AAPS PharmSciTech (2022) 23:107
https://doi.org/10.1208/s12249-022-02265-1

RESEARCH ARTICLE

# Innovative, Sugar-Free Oral Hydrogel as a Co-administrative Vehicle for Pediatrics: a Strategy to Enhance Patient Compliance

**Margarida Pereira[1] · Filipa Cosme Silva[1,2] · Sandra Simões[1] · Helena Margarida Ribeiro[1] · António José Almeida[1] · Joana Marto[1]**

Received: 28 December 2021 / Accepted: 22 March 2022


**Abstract**
Palatability and swallowability in the pediatric population are perceived as true challenges in the oral administration of medication. Pediatric patients have high sensitivity to taste and reduced ability to take solid dosage forms, which can often lead to a poor therapeutic compliance. It is crucial to find new strategies to simplify the oral administration of drugs to children. The present paper reports the development of a new hydrogel vehicle adapted to the pediatric population. Several polymers with similar properties were selected and adjustments were made to obtain the desired characteristics of the final product. The developed formulations were studied for organoleptic properties, rheology, mucoadhesion properties, preservative efficacy, and stability. Physical and chemical compatibilities between the vehicle and several drugs/medicines, at the time of administration, were also studied. Six final formulations with different polymers, odor, and color were chosen, and no known interactions with medications were observed. The proposed new oral vehicles are the first sugar-free vehicle hydrogels designed to make the intake of oral solid forms a more pleasant and safer experience for pediatric patients.

**KEywords** Pediatric vehicle · Hydrogel · Swallowability · Palatability · Oral administration

## Introduction

It is widely recognized that "children are not just small adults." In fact, children differ from adults in many aspects, including pharmacokinetic profile, reduced ability to swallow, medicine-related toxicity, and taste preferences (1). These young patients' characteristics make them worst compliers to a therapeutic regimen if this is not properly designed for them. It has been reported that adherence to a prescribed medication varies between 11 and 93% among the pediatric population, resulting in a median value of 58%, which is lower than that reported for adults. The variability of dosage form acceptance in children is correlated to their individual features (age, individual health status, disabilities, and background), difficulties in the oral administration of medication (manipulation of medicines and taste), medication-ingestion behavior (influence of family, school, and life situation/context), and culture (1).

Despite the reported challenges related to pediatric treatment, there are not many formulations suitable for children, which often leaves health care professionals with no alternative but to use adult medicines in an off-label or unlicensed way. In the EU, about 45 to 60% of all medicines prescribed to pediatric patients are off-label (2). Besides, drug compounding and mixing medication with food or drinks have also become common practices among health care professionals and caregivers. This is associated with many risks as these products have not been properly studied in the pediatric population.

Drug compounding for pediatric oral administration can be a difficult and unsafe practice given the lack of available data to validate stability, bioavailability, pharmacokinetics, pharmacodynamics, dosing accuracy, tolerability, and reproducibility. Mixing a pharmaceutical product with edibles may either be intended to mask the poor palatability of the formulation or to improve swallowing, even if the drug has reasonable palatability. This type of co-administration can be supported by updated guidelines (3). Small amounts of

✉ Joana Marto
jmmarto@ff.ulisboa.pt

[1] Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal

[2] Pharmaceutical Services, Unidade de Farmácia Pediátrica, Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, EPE, Lisbon, Portugal

Published online: 05 April 2022

liquids and/or soft foods are described by the FDA-approved product labelling as suitable vehicles for oral administration and immediate ingestion of a specific drug product (3). Nevertheless, this practice is performed without following the appropriate procedures. The impact of the co-administered edible on the absorption and subsequent pharmacokinetic profile of the drug is usually unknown. If a drug-edible mixture is not entirely consumed, the desired dose will not be administered (1).

There is still a crucial need to increase the acceptability of pediatric pharmaceutical products (especially solid dosage forms) to patients and their caregivers to enhance therapeutic outcomes in pediatrics. Recent improvements like mini-/micro-tablets help overcome swallowability issues and provide dose flexibility while also retaining the benefits associated with conventional tablets (4, 5). This can be a possible strategy to improve patient adherence, although it does not address the palatibility problem of most drugs.

Patient acceptability and compliance is determined by the characteristics of the product (aspects regarding the formulation) and the end-user (different age groups) and should be considered at an early stage in the product development pathway rather than later in the formulation development process. Two major aspects that influence acceptability in pediatrics are the swallowability and the palatability of the medicinal product (6).

The definition of swallowability is not consensual, varying from author to author, but the most used is "the patient's ability to take the drug without gagging or choking" (7). Palatability is defined as the organoleptic property of a drug product that makes it pleasant or acceptable in terms of taste, after-taste, smell, and texture (mouthfeel). The need to develop palatable medicines for children is also related to the fact that many drug substances are bitter or have other averse sensory characteristics, such as unpleasant aromas, mouth irritation, and unpleasant appearance (8).

To minimize unnecessary manipulation of medicine it is essential that prescribers consider all the factors related with its acceptability and further research is needed to identify globally acceptable and available vehicles that can be chosen as first option for co-administration with medicines (9). An example of this type of vehicles is a product named Gloup® (Rushwood BV, Netherlands), a slippery gel consisting of food-based ingredients (maltodextrin and carrageenan) that works as a medication lubricant to make the intake of solid dosage forms a more pleasant and safer experience for the patient. However, Gloup® contains sucrose, which is not acceptable for diabetics, patients on keto diets (used in selected cases of refractory epilepsy), or for long-term use (10).

The primary goal of this work was the development and optimization of a hydrogel vehicle suitable to facilitate the oral administration of solid dosage forms to pediatric patients in hospitals and pharmacies, since such a product is not yet available on the market. The aim was to obtain a cost-effective product, easy to manipulate, while targeting the specific needs of the pediatric population. This vehicle should ease the immediate ingestion of oral dosage forms, without the need to split tablets or open capsules. It is important to highlight that is not meant to be a extemporaneous formulation, but rather a ready-to-use product.

Several polymers were tested and evaluated concerning rheological (viscosity, oscillatory, adhesion) and mucoadhesion properties, stability in acidic medium, and preservative efficacy. The selected formulations were then subjected to stability and compatibility studies.

## MATERIALS AND METHODS

### Materials

The following excipients were used in formulation studies: purified water was obtained by reverse osmosis and electrodeionization (Millipore, Elix 3), and filtered (pore 0.22 µm) before use; sodium carboxymethylcellulose (CMC) and methylcellulose (MC) 1500 were a gift from Fagron (Spain); Natrosol®—hydroxyethylcellulose (HEC) was obtained from Aqualon (Spain); xanthan gum (XG) and gelatin (G) were obtained from Disproquima (Portugal); hyaluronic acid (HA) 1.8–2.2 Eyed™ was a gift from Inquiaroma (Spain); sodium methylparaben, sodium propylparaben, and sodium citrate were obtained from Fagron (Spain); sucralose and citric acid monohydrate (granulate) were obtained from A.M.S. Cruz Laboratory (Portugal); and mint and strawberry flavor and colorants CI 61,570 and CI 16,255 were obtained from DS Produtos Químicos (Portugal). The product Gloup® was purchased from Rushwood BV (Netherlands). For the mucoadhesive studies, dried mucin from porcine stomach type II was used (Sigma-Aldrich, USA). For the compatibility studies, acetazolamide, arginine hydrochloride, biotin, hydrochlorothiazide, hydrochlorothiazide + amiloride, and riboflavin were a gift from Fagron (Spain); calcium carbonate was obtained from Labesfal (Portugal); captopril was from Generis (Portugal); clindamycin was a gift from Pfizer (New York, USA); diazepam, hydrocortisone, and prednisolone tablets were obtained from Ratiopharm (Germany); and glycine was purchased from Acofarma (Spain).

### Development of Hydrogel Formulations

#### Pre-formulation Study

To select the polymers suitable for hydrogel preparation, several formulations were prepared at room temperature by dispersing the polymer in an aqueous solution containing

0.18% (w/w) sodium methylparaben, 0.02% (w/w) sodium propylparaben, 0.5% (w/w) sucralose, 0.05% (w/w) citric acid, and 0.5% (w/w) sodium citrate, with magnetic stirring. A total of 15 formulations were prepared using several polymers at different concentrations, as presented in Table I. In the case of gelatin, the polymer had to be heated to 70 °C before adding to the mixture with the other components.

After production, hydrogels were packaged in 30-g aluminum tubes with an inner epoxy coating. All compounding operations for hydrogels were carried out according to the PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments (11).

## Characterization of Hydrogel Formulations

The macroscopic features of each hydrogel were assessed by visual observation for texture, appearance, and color. The pH was determined using a digital pH-meter with a glass electrode (SevenEasy™ by Mettler Toledo) and it was ensured that the pH of the gel was within the desired range (pH 5.5–7.0). Whenever needed, pH adjustments were made using a citric acid solution 50% (w/v).

## Rheological Characterization

The rheological studies were conducted in a controlled stress Kinexus Lab + Rheometer (Malvern Instruments, Worcestershire, UK), at 25 °C. Formulations were characterized using (i) viscosity testing; (ii) oscillation testing; and (iii) tackiness and adhesion testing. Viscosity and oscillation were assessed using a cone-plate geometry (truncate angle 4° and radius of 40 mm). The range of shear rate varied from 0.1 to 100 $s^{-1}$ for viscosity measurements. Oscillation frequency of hydrogels was determined using frequencies ranging from 0.1 to 10 Hz. The shear strain was 3.6%. For evaluation of tackiness and adhesion, a pull away test using a plate-plate geometry was performed. Parameters used were 0.1 mm/s for gapping speed, 5 mm for final gap and 0.2 mm for working gap. Testing was performed in three replicates of the same hydrogel.

The results obtained in the assays described in the sections "Characterization of Hydrogel Formulations" and "Rheological Characterization" were used to select two final hydrogel formulations with the desired product profile, to develop final formulations supplemented with flavor and color.

### Osmolality Measurement

The osmolality of the final vehicles was determined using an osmometer (OSMOMAT 030, GONOTEC) and expressed in mOsm/kg units. The measuring technique was based on the determination of the freezing point depression. The instrument was calibrated using a standard solution of 1500 mOsm/kg and distilled water for 0 mOsm/kg. All measurements were performed in triplicate, and the probe was carefully washed with distilled water in-between measurements.

### Flavor and Color Assessment

This study was based on a survey conducted in several preschools and schools, to be answered by young children, according to their preferences in terms of taste and color, after the visualization of a panel (Fig. S1) presenting flavor-remembering images ("images of flavor") and a panel of colors, respectively. For the questionary, a verbal consent from each caregiver was previously required. The specific inclusion criteria defined in the protocol were the following ones: (i) age — under 12 years old and (ii) gender — female or male. Individuals with associated physical or mental health problems/diseases that could affect the reliability of the sensory questionnaire were excluded.

The aim of the survey was to further identify which flavors and colors were most appealing to children from different age groups. The collected information was essential to make a more thoughtful decision about the sensorial aspects of the formulation throughout its development and to select the flavor and color to use in the vehicle.

A total of 157 volunteers completed the survey and provided demographic information about their age and gender.

**Table I** Percentage of Polymer Used in Each Formulation

| | Formulation | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Polymer (%, w/w) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 | F13 | F14 | F15 |
| Sodium Carboxymethylcellulose | 1.5 | 2.0 | | | | | | | | | | | | | |
| Methylcellulose | | | 1.5 | 2.0 | | | | | | | | | | | |
| Hidroxyethylcellulose | | | | | 1.5 | 2.0 | | | | | | | | | |
| Xanthan gum | | | | | | | 2.5 | 1.5 | 1.0 | | | | | | |
| Gelatin | | | | | | | | | | 1.5 | 2.0 | 3.0 | 5.0 | 10.0 | |
| Hyaluronic acid | | | | | | | | | | | | | | | 1.5 |

Children were instructed to choose only one option in each question and no further information was requested.

### Effect of Gastrointestinal Tract Conditions

Formulations were tested for viscosity, oscillation, and adhesion using the Kinexus Lab + Rheometer (Malvern Instruments, Worcestershire, UK), as described in the "Rheological Characterization" section. The shear strain used for the oscillation frequency test was 1.1%. The commercial formulation Gloup® was used as a control.

#### Mucoadhesion Test

The mucoadhesive profile of the different polymers was evaluated using a rheological method that includes the three rheological tests described before. Through the changes in the rheological behavior of each formulation it was possible to evaluate the presence of mucoadhesion interactions. For this purpose, mucin (M) was hydrated with water by gentle stirring until complete dissolution to yield a dispersion of 4% (w/w) at 25 °C, and artificial saliva (S) was prepared according to a previous published work (12). Each formulation was mixed with mucin (1:1), artificial saliva (1:1), and both (1:0.5:0.5). The mucin and artificial saliva alone, plus a sample containing the combination of the two (1:1), were also submitted to testing.

#### Impact of Acidic pH on the Formulations

To predict the behavior of hydrogels in gastric medium, formulations were mixed with artificial gastric fluid (AGF) (pH = 2) in the proportion of 1:1. This fluid was prepared using 0.2% (w/v) sodium chloride, 0.7% (w/v) hydrochloric acid, and purified water as solvent (13).

### Efficacy of Antimicrobial Preservation

The efficacy of antimicrobial preservation was carried out according to the European Pharmacopoeia (Ph. Eur.) 10th Edition, 5.1.3. *Efficacy of antimicrobial preservation* (14). Antimicrobial activity was measured through the log reduction of the colony-forming units (cfu) by enumeration at time zero and then monitoring the viable microorganisms at days 14 and 28, applying the criteria for oral preparations.

### Stability of Final Formulations

The final hydrogel formulations were packaged in aluminum tubes and submitted to long-term stability testing at 25 ± 2 °C/60 ± 5% relative humidity (RH), and 40 ± 2 °C/75 ± 5% RH (15). Samples were collected and analyzed at days 0, 14, 28, 60, 90, and 180. Organoleptic characteristics, pH, and rheological parameters were evaluated. Microbiological testing was also performed at days 0, 28, 90, and 180, according to the Ph. Eur. 10th Edition, 5.1.4. *Microbiological quality of non-sterile products for pharmaceutical use* (12).

### Compatibility Studies

To evaluate possible interactions between the vehicle and the active substances/medicines at the time of administration, the hydrogels were subjected to viscosity testing and pH determination. Each test was performed using the previously mentioned conditions.

A total of 13 active pharmaceutical ingredients (APIs) were selected, among the most frequently used medicines in the Pediatric Services, Hospital de Santa Maria, Lisbon, Portugal: acetazolamide, arginine hydrochloride, biotin, calcium carbonate, captopril, clindamycin, diazepam, food supplement, glycine, hydrochlorothiazide, hydrochlorothiazide + amiloride, hydrocortisone, prednisolone tablets, and riboflavin. All APIs were tested in powder form, except for prednisolone which was only available as tablets. This study evaluated the interaction of the vehicle with different solid dosage forms and also tested common medicines used for pediatric patients.

### Statistical Analysis

Data were expressed as mean and standard deviation (mean ± SD) of separate experiments. Statistical evaluation of data was performed using a Chi-square test. Differences were considered to be significant when $p < 0.05$.

## RESULTS AND DISCUSSION

### Formulation Development

The first aim of the work is to develop an odorless, colorless, translucent, and homogeneous hydrogel, with a suitable pH for oral intake and appropriate viscosity to ease swallowability. For formulation development, the marketed product Gloup® was used as a reference, and a series of protein and polysaccharide polymers with similar properties were tested (Table I). The effect of the different polymers, in different concentrations, on formulation stability and organoleptic features was evaluated by trial and error method. Also, the compatibility of the selected polymers with the excipients was evaluated by pre-formulation studies, as described in previous reports (16).

The developed formulations F1–F15 were evaluated in terms of organoleptic and rheological features to select the ideal proportion of the different polymers in each hydrogel.

Macroscopically, all the formulations presented appropriate characteristics. The behavior of viscosity as a function of shear rate showed that all polymers behaved as shear thinning (non-Newtonian) fluids, given that their viscosity decreased as the shear rate applied increased (Fig. 1). This means that the long-chain molecules of these polymers tend to momentarily orient themselves in the direction of flow. The diminished viscosity translates into a more liquid state of the formulation that will ease the homogenization of suspended particles, allowing a more precise dosing and also increasing the vehicle's swallowability. From the sensory evaluation standpoint, polymers showing this type of behavior tend to cause less sensation on the buds in the mouth than those with Newtonian behavior (13). Taken together, these results, combined with the macroscopic evaluation, suggest that formulations F2 (2.0% CMC) and F9 (1.0% XG) were the most similar to the reference. In contrast, formulations with high amounts of gelatin, F13 (5.0% G) and F14 (10.0% G), showed the least similarity to the reference.

It was also observed that the shear thinning behavior of XG formulations (F7, F8, and F9) was more pronounced than that of other polysaccharide systems, due to its unique rod-like conformation that makes this polymer more responsive to shear (14). In comparison, Gloup® is mainly composed of maltodextrin and carrageenan. At low concentrations, carrageenan water gels have thixotropic rheological properties, justifying the non-Newtonian behavior of the reference product (15). However, XG still has a greater shear thinning ability due to its structure.

Concerning the oscillation frequency test (Fig. 2), both Gloup® and formulation F9 exhibited predominantly elastic behavior, evident from the greater magnitude of the elastic module ($G'$) compared to that of the viscous module ($G''$).

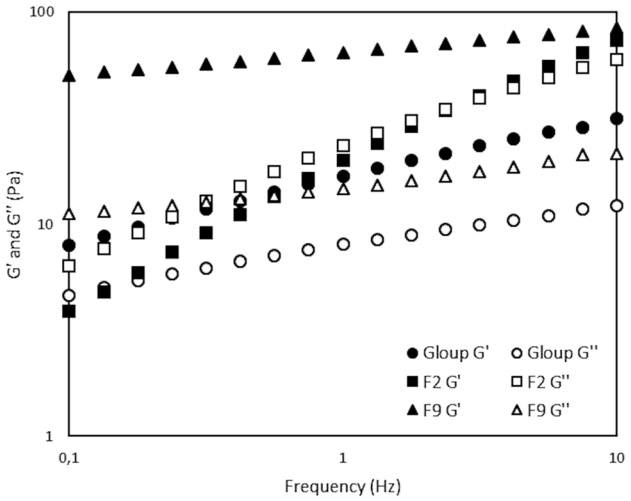



**Fig. 2** Frequency sweep test for Gloup® and formulations F2 and F9

This means that the structure of the gel remained intact through the entire range of frequencies, confirming that the two hydrogels present a strong network and a solid-like behavior ($G' > G''$). For formulation F2, at lower frequencies $G''$ was higher, but at the highest frequencies a transition was observed, and $G'$ became higher than $G''$. Under these experimental conditions, F2 behaved like a shear thickener.

Finally, the tack and pull away test pointed that the hydrogels containing XG had more adhesive properties, as observed by the obtained high values of the area under the curve (Table II), which represent the adhesive/cohesive strength of the material (17).

Considering the results obtained from rheological characterization, hydrogels F2 and F9 were selected for further

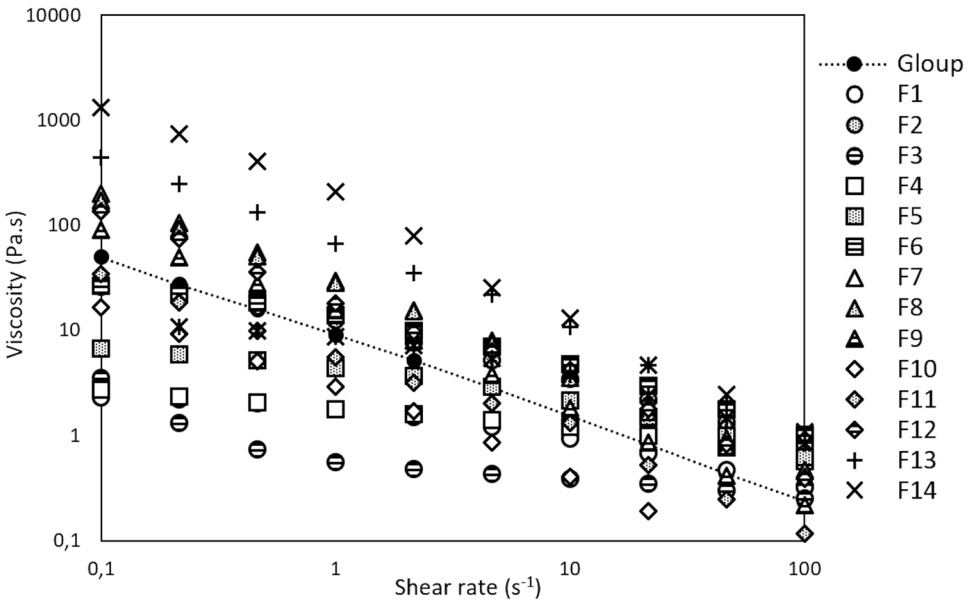



**Fig. 1** Viscosity *vs* shear rate for all prepared formulations and the reference formulation (Gloup®). The amount of each polymer is as described in Table I: F1 (1.5% CMC), F2 (2.0% CMC), F3 (1.5% MC), F4 (2.0% MC), F5 (1.5% HEC), F6 (2.0% HEC), F7 (2.5% XG), F8 (1.5% XG), F9 (1.0% XG), F10 (1.5% G), F11 (2.0% G), F12 (3.0% G), F13 (5.0% G), F14 (10.0% G), and F15 (1.5% HA)

**Table II** Adhesive Properties of Gloup® and Formulations F2 and F9, Determined by the Parameters: Area Under Force Time Curve (N.s) and Peak of Normal Force (N) (Mean ± SD, $n = 3$)

| Formulation | Area under force time curve (N.s) | Peak of normal force (N) |
|---|---|---|
| Gloup® | 1.27 ± 0.20 | − 0.37 ± 0.01 |
| F2 | 1.47 ± 0.08 | − 0.88 ± 0.02 |
| F9 | 2.91 ± 0.06 | − 0.23 ± 0.02 |

studies. From here on these formulations will be named as formulation F1-CMC and F1-XG, respectively.

## Selection of the Flavor and the Coloring Agents

To select the flavor and the coloring agents to be used in the final formulations, a non-invasive survey was performed. Participants in this study were aged between 2 and 12 years old, with a mean age of 7 ± 2.6 years. Regarding the gender of the children, 50.3% were female and 49.7% were male.

Results from the survey showed an overall stronger liking for sweet flavors. Most volunteers chose strawberry (27.4%) as their favorite flavor, followed by vanilla (22.3%) and caramel (12.7%). Grape (11.5%), banana (10.8%), mint (10.2%), and orange (5.1%) were the least favored. This finding was statistically significant ($p < 0.05$). However, there was a concern about these flavors not being strong enough to mask some of the active substance's unpleasant and intense taste.

Mint, although only selected by a small percentage of the volunteers, could possibly mask the more bitter drugs due to its metallic basic taste. In fact, the use of mint is frequently mentioned as an effective strategy to improve the palatability of multiple medicines (16, 18). As strawberry and vanilla have a similar sweet taste, there would be no significant difference between the two developed hydrogels or their action on masking different API flavors. It is expected that the distinct taste of the two final hydrogels will allow the disguise of a wider spectrum of drugs.

Regarding color, red (29.3%) and pink (26.8%) were the most selected by children. Blue (14.7%) was also chosen as one of the favorite colors. Less children chose brown (8.3%), green (7.6%), orange (7.0%), and yellow (6.4%). This finding was statistically significant ($p < 0.05$). Thus, it was decided that one of the formulations would present a strawberry flavor coupled with a pink color. As a blue color would give the vehicle an artificial aspect, it was altered into light green, and coupled with the mint flavor.

This assay also showed an influence of gender in the selection of both color and flavor options, although this effect was more pronounced in the color panel. The majority of volunteers that chose pink were girls (66.7%), while most of the votes favoring the color green came from boys (83.3%).

Based on these results, two coloring agents (CI 61,570 — green, and CI 16,255 — red) and two flavors (mint and strawberry) were added to formulations F1-CMC and F1-XG. As stated, green CI 61,570 was combined with mint flavor (formulations F2-CMC and F2-XG), and red CI 16,255 was combined with strawberry flavor (formulations F3-CMC and F3-XG). The detailed qualitative and quantitative composition of each formulation is presented in Table III.

In this work, the carbohydrate sweetener was replaced by sucralose obtaining a sugar free vehicle for children, since it is a safer non-caloric sweetener. Also it is suitable for patients in a ketogenic diet (19). In addition, lower concentrations are needed to obtain an equal pleasant flavor, given that sucralose is approximately 600 times sweeter than sugar (20, 21). Other excipients present in the formulation ensured the electrolytic stability (citric acid and sodium citrate) and antimicrobial preservation (sodium methyl and propylparaben) of the developed formulations (22).

**Table III** Composition of CMC and XG Final Formulations

| Excipients (%) | Formulation | | | | | |
|---|---|---|---|---|---|---|
| | F1-CMC | F1-XG | F2-CMC | F2-XG | F3-CMC | F3-XG |
| Sodium carboxymethylcellulose | 2.00 | - | 2.00 | - | 2.00 | 1.00 |
| Xanthan gum | | 1.00 | - | 1.00 | - | - |
| Sodium methylparaben | 0.18 | 0.18 | 0.18 | 0.18 | 0.18 | 0.18 |
| Sodium propylparaben | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 | 0.02 |
| Sucralose | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Citric acid | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 | 0.05 |
| Sodium citrate | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 | 0.50 |
| Mint flavor | - | - | 0.20 | 0.20 | - | - |
| Strawberry flavor | - | - | - | - | 0.50 | 0.50 |
| CI 61,570 | - | - | 0.01 | 0.01 | - | - |
| CI 16,255 | - | - | - | - | 0.01 | 0.01 |
| Purified water | qs 100 | qs 100 | qs 100 | qs 100 | qs 100 | qs 100 |

Regarding pH, the range values suitable for an oral intake is 5 to 8 (23). The pH of the developed formulations were within this range. Most hydrogels had pH values between 5 and 7. Further testing was performed to ensure stability throughout time.

In terms of viscosity, the target values were chosen based on a macroscopic evaluation and rheological testing, suitable for facilitating the swallowability of co-administrated drugs.

Finally, according to the American Academy of Pediatrics, oral formulas for healthy infants (from birth to 12 months of age) should have concentrations no greater than 400 mOsm/kg (24). It has been shown that hypertonic solutions have a negative impact on the intestinal mucosa of infants and can lead to several complications at an early age (25). The vehicle's osmolality is low (100–200 mOsm/kg) in order to prevent such adverse events, thus making it suitable to being used for younger patients within the pediatric population.

## Characterization of Final Formulations

The macroscopic appearance of the final formulations is presented in Table IV.

### Effect of Gastrointestinal Tract Conditions

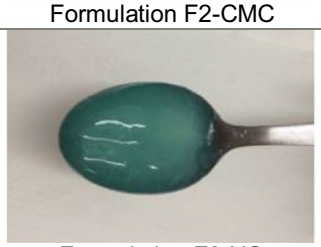
To predict the vehicle's behavior after oral ingestion, rheological tests were performed. The mucoadhesion test aimed at mimicking adhesion in the oral cavity, whereas the gastric stability test focused on determining the influence of acidic pH. Ultimately, these results allow to foresee if the hydrogel provides a safe co-administration with drugs without affecting its bioavailability.

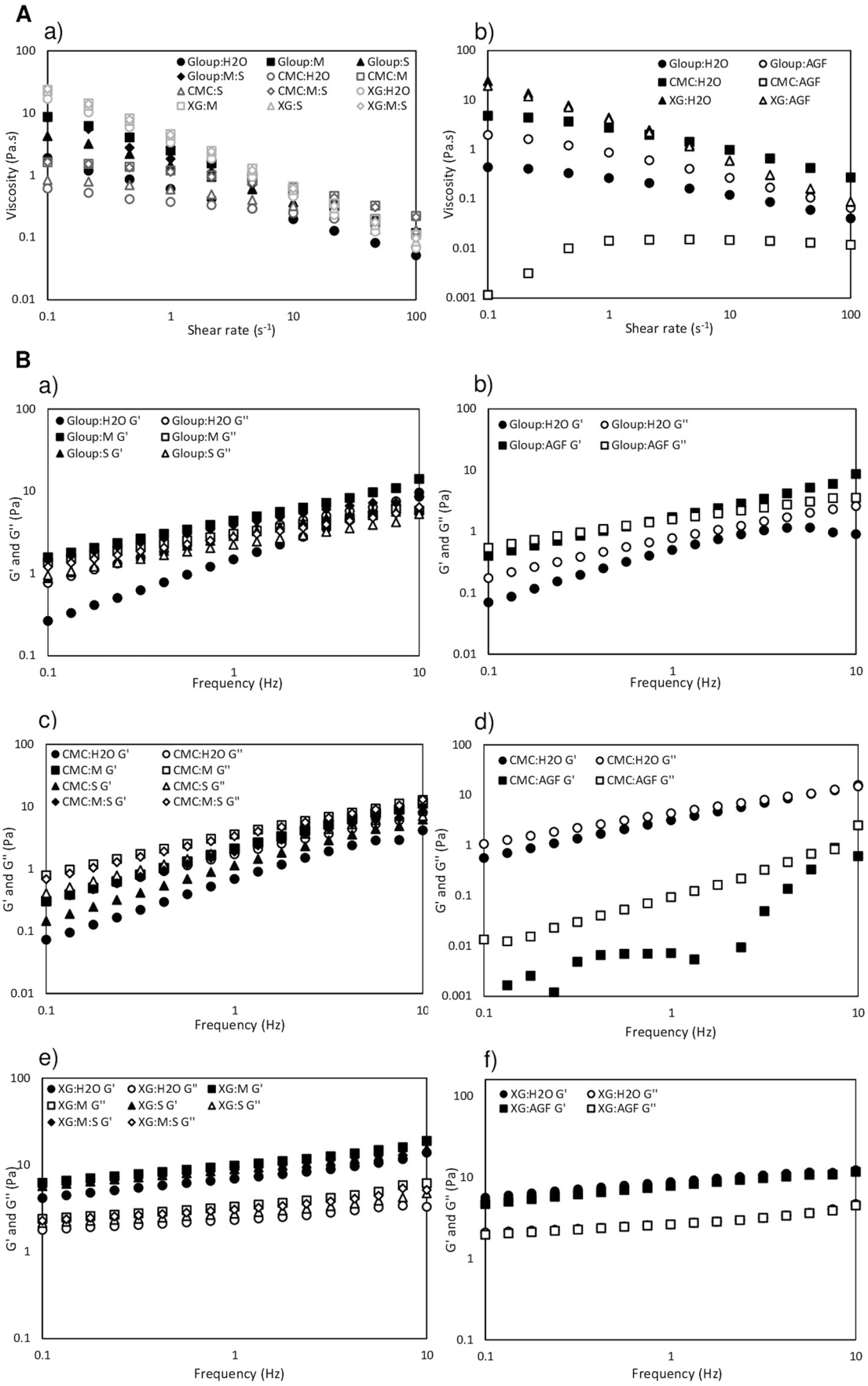
Mucoadhesion was performed for Gloup® and the two final formulations (F1-CMC and F1-XG), in a simulated physiological environment using mucin and artificial saliva at 1:1 proportion. This method included three rheological tests — viscosity, oscillation frequency, and tackiness. The behavior of the hydrogels was determined by comparing the rheological properties of formulation-mucin and formulation-artificial saliva mixtures with those of the formulations separately.

All vehicles exhibited a higher viscosity in the mixtures, showing rheological synergism (Fig. 3A). According to Hassan and Gallo, the synergism is attributable to physical chain entanglements and non-covalent bonds (hydrogen, Van der Waals, etc.) between polymer and mucin chains (26, 27). For each formulation the rheological synergism decreases with increasing shear rate, suggesting that, at low shear rate, the disentanglements and disruption of the sample are less dramatic. The formulation more affected by the presence of mucin and/or artificial saliva was F1-CMC, suggesting that, after oral administration, CMC is likely to form stronger bonds with mucus than XG.

The results of the oscillation test (Fig. 3B) confirmed what was previously stated. When mixed with mucin and/or artificial saliva, the hydrogels achieve higher values of the elastic module ($G'$). The increase of $G'$ is presumably due not to the contribution of mucin or artificial saliva, whose viscoelastic properties are in fact not detectable at the concentration used, but to the formation of a gel-like structure based on polymer-mucin/artificial saliva interactions.

**Table IV** Macroscopic Appearance of the Final Formulations

| | No coloring agent + No flavor | Green coloring agent + Mint flavor | Red coloring agent + Strawberry flavor |
|---|---|---|---|
| CMC 2% |  Formulation F1-CMC |  Formulation F2-CMC |  Formulation F3-CMC |
| XG 1% |  Formulation F1-XG |  Formulation F2-XG |  Formulation F3-XG |


A
a)
Gloup:H2O
Gloup:M
Gloup:S
Gloup:M:S
CMC:H2O
CMC:M
CMC:S
CMC:M:S
XG:H2O
XG:M
XG:S
XG:M:S
Viscosity (Pa.s)
Shear rate (s-1)
b)
Gloup:H2O
Gloup:AGF
CMC:H2O
CMC:AGF
XG:H2O
XG:AGF
Viscosity (Pa.s)
Shear rate (s-1)
B
a)
Gloup:H2O G'
Gloup:H2O G''
Gloup:M G'
Gloup:M G''
Gloup:S G'
Gloup:S G''
G' and G'' (Pa)
Frequency (Hz)
b)
Gloup:H2O G'
Gloup:H2O G''
Gloup:AGF G'
Gloup:AGF G''
G' and G'' (Pa)
Frequency (Hz)
c)
CMC:H2O G'
CMC:H2O G''
CMC:M G'
CMC:M G''
CMC:S G'
CMC:S G''
CMC:M:S G'
CMC:M:S G''
G' and G'' (Pa)
Frequency (Hz)
d)
CMC:H2O G'
CMC:H2O G''
CMC:AGF G'
CMC:AGF G''
G' and G'' (Pa)
Frequency (Hz)
e)
XG:H2O G'
XG:H2O G''
XG:M G'
XG:M G''
XG:S G'
XG:S G''
XG:M:S G'
XG:M:S G''
G' and G'' (Pa)
Frequency (Hz)
f)
XG:H2O G'
XG:H2O G''
XG:AGF G'
XG:AGF G''
G' and G'' (Pa)
Frequency (Hz)

◂**Fig. 3** Rheological behavior of formulations F1-CMC and F1-XG in conditions simulating the gastrointestinal tract, in comparison with the reference formulation (Gloup®). **A** Viscosity *vs* shear rate for Gloup® and formulations F1-CMC and F1-XG: **a** mixed with mucin (M) and artificial saliva (S) and **b** mixed with artificial gastric fluid (AGF).**B** Frequency sweep test results of Gloup® (**a** and **b**), F1-CMC (**c** and **d**), and F1-XG (**e and f**) under the influence of mucin and artificial saliva and/or artificial gastric fluid

Ultimately, this phenomenon translates as a positive interaction caused by mucoadhesion (27, 28).

Regarding the results of the adhesion test, it was observed that XG was more adhesive than CMC because it has higher values of the area under force time (data not shown). However, the results obtained with the formulation alone and in the mixtures are very similar. CMC, despite showing less adhesive strength, was more affected by the presence of mucin and artificial saliva.

The determination of normalized rheological synergism parameters allowed the prediction of the *in vivo* performance of the hydrogels. Both Gloup® and F1-CMC showed a greater ability to form bonds with the mucin and the artificial saliva, meaning that they will remain longer in the oral cavity at the time of administration. On the other hand, F1-XG was not affected by mucin or saliva, which can be an advantage for the oral intake of the vehicle.

To predict the vehicle's behavior when reaching the gastrointestinal tract, a series of rheological tests were performed — viscosity, oscillation frequency, and adhesion. Formulations were mixed with a simulated gastric fluid (pH = 2), at 1:1 proportion. From the obtained results it was possible to infer variations in the hydrogel's structure under low pH conditions. Formulation F1-CMC was the most affected by the acidic environment (Fig. 3A). It was reported that for pH values below the pKa of CMC (≈4.4), there is a decrease in viscosity due to a lower density of negative charges in the molecule (29). This data is consistent with the results gathered from the frequency sweep test (Fig. 3B), where the elastic module suffers a significant decrease. Also, $G''$ was higher than $G'$ throughout the entire range of frequencies, indicating a disruption of the hydrogel's network. Lastly, the adhesion test showed a weak association between particles with a decline in area under force time values. Gloup® and formulation F1-XG were not as affected by the pH conditions. The results obtained for XG were unexpected, given that multiple sources describe a decreased viscoelasticity of this polymer with acidic pH. This is due to the protonation of the anionic carboxylic groups of xanthan chains under acidic conditions, which become uncharged and partially flexible, resulting in a less viscous structure (30). However, the results obtained in this work did not show pH-related changes in XG rheological proprieties.

Despite showing more pronounced mucoadhesive properties, the CMC hydrogel shows a significant loss of structure due to the acidic pH found in the stomach. On the other hand, the XG hydrogel displayed a poor mucoadhesive behavior and is known to be very responsive to shear. So, although it was not affected by the acid medium, its accentuated shear-thinning character can be advantageous if we consider the peristaltic movements that occur during the digestion process. Taken together, the results suggest that none of the vehicles represent a challenge for the release of co-administered drugs in the gastrointestinal tract and probably will not affect their bioavailability.

### Efficacy of Antimicrobial Preservation

There was no observable increase in the number of viable microorganisms between days 14 and 28; thus, the recommended efficacy of antimicrobial preservatives was achieved in both formulations, providing adequate protection against microbial contamination.

### Stability of Final Formulations

Stability testing included all quantifiable parameters that could possibly change during storage, such as appearance, pH, and viscosity. Throughout the study, visual inspection of the vehicles showed no significant changes in their organoleptic properties.

The obtained results show that temperature did not have a critical effect on hydrogels containing CMC. However, it was possible to observe a small decrease of viscosity after 90 and 180 days at 40 °C for all formulations (F1-CMC, F2-CMC, and F3-CMC) (Fig. 4A). The decrease in viscosity with temperature is well known for this polymer and is usually explained by an increase in thermal activity of molecules causing an increase in molecule free volume and, simultaneously, a decrease in intermolecular and/or intramolecular interactions (30). This effect is often reversible and only long periods of heating at high temperatures (> 100 °C) will degrade the polymer and permanently reduce viscosity (31).

Formulations containing XG, stored at 40 °C, showed several inconsistencies regarding viscosity and pH values (Fig. 4). This could be explained by the fact that under high temperatures (> 36 °C) the xanthan chains assume a coil conformation; thus, the negative charges are far more exposed and the molecule becomes more sensible to environmental changes (29).

Regarding pH, the formulations must be suitable for oral administration, with stable pH values in the range of 5.5–7.0. At day 180, the pH of formulation F1-CMC was outside of this range (Fig. 4B). Thus, this vehicle must be further evaluated for chemical stability, to determine the cause for the pH increase.

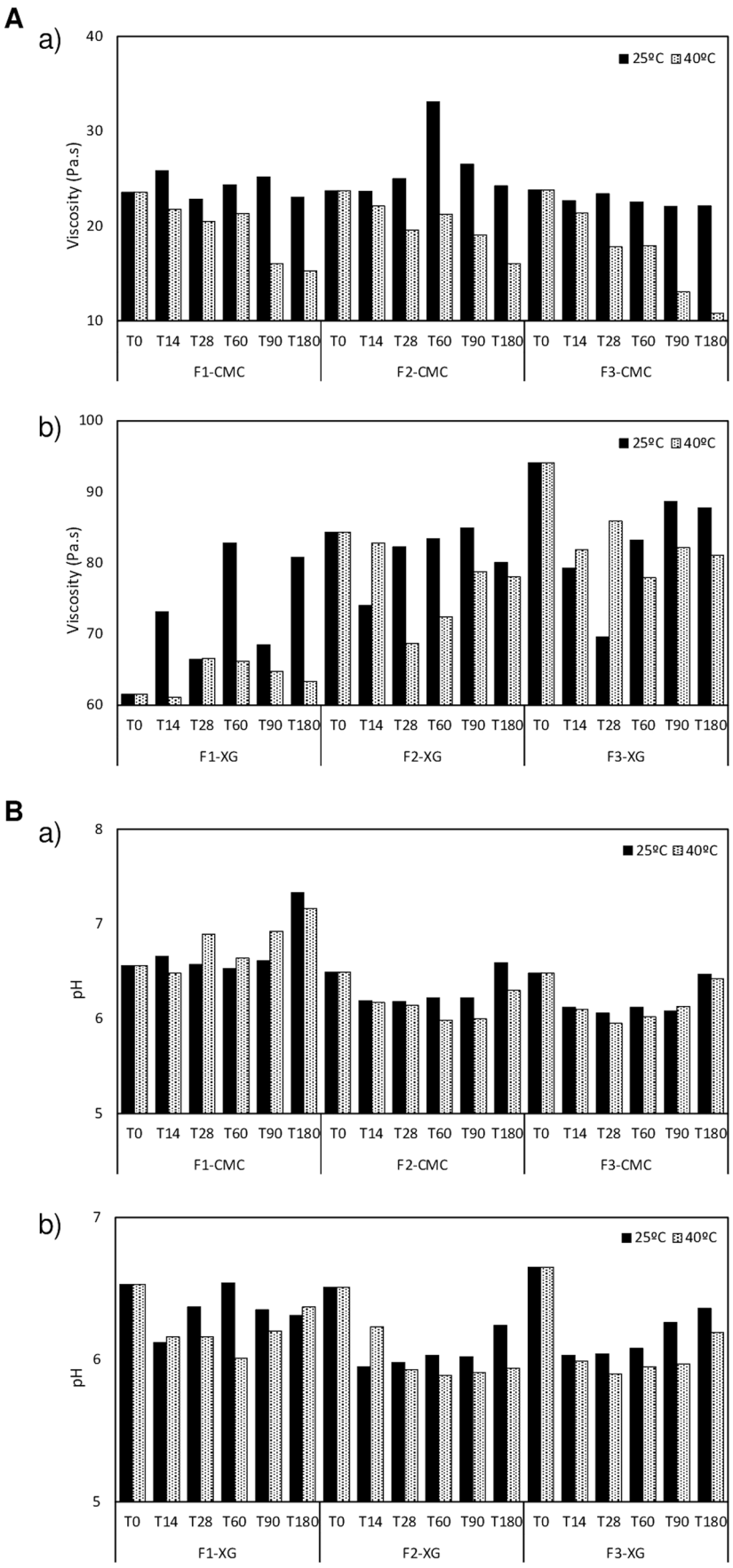



**Fig. 4** Evaluation of viscosity and pH of the final hydrogels during stability studies. **A** Apparent viscosity at 0.1 $s^{-1}$ for formulations: **a** F1-CMC, F2-CMC, and F3-CMC and **b** F1-XG, F2-XG, and F3-XG. **B** pH values of formulations: **a** F1-CMC, F2-CMC, and F3-CMC and **b** F1-XG, F2-XG, and F3-XG

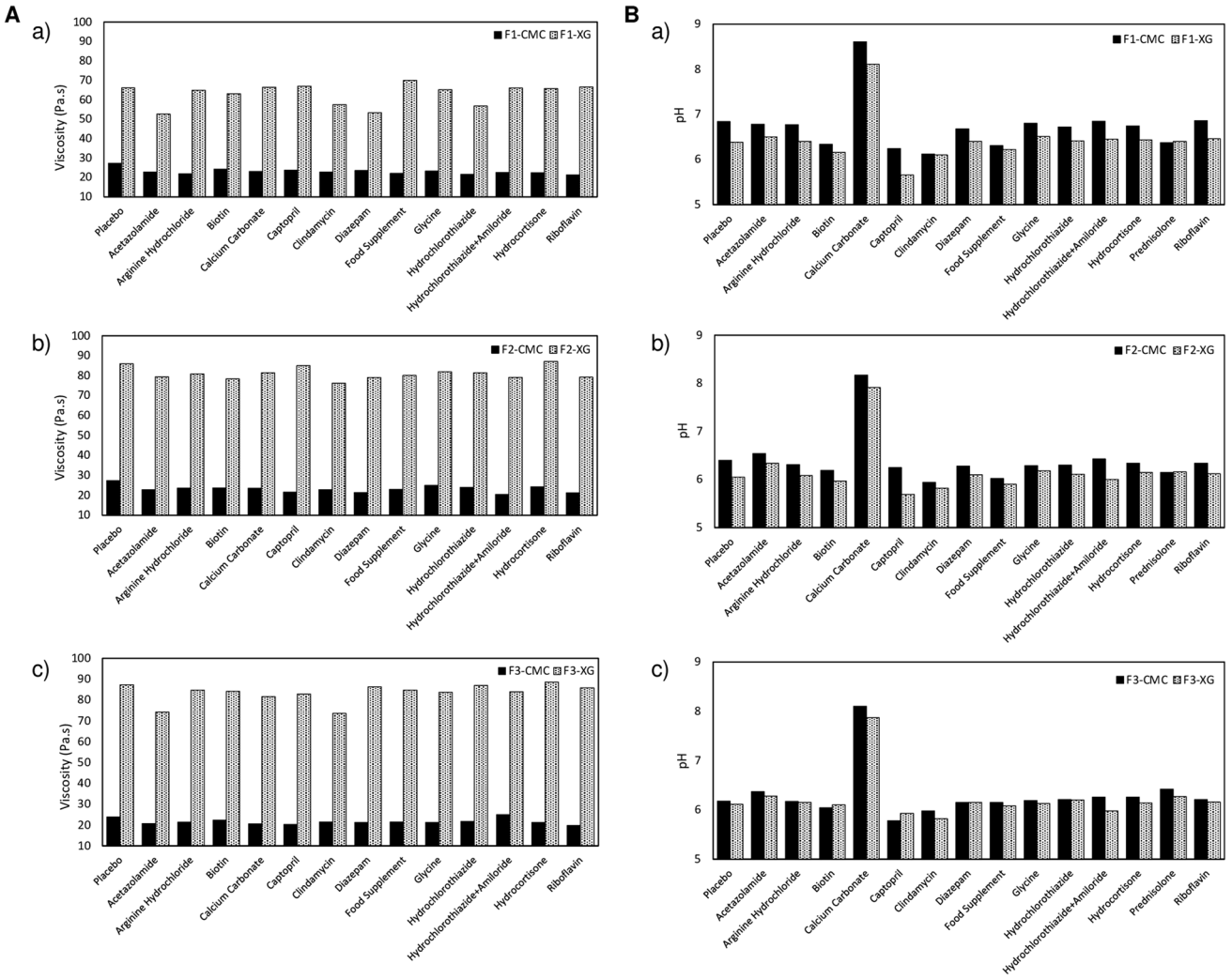



**Fig. 5** Viscosity (at 0.1 $s^{-1}$) and pH determination of the final hydrogels combined with drugs or medicines. **A** Apparent viscosity for formulations: **a** F1-CMC *vs* F1-XG, **b** F2-CMC *vs* F2-XG, and **c** F3-CMC *vs* F3-XG. **B** pH values of formulations: **a** F1-CMC *vs* F1-XG, **b** F2-CMC *vs* F2-XG, and **c** F3-CMC *vs* F3-XG

Concerning microbiological stability, all six formulations, regardless of the storage conditions and the time points of evaluation, showed no microbial growth, including a total absence of *Escherichia coli*.

Overall, stability data suggest that CMC-based and XG-based hydrogels are stable at long-term conditions, for at least 180 days. In terms of storage conditions, hydrogels containing CMC 2% were stable for 3 months whereas vehicles with XG 1% maintained their stability for a period of 6 months, when stored at room temperature.

## Compatibility Studies

The final formulations were mixed with several active substances (API) and submitted to viscosity testing (using the same parameters described previously) and pH determination. The obtained results were directly compared with the placebo allowing the determination of possible interactions between the hydrogel vehicle and the drugs or medicines (Fig. 5). Most APIs were used as raw materials, arginine hydrochloride and glycine were used as paper powder, and prednisolone as tablets.

The majority of the hydrogels did not show substantial changes in pH, viscosity, odor, or physical appearance in the period during which the vehicle with drug/medicine was evaluated (approximately 5 min). A slight pH decrease was observed for all formulations with captopril and an expected increase was observed upon addition of calcium carbonate. Importantly, it was possible to obtain a homogenous hydrogel for calcium carbonate using these vehicles, despite its poor solubility in water. It was also observed that some medicines changed the macroscopic appearance of the hydrogels

(Figs. S2 and S3), such as riboflavin that has a strong and characteristic orange color.

In summary, these vehicles provided satisfactorily safe and stable hydrogels to oral administration of several drugs in pediatrics. Also, the used excipients are frequently used in drug development and have a lower risk of interacting with the drugs, and no relevant incompatibilities have been reported (22).

## CONCLUSIONS

Appropriate vehicles are a possible solution to overcome many difficulties in the oral administration of solid dosage forms to children. In the present work, the developed hydrogels had appealing features like sweet flavor and odor, colorful appearance, and improved swallowability.

In this work, stable, sugar-free vehicles were developed and characterized. The preparation method has proved simple and workable in the daily practice of medicine preparation handled in Hospital Pharmacies and suitable for the intended purpose. The vehicles did not show substantial interaction with the tested active substances. The vehicles composed of sodium carboxymethylcellulose were stable for 3 months, while the hydrogels containing xanthan gum were stable for 6 months, when stored at room temperature.

Thus, these vehicles appear to be a viable option to enhance drug administration and compliance in pediatrics. However, a clinical evaluation is always required.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1208/s12249-022-02265-1.

**Author Contribution** M. P., F. C. S., and J. M. conceived and designed the research. M. P. wrote the manuscript. M. P.., F. C. S., S. S., H. M. R., A. J. A., and J. M. reviewed and edited the manuscript. All authors have read and approved the manuscript for publication.

**Funding** This research was funded by FCT (Fundação para a Ciência e a Tecnologia) through iMed.ULisboa UID/DTP/04138/2020 and UIDB/04138/2020). Joana Marto is financed through FCT, I.P., under the Scientific Employment Stimulus—Institutional Call (CEECINST/00145/2018).

## Declarations

**Conflict of Interest** The authors declare no competing interests.

## References

1. Martir J, Flanagan T, Mann J, Fotaki N. Recommended strategies for the oral administration of paediatric medicines with food and drinks in the context of their biopharmaceutical properties: a review. J Pharm Pharmacol. 2017;69(4):384–97.
2. Ivanovska AV, Carin MA. Pediatric drug formulations : a review of challenges and progress. 2014;134(2):361–72.
3. Guidance D. Use of liquids and/or soft foods as vehicles for drug administration: general considerations for selection and in vitro methods for product quality assessments. (July 2018).
4. Mitra B, Thool P, Meruva S, Aycinena JA, Li J, Patel J, *et al*. Decoding the small size challenges of mini-tablets for enhanced dose flexibility and micro-dosing. Int J Pharm [Internet]. 2020;574:118905. Available from: https://doi.org/10.1016/j.ijpharm.2019.118905
5. Gupta S, Thool P, Meruva S, Li J, Patel J, Agrawal A, *et al*. Development of low dose micro-tablets by high shear wet granulation process. Int J Pharm [Internet]. 2020;587(July):119571. Available from: https://doi.org/10.1016/j.ijpharm.2020.119571
6. Lopez FL, Ernest TB, Tuleu C, Gul MO. Formulation approaches to pediatric oral drug delivery: benefits and limitations of current platforms. Expert Opin Drug Deliv. 2015;12(11):1727–40.
7. Liu F, Ranmal S, Batchelor HK, Orlu-Gul M, Ernest TB, Thomas IW, et al. Formulation factors affecting acceptability of oral medicines in children. Int J Pharm. 2015;492(1–2):341–3.
8. Squires LA, Lombardi DP, Sjostedt P, Thompson CA. A systematic literature review on the assessment of palatability and swallowability in the development of oral dosage forms for pediatric patients. Ther Innov Regul Sci. 2013;47(5):533–41.
9. Batchelor H, Kaukonen AM, Klein S, Davit B, Ju R, Ternik R, et al. Food effects in paediatric medicines development for products co-administered with food. Int J Pharm. 2018;536(2):530–5.
10. Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. J Child Neurol. 2009;24(8):979–88.
11. Pharmaceutical Inspection Convention - Pharmaceutical Inspection Co-operation Scheme. PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments. 2014;(March):1–56. Available from: http://www.picscheme.org/publication.php. Accessed 14 July 2014.
12. Silva F, Marto J, Salgado A, Machado P, Silva A, Almeida A. Nystatin and lidocaine pastilles for the local treatment of oral mucositis. Pharm Dev Technol. 2016;8:1–32.
13. Sriamornsak P, Wattanakorn N. Rheological synergy in aqueous mixtures of pectin and mucin. Carbohydr Polym. 2008;74(3):474–81.
14. Pharmacopoeia E, Pharmacopoeia E. 5.1.3. Efficacy of antimicrobial preservation. :505–6.
15. Niazi SK. Stability testing of new drug substances and products. Handb Pharm Manuf Formul. 2001;2020:31–40.
16. Marques-marinho FD, Vianna-soares CD. Cellulose and its derivatives use in the pharmaceutical compounding practice. In: Cellulose - Medical, Pharmaceutical and Electronic Applications. 2013. p. 141–62.
17. Pharmacopoeia E, Pharmacopoeia E. 5.1.4 Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use. :501–4.
18. Alves L, Costa DS, Campos MI, Druzian JI, De Oliveira AM, Nazaré E, et al. Biosynthesis of xanthan gum from fermenting shrimp shell: yield and apparent viscosity. Int J Polym Sci. 2014;1–8.
19. Song K, Chang G, Kuk H-Y. Rheology of concentrated xanthan gum solutions: oscillatory shear flow behavior. Korea-Australia Rheol J. 2006;18(2):67–81.
20. Stephen AM, Phillips GO, Williams PA. Food polysaccharides and their applications: second edition. Food Polysaccharides and Their Applications: Second Edition. 2016. 1–733 p.
21. Measurement T. Using a rotational rheometer to assess adhesion and tackiness. 2015;1–6.
22. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet:

recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009;50(2):304–17.
23. Rowe RCR, Sheskey PJS, Cook W. Handbook pharmaceutical excipients,sixth edition. 2009. 1064 p.
24. Afifi NA. Pharmaceutical solutions for oral administration. Pharm Dos Form Des. 2016;1–41.
25. Committee T. Commentary on breast-feeding and infant formulas, including proposed standards for formulas. Nutr Rev. 1976;34(8):248–56.
26. Fernández Polo A, Cabañas Poy MJ, Clemente Bautista S, Oliveras Arenas M, Castillo Salinas F, Hidalgo AE. Osmolality of oral liquid dosage forms to be administered to newborns in a hospital. Farm Hosp órgano Of expresión científica la Soc Española Farm Hosp. 2007;31(5):311–4.
27. Lopes AR. Caracterização de soluções poliméricas para aplicação em revestimentos para a conservação de produtos alimentares. 2016;
28. Espert M, Salvador A, Sanz T. Rheological and microstructural behaviour of xanthan gum and xanthan gum-Tween 80 emulsions during in vitro digestion. Food Hydrocoll. 2019;95:454–61.
29. Petri DFS. Xanthan gum: A versatile biopolymer for biomedical and technological applications. J Appl Polym Sci. 2015;132(23).
30. Vega ED, Vásquez E, Diaz JRA, Masuelli MA. Influence of the Ionic Strength in the Intrinsic Viscosity of Xanthan Gum. An Experimental Review. J Polym Biopolym Phys Chem. 2015;3(1):12–8.
31. Hercules Incorporated 1999. Physical and Chemical Properties of AQUALON CMC.