

Exploring the effect of rheological modifiers and preservatives on the *in vitro* release of caffeine from gel formulations

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Introduction

To start the process of skin penetration, an active ingredient has to be released, i.e. it has to diffuse through the formulation and reach the stratum corneum in sufficient quantity.

In this study, we have explored two formulation parameters that may influence the diffusion of caffeine through the hydrogel system: **the type of gelling agent** and **the presence of a preservative system**. The aim was to assess whether and to which extent the changes in rheological properties exerted by the above two parameters affect the *in vitro* release of caffeine from the hydrogels.

Materials and Methods

A simple hydrogel (Table I) was used as a model formulation. Twelve hydrogels were formulated with preservative (a mixture of methylparaben 15%, ethylparaben 10% and phenoxyethanol 75%) at 1% w/w, each containing a different gelling agent. Further twelve hydrogels were formulated with the same gelling agents used as above, but without preservative.

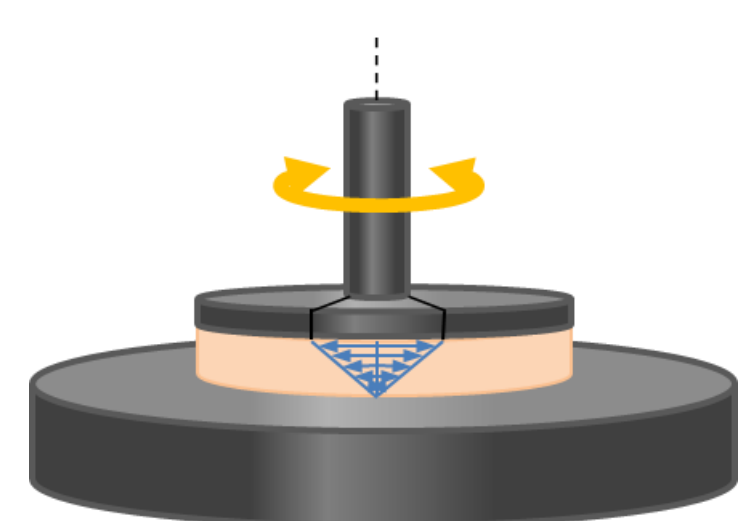
Table I Generic hydrogel formulation

Phase	INCI name	% w/w
A	Aqua	up to 100.0
	Caffeine	2.0
B	Gelling agent	q.s. to required viscosity
C	Methylparaben, ethylparaben and phenoxyethanol	1.0 (if used)
	Citric acid	q.s. to required pH
D	Sodium hydroxide	q.s. to required pH

A range of 12 gelling agents, belonging to 5 chemical categories, have been used, as follows: **cellulose derivatives** (Na carboxymethyl cellulose, hydroxyethyl cellulose), **clays** (hectorite, Mg Al silicate), **natural polymers** (xanthan gum, carrageenan, gellan gum), **polyacrylic acid polymers** (carbomer, acrylates C10-30/alkyl acrylate crosspolymer, Na polyacrylate) and **silica-based thickeners** (hydrated silica and silica). All 24 hydrogels had a viscosity of 44 Pa.s (+/- 10%) at 20°C (Brookfield DV-E, Brookfield Ametek, UK) and a pH of 5.9- 6.0.

Caffeine, a methylxanthine derivative with molecular weight of 194.2 Da and Log P_{o/w} of -0.07, was used as a model hydrophilic active ingredient.

(a)



(b)

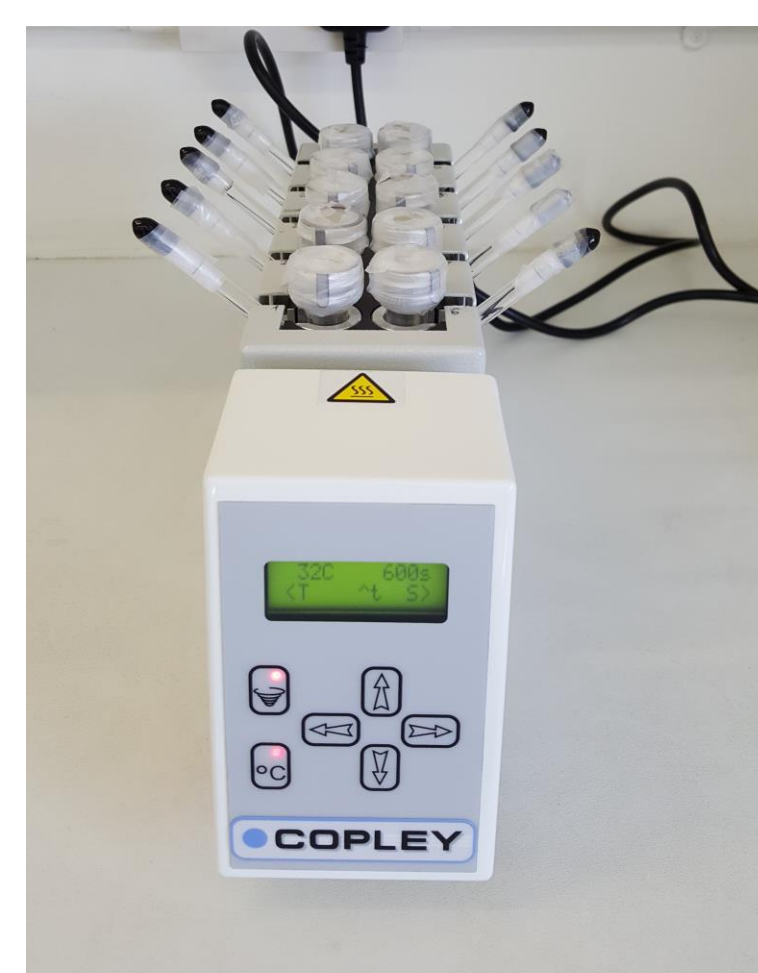


Fig. 1 Visual representation of the parallel plate rheological method (a) and an image of the Franz cell vertical diffusion system (b)

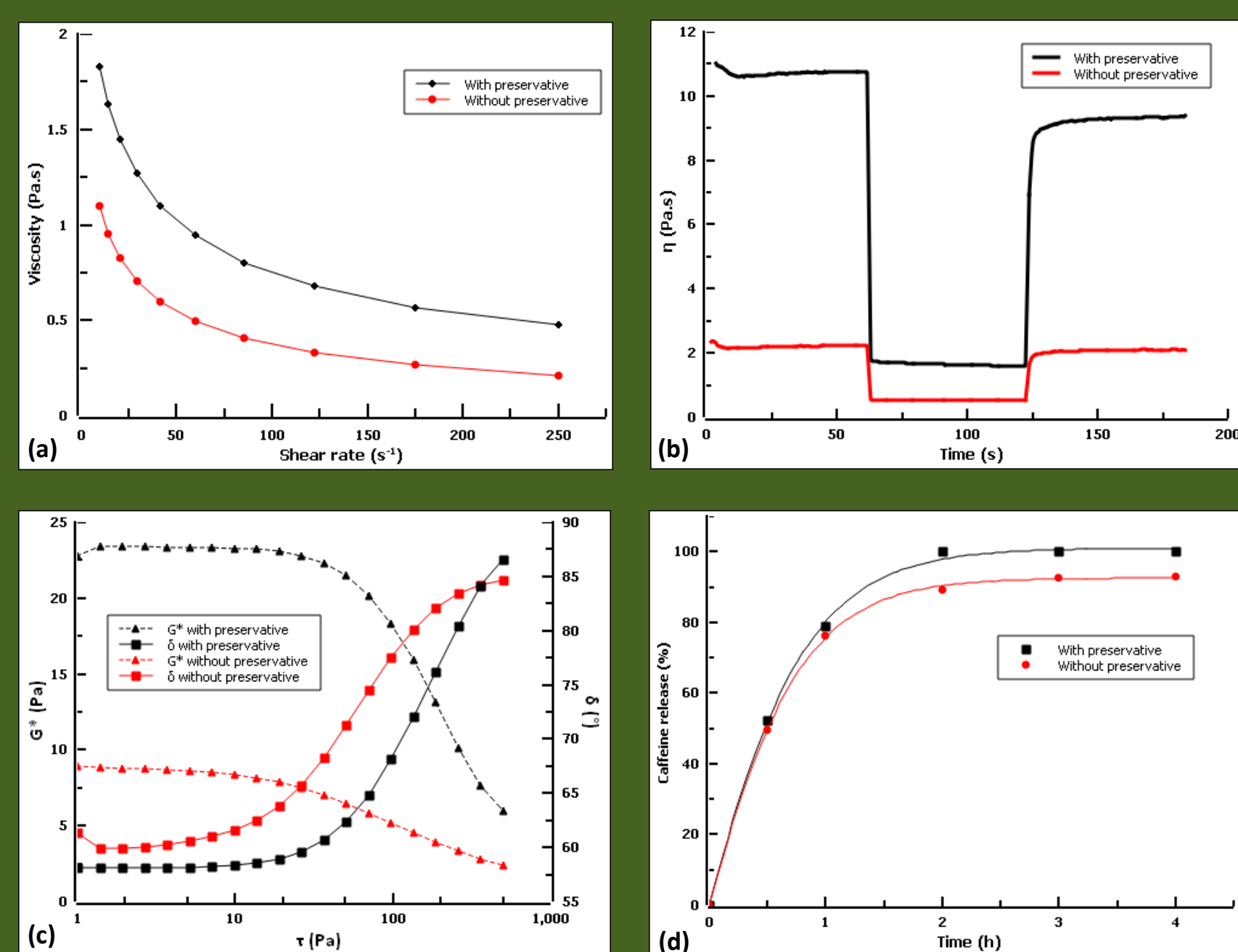
Rheological measurements were carried out on the RheoStress RS75 Rheometer (Haake, Germany, Fig.1a), using a 35-mm serrated parallel plate and the gap of 1 mm. Continuous flow and dynamic (oscillation) tests were used in conjunction to produce complete rheological profiles of the test samples.

Release studies were performed on the Franz cell vertical diffusion system (Copley Scientific, UK, Fig. 1b), using the hydrophilic polysulphone membrane Tuffryn HT-450 (Pall Life Sciences, USA), during the period of four hours. Samples were analysed with a UV-vis spectrophotometer, Nanodrop (Thermo Scientific, USA) to determine the concentration of caffeine that had released through the hydrogels.

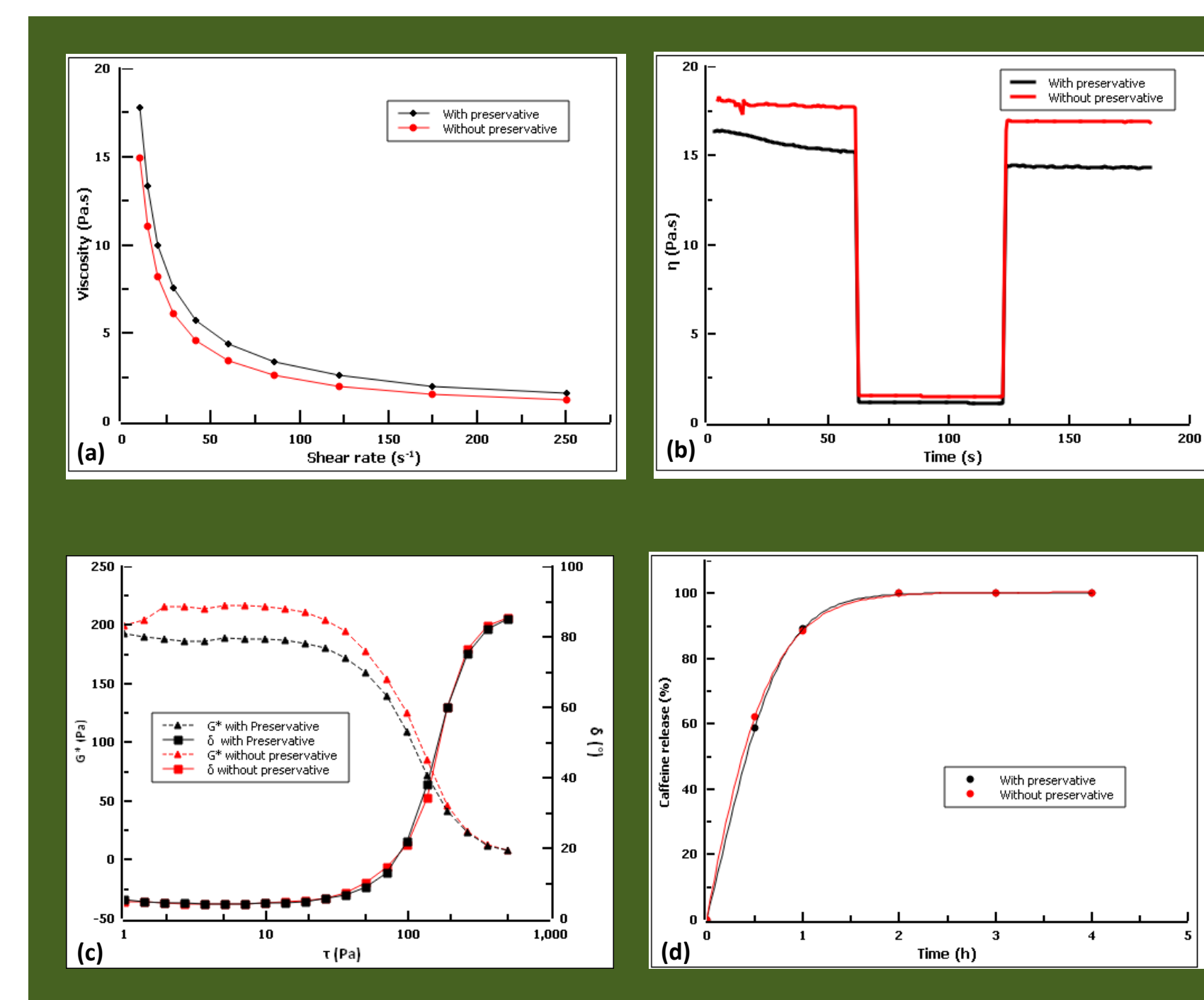
Results and Discussion

An example of a complete data set obtained for the gelling agent (in this case Na CMC) is given in Fig. 2. In common with all tested samples, it has shown a plastic flow (shear-thinning with yield stress) and thixotropy. The preservative has caused distinct changes in rheological parameters and a small increase in caffeine release.

Fig.2 Results of the rheological tests of Na CMC hydrogel, with and without preservative, using shear rate sweep (a), 3-step thixotropy test (b), oscillatory stress sweep (c) and *in vitro* caffeine release profiles (d)



The addition of preservative has, in most cases, strengthened the hydrogel internal structure, evidenced by increased viscosity, complex modulus (rigidity) and yield stress. The opposite trend was observed in the cases of both tested clays and hydrated silica.



Interestingly, the expected pattern of decreased diffusion rate with an increase in viscosity (within the test limits) was not consistently observed, with all polyacrylic acid and silica-based hydrogels being exceptions. Fig. 3 reveals small changes in rheological parameters (a, b, c) for acrylates crosspolymer, which did not affect the release profile of caffeine (d).

Fig.3 Results of acrylates/C10-30 alkyl acrylate crosspolymer hydrogel, with and without preservative, using shear rate sweep (a), 3-step thixotropy test (b), oscillatory stress sweep (c) and the caffeine release profiles (d)

The hydrogels have shown a variety of *in vitro* release patterns, which were both gelling agent- and preservative-dependent. All hydrogels have released a 100% of caffeine within four hours, most of them between the first and second hour of the experiment, with the exception of xanthan gum (max. 80% release).

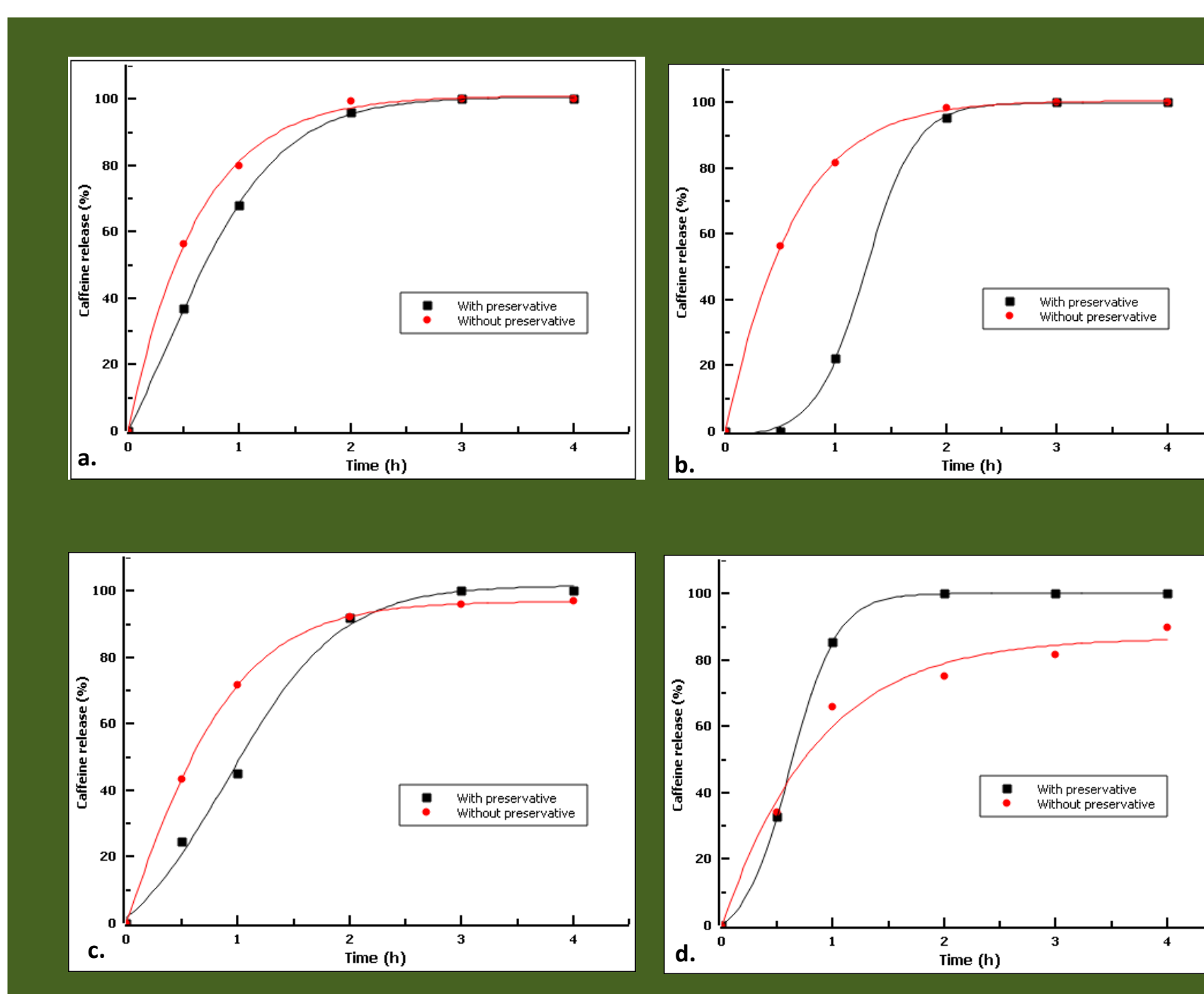


Fig.4 Results of the *in vitro* release of caffeine from carrageenan (a), gellan gum (b), hydrated silica (c) and silica (d) hydrogels

The addition of preservative has generally produced either identical or higher release rates than the sample without preservative (Fig.2d, Fig.3d, Fig. 4d). The exceptions were all natural gums (Fig. 4 a-c), whereby a lower release rate was detected during the first three hours, with the tendency to equalise later, and xanthan gum (Fig. 5c).

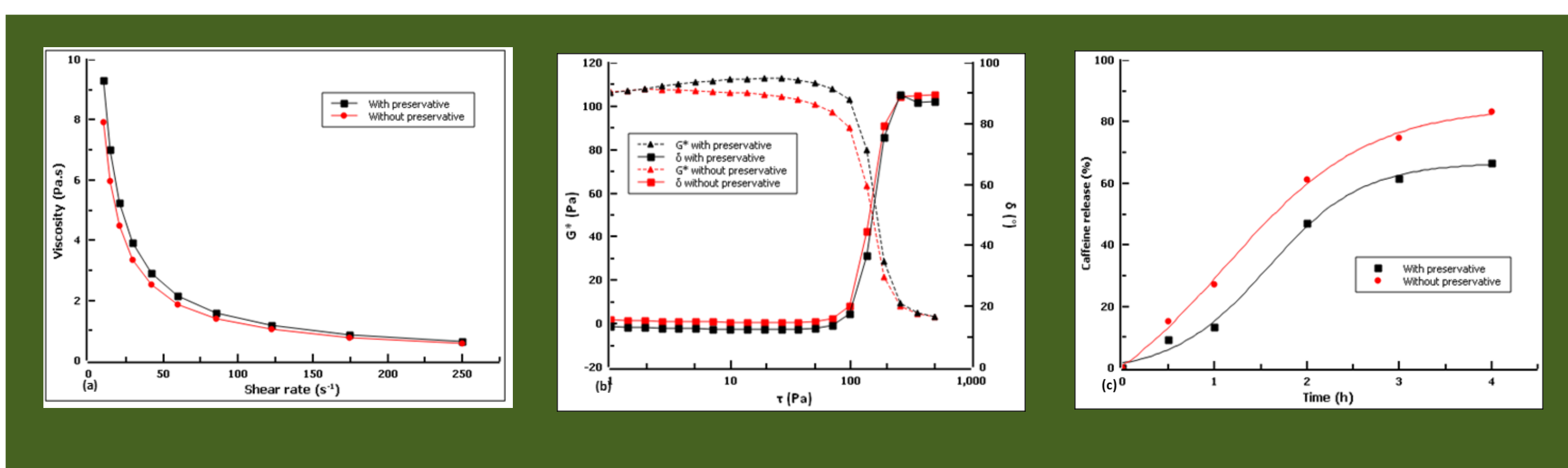


Fig.5 Results of the rheological characterisation of xanthan gum hydrogel, with and without preservative, using shear rate sweep (a) and oscillatory stress sweep (b), alongside *in vitro* caffeine release profiles (c)

Low release of caffeine from xanthan gum hydrogel is in line with the observation by Talukdar and Kinget (1997), who measured the diffusivity of three drugs, including caffeine, from the hydrated polymeric matrices of xanthan gum and HPMC and found that it was lower in the case of xanthan gum. Without further work, it is not clear why this phenomenon occurs, but it could be used to control caffeine release from both solid and semisolid forms. Further work should include measuring the release profile of caffeine during a longer period (e.g. 8 hours) to establish whether and at which time point a complete release occurs.

Conclusion

This study has shown that the presence of preservative, in addition to the type of gelling agent, could strongly affect the rheological properties of the hydrogel vehicles used for topical delivery. As expected, the change in rheological properties affected the rate of *in vitro* release of caffeine from the formulation for the majority of hydrogels evaluated in this study, hence this effect could be used to control the initial stage in the complex process of topical delivery.

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