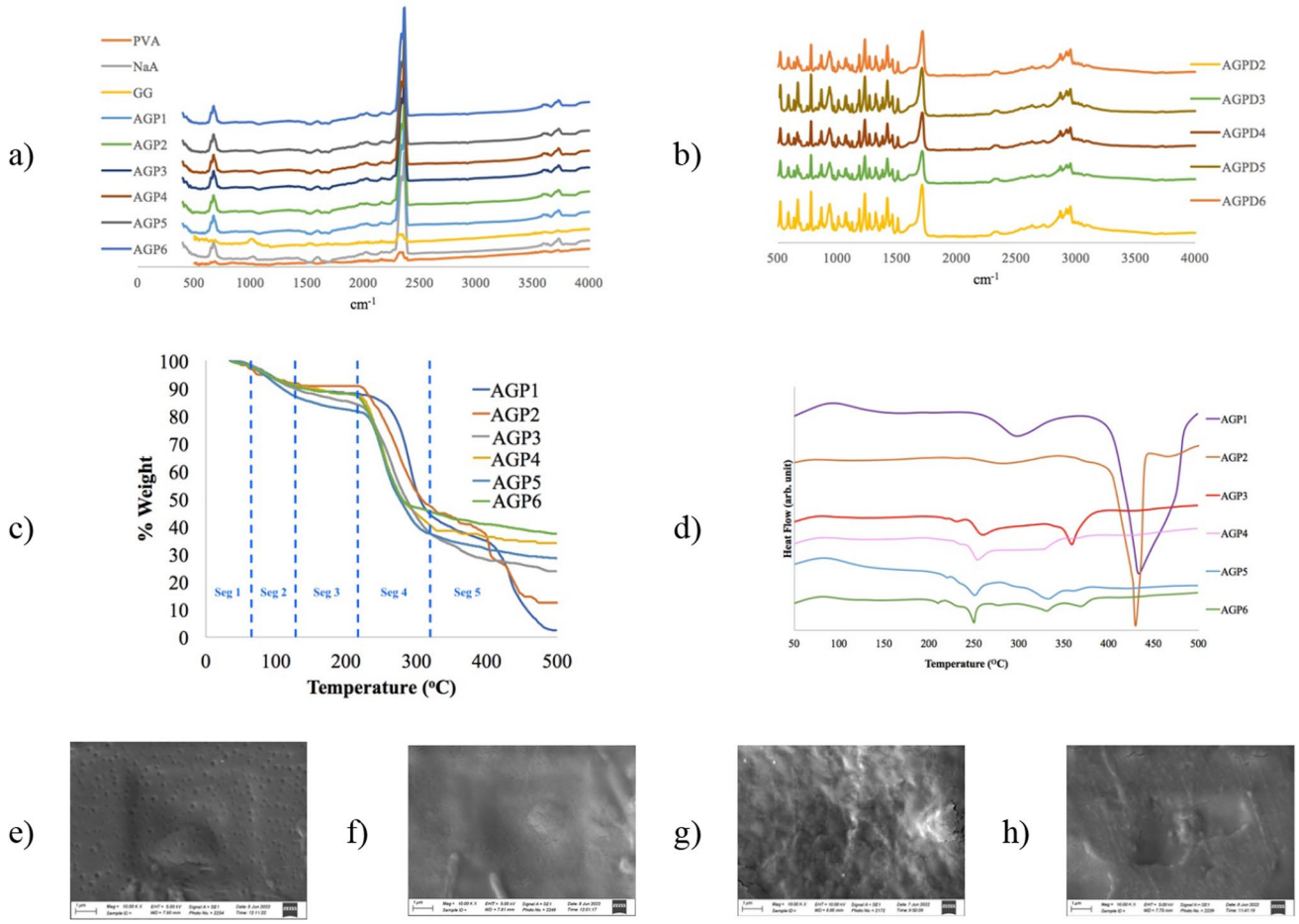


Fig. 2. FTIR of Hydrogel (**a**) Neat hydrogels, (**b**) Drug Loaded Hydrogels, (**c**) TGA, (**d**) DSC of prepared hydrogels, (**e**–**h**) SEM of AGP2, AGP3, AGP4, AGP5.

correspond to C–H stretching and bending, respectively[31]. All peaks in drug loaded samples (Fig. 2b) have confirmed successful loading of ibuprofen in samples.

Gel contents

Gel contents of prepared samples were calculated to find out their degree of cure (Table 3). Sample AGP1 showed the least degree of cure (88.7%), indicating imperfect polymerization between GG and PVA. All the other samples, having 0.1–0.5 g NaA, showed excellent gel content (> 99%). NaA incorporation in hydrogel recipe, as an active ingredient signposts excellent crosslinking density during hydrogel formation. Results of gel content in water showed perfect polymerization as the concentration of NaA increses and shown in Table 3.

Thermal analysis

TGA of prepared samples was studied in temperature range of 25–500 °C at 10 ml/min nitrogen flow rate (Fig. 2c), and found to have decomposition pattern in 5 segments, as follows: 1st segment demonstrated thermal stability, 2nd segment, from 50 °C onwards, presented weight loss of all the samples signposting desorption of physically adsorbed water; 3rd segment, occurring about 110–200 °C, entailed the elimination of structural water by a dehydration process; 4th segment, from 200–300 °C, presented a huge chunk of weight loss which signposts polymeric decomposition through decarboxylation; 5th segment dealt with the creation of aromatic hydrocarbon polynuclear structures.

All sample showed better thermal stability in segment 1 indicating least solvent evaporation. During the second and third segments, all samples exhibited a significant dehydration process. This was subsequently followed by a noteworthy plateau of decomposition, leading to the highest weight loss observed in segment 4. Samples AGP1-3, with high GG concentration, showed better thermal stability than the counterparts AGP4-6, with low GG concentration. Whereas segment 5 presented a reversal in thermal stability behavior of samples. This weight loss trend confirms typical arrangement of NaA and PVA in the core of polymer with a coat of GG, as aimed by sequential addition method. In segment 4, harsh temperature peeled off GG thick layer from samples AGP1-3 and caused a greater structural damage as indicated in segment 5, because of abrupt removal of GG peel. On the contrary, samples with low GG concentration showed excessive damage in segment 4 and sustained the structural integrity in segment 5. This better thermal stability might be attributed to increased NaA concentration, which induced better crosslinking pattern in polymer.

DSC of prepared samples (Fig. 2d) revealed a very loud difference in T_g and T_0 of samples (Table 3), highlighting a clear difference in cross-linking pattern. AGP1 showed highest T_g, signposting high rigidity in sample, along with decomposition temperature (T_0) indicating trivial crosslinking in sample[33]. AGP2 showed almost similar response with slightly reduced values. For other samples, it has been observed from the data that NaA incorporation induced multiple T_g in samples both for flexible and crystalline components in polymeric chains. However, decrease in T_g was obstinate. Likewise, T_0 also got diffused and divided into two segments, indicating non-uniformity in samples, except for AGP4 which presented single T_0 with least value, and highly flexible nature like paper. The composition seems to be perfectly proportionated for suitable connectivity in functional groups, enabling pH-responsive interactions. This conclusion is based on counter confirmation of data set from swelling ratio.

SEM

Only samples with reportable data were analyzed through SEM. A very clear difference in surface morphology of prepared samples has been observed (Fig. 2e–h). AGP2 presented evenly distributed small granular bumps throughout the sample surface, which may be attributed to small portion of NaA. Sample AGP3 presented very smooth surface, indicating a homogenous interaction between different components added in the sample. Sample AGP4, having NaA in slight excess to GG, presented very rough, uneven and irregular surface. This sample has shown better thermal stability and very minute DSC peaks (Fig. 2d), indicating a properly crosslinked polymeric network. Sample AGP5 has been observed with small craters on the surface, which may be attributed to small portion of GG in the sample.

Degradation analysis

Degradtion is used when biomaterials has been employed for medical purposes, because the time period they remain in the body determine their performance for specific applications. Biodegradable hydrogels with sustained drug release have the potential to avoid a chronic immune reaction, as well as to avoid removal surgery. The degradation analysis of hydrogels was performed to determine their degradability. The all hydrogels in basic

Sample ID	Gel contents (%) in DCM	Gel contents (%) in water	T_g (°C)	T_0 (°C)
AGP1	88.70	74.80	279	434
AGP2	99.20	83.06	265	428
AGP3	99.60	85.01	225–252	358
AGP4	99.04	95.04	232–248	329
AGP5	99.30	97.30	217–230–244	331–360
AGP6	99.10	98.00	209–224–240	330–366

Table 3. Gel contents, T_g and T_m of prepared samples.

buffer shows maximum degradation and in acidic buffer shows minimum degradation. In basic buffer hydrogel AGP1 was completely dissolve within 2 min and the remaining samples AGP2 to AGP6 start degradation in first 15 min. After 15 min samples transformed to soft gel without being dissolved and was unable to weigh. The Crosslinking of hydrogel was brokendown, but connectivity between the hydrogel and drug remained till 12 h. So all the sample showed complete degradation within 12 h. It can be seen from Fig. 3a–b, that hydrogel AGP1 has fast degradation rate and dissolved in 1 min, hydrogel AGP4 contained equal concentraton of NaA and GG due to which it showed higher stability upto 15 min and lowest degration. While AGP2 and AGP3 remained in stable form till 14 and 13 min respectivel. Sample AGP5 and AGP6 transformed to soft gel in 5 and 3 min as excess of NaA dissolved but connectivity of drug and NaA release slowly. Due to the degrading nature of hydrogels interacting with PBS media at 37 °C and 7.4 pH, these interactions weakened. It was observed that increasing crosslinking has an inverse effect on degradation.

Hydrogel stability

Hydrogel stability results showed that as the hydrogel strips dipped in buffer system (Fig. 3c) change in shape was observed. Within first 3 min, AGP1 dissolved (Fig. 3d), AGP5 and AGP6 transformed into soft gel (Fig. 3e), other hydrogels remains unchnaged (Fig. 3f–g), AGP2 and AGP3 transformed into soft gel (Fig. 3h) and AGP4 cahnged from film to thick gel (Fig. 3i), Fig. 3j–k showed no change after 1 and 2 h, (Fig. 3l–m) hydrogels in thick gel form, after 24 h hydrogels was completely dissolved (Fig. 3n).

Swelling ratio

The swelling rate of pH-responsive cationic hydrogels is influenced by lower PKb of corresponding pendent group relative to surrounding pH of swelling medium. Increase in fixed positive charge on the polymer chain and negative charge in solution and hydrophilic nature of hydrogel which causes repulsion of the chain and swelling of hydrogel and vice versa. On the contrary, anionic hydrogel in higher pH then PKa of acidic pendent group causes ionization and increases in positive charge in the solution. Negative charge on polymer chain causes repulsion, leading to swelling and entrapment of drug.

In current study prepared samples have a precise control over swelling due to cross-linking pattern and cross-linking density in polymeric network. Variation in swelling ratios observed at different pH values, which were utilized to determine the drug's release rate and water absorption capacity, served as indicator of hydrogels' pH responsiveness at 37 ℃. Phosphate buffer solutions (PBS) of pH 1.2 and pH 7.4, have been utilized to assess the swelling ratio of prepared samples. AGP4 and AGP5 (pH 7.4) have been observed with the highest water withholding capacities. The observed optimal swelling ratio in AGP4, at both acidic and neutral pH conditions, can be attributed to a unique crosslinking pattern inside the hydrogel. This crosslinking pattern has resulted in a significant number of functional groups available to play a crucial role in bond formation and breaking against a specific pH response. Similar trends have been observed by sample AGP5, displaying great swelling behavior at pH 7.4. Hydrophobic nature of produced blends facilitated their ability to respond to pH variations over a spectrum of media, ranging from acidic to neutral, without inducing any dissolution.

The increase in NaA monomer concentration throughout the synthesis process has led to a noticeable shift in the swelling ratios of the generated samples. This change has been corroborated by TGA data, which indicate a distinct networking pattern.

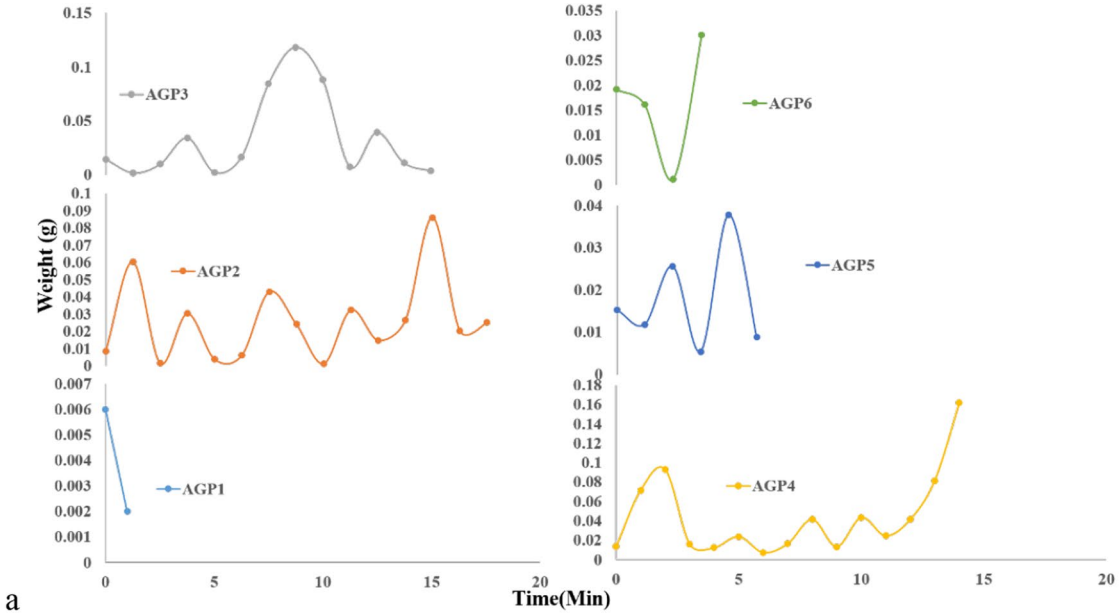
According to studies, prepared samples showed maximum swelling at pH 7.4 than at pH 1.2 (Fig. 4a–c). Samples exhibited the highest level of swelling within initial 20 min after being submerged in the solution. Samples with a pH of 7.4 exhibited more swelling in comparison to those with a pH of 1.2. The greater number of carboxylate anionic groups that were responsible for repulsion between polymeric chains at pH 7.4 may be the cause of the increased swelling capacity. At pH 1.2, carboxylate ions changed into carboxylic groups and ceased to repel one another, causing a drop in swelling ratio. Change in swelling behavior with pH change indicates pH sensitivity of prepared tertiary blends. Empirical investigations demonstrated that hydrogels has the potential to serve as effective vehicles for pH-responsive drug delivery.

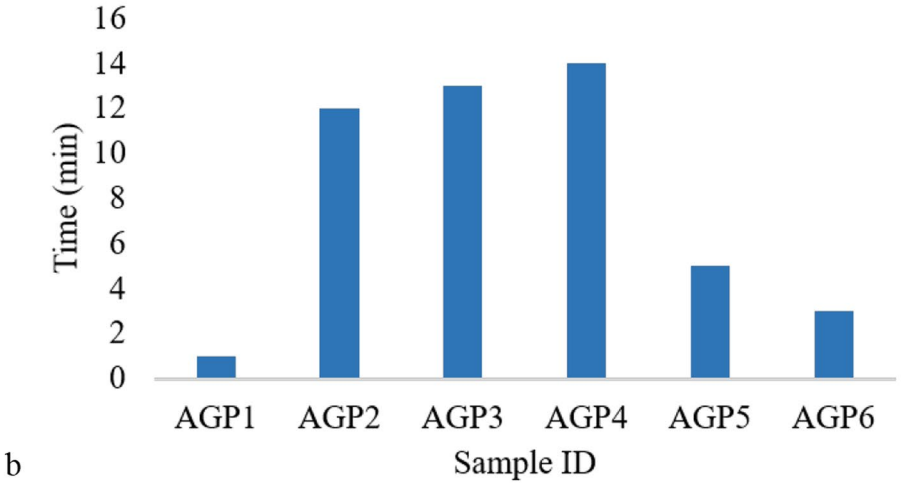
Drug release studies

The swelling dynamics of the hydrogel are influenced by the cross-linking density. In order to examine the drug release behavior of hydrogel samples, ibuprofen was utilized as a model drug. Due to the sample's total disintegration in the swollen medium, the drug was not able to load on AGP1. Ibuprofen loading efficiency was seen in sample AGPD2-AGPD6, with an increase in hydrophilic character and hydrogen bonding possibly being the cause of the drug's entrapment.

Release studies were observed in phosphate buffer solution of pH 1.2 and pH 7.4 which corresponded to the environment of stomach and intestine, respectively. pH acted as important factor in the sustained drug delivery. At pH 7.4 the maximum release rate was 82.34% while at pH 1.2 this rate was 17.84% as shown in Fig. 4d–e. After 12 h there was no release was observed. This difference in drug release rate clearly indicates difference in pH responsiveness of hydrogel films.

Based on the observed swelling behavior (Fig. 4a–c), the sample transformed into a swelled gel within the first 20 min. However, the release of the drug was gradual and continued for several hours. The presence of hydrophilic groups within the three-dimensional network polymer hydrogel may be responsible for this phenomenon. These groups exhibited swelling yet had a strong attraction to drug. The initiation of drug release occurred promptly upon the infiltration of water molecules into the biopolymer network. Consequently, the hydrogel underwent expansion, leading to the diffusion of the medication into the PBS from the network. The migration of ibuprofen from hydrogel to PBS at pH 1.2 is hindered due to reduced swelling and the protonated nature of hydrophilic groups present in polymeric materials. The migration of ibuprofen towards PBS was seen to be more pronounced at an alkaline pH of 7.4. This can be attributed to the increased swelling and anionic properties of the hydrophilic





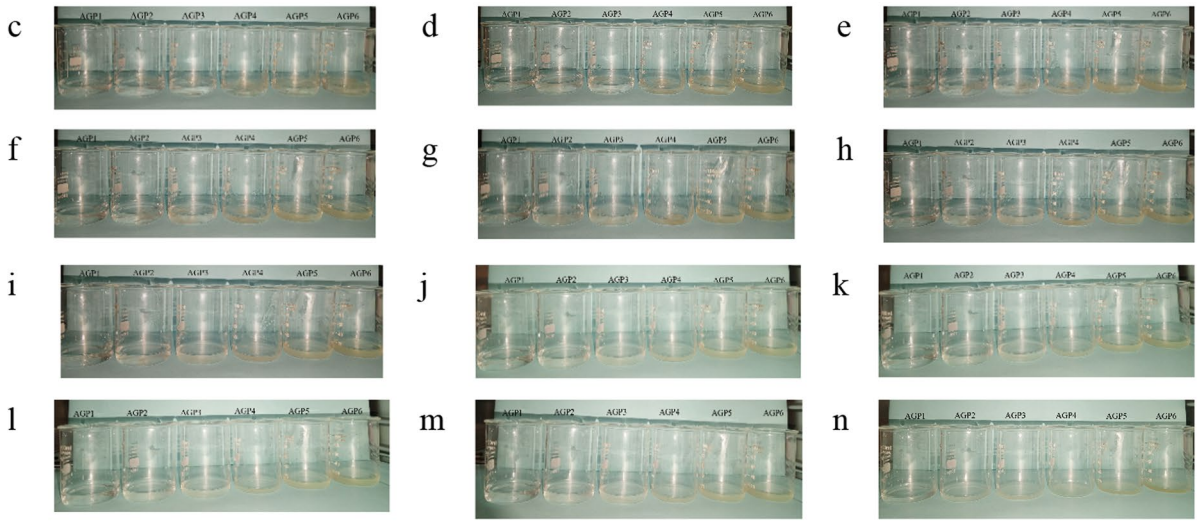


Fig. 3. (**a**) Weight change of hydrogel samples in phosphate buffer (pH 7.4), (**b**) hydrogel stability against aqueous buffer system and (**c**–**n**) pictorial reperesntaion of hysrogel stability against aqueous buffer system.

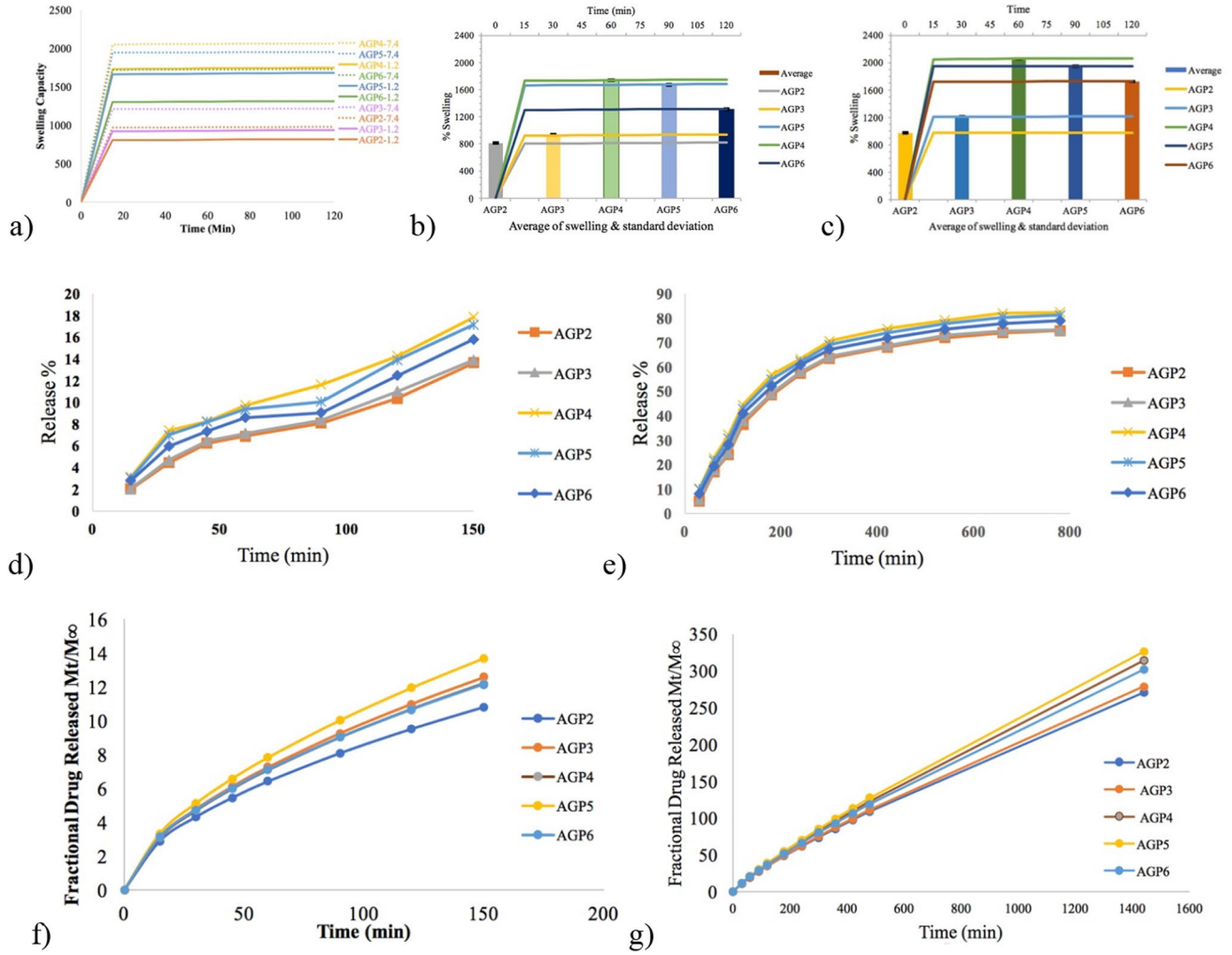


Fig. 4. (**a**) Comparison of hydrogels swelling capacity; (**b**) swelling average and SD at pH 1.2, (**c**) swelling average and SD at 7.4, (**d**) Release rate of ibuprofen at pH 1.2 and (**e**) Release rate of ibuprofen at pH 7.4, (**f**) Korsmeyer Peppas model for mechanism of fractional drug release at pH 1.2 (**g**) Korsmeyer Peppas model for mechanism of fractional drug release at pH 7.4

groups within the polymeric network, resulting in a higher rate of ibuprofen release. The drug release studies demonstrated that the hydrogels developed have the potential to serve as efficient carriers for drug delivery and warrant further exploration for potential therapeutic applications.

The Drug release kinetics of various compositions are compared in the Korsmeyer Peppas model by plotting fractional drug released (M_t/M_∞) against time as shown in Fig. 4f–g, according to which k determines the release constantly, and n specifies the order of drug release as there is n near about 1, which means that drug release follows zero-order kinetics as non-fickian diffusion. The swelling or relaxation of hydrogel drives the drug release mechanism[34].

As we synthesize hydrogel in sequential manner, NaA first interacted with PVA and formed a network, which is followed by interaction with GG. It resulted in a spherical arrangement of NaA in the core and GG at the coat. The concentration of drug release is affected by the concentration of GG. In sample AGP4 and AGP5 concentration of guargum is less then the concentration of NaA, follows first orde kinetics. As the concentration of GG increases the rate of drug realese changes from abrupt release to sustained, which results in change of order from first to zero. GG concentration increses entrapment efficiency and prevent rapid dissolution in higher pH, ensuring controlled release. In this way hydrogels with same components follows two different release kinetics by controlling their chemistry using sequential addition method.

Table 4 presents summary of zero and first order drug release kinetics from hydrogel. In zero order and first order R^2 describe the drug release rate relationship with concentration of drug[28] as shown in Table 4 where K_o value is constant for zero order. According to Eq. 4 the slope of the line corresponds to zero order constant. Therefor the rate of drug dissolution is K_o.

Korsmeyer Peppas model						
ID	k	n	R^2	k	n	R^2
AGP2	0.620470	0.570395	0.984575	0.658400	0.827413	0.912980
AGP3	0.619425	0.600531	0.988684	0.642518	0.834980	0.909185
AGP4	0.623576	0.593430	0.991370	0.627850	0.855006	0.902446
AGP5	0.642930	0.610529	0.985375	0.641366	0.856936	0.902985
AGP6	0.644831	0.586040	0.984502	0.643671	0.845799	0.905752

For First and Zero Order Kinetics							
		Zero Order kinetics		First Order kinetics			
ID	pH	K_o (s^{-1})	r	K_o (s^{-1})	r	Order	Mechanism
AGP2	1.2	0.000139	0.976	0.00000006	0.0753	Zero order	Non-Fickian diffusion method
	7.4	0.000045	0.779	0.00000001	0.0052		
AGP3	1.2	0.000145	0.962	0.00000006	0.0745		
	7.4	0.000046	0.733	0.00000001	0.0038		
AGP4	1.2	0.000204	0.944	0.00000009	0.0847	First order	Non-Fickian diffusion method
	7.4	0.000056	0.761	0.00000001	0.0005		
AGP5	1.2	0.000190	0.944	0.00000009	0.1392		
	7.4	0.000054	0.768	0.00000001	0.0007		

Table 4. Release parameters. Drug release rate constant (k), correlation coefficient (R^2), release exponent (n) according to Korsmeyer Peppas model. K_o is a zero-order constant, K is first order constant, R^2 is correlation coefficient or drug release rate relationship with concentration of drug.

Conclusion

Sequential addition method for synthesizing hydrogels involves adding components in a specific order to achieve a precise three-dimensional orientation of the material to control drug release kinetics. In the current study, a NaA core was created, and GG was applied on top. Various combinations of NaA and GG have been experimented with in order to get a precise thickness for both the core and the coat. For regulated release in pH-stimulated drug delivery, the careful choice of polymers and cross-linkers is essential. Samples with a high proportion of GG exhibited drug release kinetics that followed a zero-order pattern. When the concentration of GG decreased or the concentration of NaA increased in the compositions, the reaction started following first-order kinetics. AGP4 (50% NaA) presented a flexible and stable polymeric network, with 82.34% drug release in 800 min, at pH 7.4. Upon comparison to pH stimulus, the uniform distribution of –COOH groups on polymeric structures resulted in a plausible drug release mechanism with 17.84% and 50.12% drug release (in 150 min) at pH 1.2 and 7.4, respectively. Sequential addition methods hold promise for advanced drug delivery systems. Potential developments may include enhanced biocompatibility, tunable release kinetics, and tailored formulations for specific therapeutic applications. Sequential addition method for the synthesis of pH-responsive hydrogels, with adjustable pH responsiveness and biocompatibility, exhibits significant promise for many biomedical and industrial applications like drug delivery, tissue engineering, and environmental monitoring. Additionally, this methodology has demonstrated enhanced control over gel properties, hence enabling advancements in the fabrication of personalized materials.

Data availability

The authors declare that the data supporting the findings of this study are available within the paper. Should any other raw data files be needed in another format, they are available from the corresponding author upon reasonable request.

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Declarations

Competing interests

The authors declare no competing interests.

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