Universidade de Lisboa

Faculdade de Farmácia

Children Friendly Medicines

Medicated Lollipops

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Trabalho de Campo orientado pela Professora Doutora Catherine Tuleu, Professora de Farmácia Pediátrica, da University College London, School of Pharmacy, e coorientado pelo Professor Doutor João Fernandes de Abreu Pinto, Professor Associado, da Faculdade de Farmácia da Universidade de Lisboa.

Mestrado Integrado em Ciências Farmacêuticas

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Neste projeto vê-se retratado o desenvolvimento de chupa-chupas isentos de açúcar medicados com ácido cítrico para o alívio da tosse em crianças a partir dos 3 anos, um dos sintomas mais prevalentes entre a população pediátrica. Chupa-chupas medicados, são uma forma farmacêutica que demonstra ser promissora em termos de aceitabilidade por parte das crianças, no sentido em que têm o potencial para garantir flexibilidade de dose, tamanho e aspeto, de modo a colmatar problemas de sub ou sobredosagem, deglutição e palatabilidade. Para dar corpo ao chupa-chupa utilizou-se como excipientes principais uma base comercial – PCCA Sorbitol Lollipop™ – e isomalte, quer fundido, quer em forma de xarope, ambos submetidos a uma análise térmica cuidadosa. Estes, foram submetidos a um processo de aquecimento e arrefecimento lento, antes da adição dos restantes excipientes da formulação e da deposição da mistura final nos respetivos moldes. Procedeu-se a uma avaliação da uniformidade e características organoléticas dos diversos chupa-chupas, assim como a estudos de dissolução. Verificou-se que o processo de fabrico e as condições de armazenamento poderão ter afetado as características organoléticas e a estabilidade de certos chupa-chupas. No entanto, de um modo geral, os chupa-chupas apresentaram o aspeto desejado, nomeadamente aqueles cujo excipiente principal utilizado foi o xarope de isomalte, e sabor a mel. Os chupa-chupas que continham isomalte foram os que demonstraram ser mais estáveis e seguros para os doentes pediátricos, considerando a estabilidade e os efeitos laxantes do sorbitol (principal excipiente do PCCA Sorbitol Lollipop™), respetivamente. Para além disso, foram os que revelaram um perfil de dissolução mais longo, proporcionando uma ação local prolongada do ácido cítrico, quando comparados com os chupa-chupas que continham PCCA Sorbitol Lollipop™. Este projeto mostrou a possibilidade de transformar um produto alimentar conhecido e comercializado há décadas, numa forma farmacêutica isenta de açúcar passível de ser utilizada em terapia no tratamento da tosse moderada em doentes pediátricos, como alternativa às previamente aprovadas e disponíveis no mercado.

Palavras-chave: Chupa-chupas medicados; Isomalte; População Pediátrica; PCCA Sorbitol Lollipop™.

Abstract

This project portrays the development of sugar-free medicated lollipops for children from 3 years old containing citric acid for mild cough relief, one of the most prevalent symptoms among the paediatric population. Medicated lollipops are a dosage form that has the potential to be well accepted by children while also offering flexibility in dose, size and appearance to address issues related to under- or overdosing, swallowing, and palatability. To embody the lollipop, it was used a commercial base – PCCA Sorbitol Lollipop^{TM} – and isomalt, either melted neat or in syrup form, as the main excipients of the lollipop matrix, both submitted to a careful thermal analysis. These excipients were subjected to a slowly heating and cooling method before addition of the rest of the formulation excipients and pouring the final mixture into the lollipop moulds. The various lollipops were characterized for uniformity, and organoleptic and drug dissolution properties. It was found that the manufacturing process and storage conditions may have affected some lollipops organoleptic features and stability. Nonetheless, the lollipops presented a desirable appearance, particularly those whose main excipient was isomalt syrup, and a honey-like taste. Lollipops made with isomalt proved to be most stable and safer for the paediatric patients, taking into consideration sorbitol's (main excipient of PCCA Sorbitol Lollipop^{TM}) stability and laxative effects, respectively. In addition, these were the ones that revealed a longer release profile, providing an extended local action of citric acid, when compared to PCCA Sorbitol Lollipop^{TM} based lollipops. The aim of this work was fulfilled by the use of a product that has been sold and advertised for years as a candy in a way that avoids the side effects of sugar and that may not be used for recreational purposes but therapeutically, in order to deliver drugs to paediatric patients. As such, it was possible to develop an alternative dosage form to those previously approved and available in the market for the treatment of mild cough in paediatric patients.

Keywords: Isomalt; Medicated Lollipops; Paediatric Population; PCCA Sorbitol Lollipop^{TM}.

Acknowledgments

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Abbreviations

ADI – Acceptable Daily Intake

API – Active Pharmaceutical Ingredient

BNFC – British National Formulary for Children

DSC – Differential Scanning Calorimetry

SD – Standard Deviation

Tg – Transition Glass Temperature

TGA – Thermogravimetric Analysis

UK – United Kingdom

USA – United States of America

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1 Introduction

Coughing is a highly prevalent symptom throughout childhood. According to studies, in paediatrics, cough is usually caused by a viral respiratory tract infection and goes away on its own. Even so, it is one of the most common reasons for paediatric healthcare visits, having a negative impact on life quality for both children and their caregivers, making it reasonable to develop child-friendly medicines for the treatment of cough (1,2).

Despite the oral route being the preferred route of drug administration, selecting the appropriate dosage form can be challenging when dealing with children from 2 to 11 years old (3). Dosage form efficacy, safety, ease of use, and patient access are features that must be considered when choosing the appropriate dosage form to a certain age group, especially when paediatric patients are considered (4,5). As a result, there has been a growing need to develop new dosage forms in the past decades, particularly after the Paediatric Regulation was implemented, in 2007, with the purpose of improving children's health in Europe (6,7). In this context, a lot of effort has been made into developing dosage forms that avoid the swallowability issues that come along with traditional dosage forms, like tablets and capsules, as well as palatability concerns associated with most dosage forms (e.g., the undesirable taste of liquid dosage forms or the bitter taste of several dosage forms) (3).

For instance, the selected dosage form must be constructed in such a way that patient acceptance and compliance are ensured, and this can be accomplished by designing products with a low impact on lifestyle and a pleasant look, such as colour and palatability (4,8). Nevertheless, when formulating children friendly medicines, it is important to guarantee patients' safety, avoiding accidental poisoning, as such, manufacturing medicated lollipops, can be a challenge as they can be regarded as candies by children, particularly when the organoleptic properties are overly tempting (9).

Confectionery dosage forms (e.g., medicated lollipops) have a long history of use for medicinal purposes, but relevant data related to this topic is scarce in the literature (10). Despite that, it is known that lollipops, as a pharmaceutical dosage form, have several advantages namely greater drug bioavailability, reduced stomach discomfort, and avoidance of first-pass effect, given the fact that there is an excellent blood supply in the mouth, minimizing metabolization in a specific location of the body prior of reaching the site of action, such as the liver. Thus, the release of the active pharmaceutical ingredient (API) in the mouth might enable

either a buccal and sublingual absorption, or a local effect of the API, while the lollipop is being held, avoiding first pass effect (11,12).

Palatability is a key consideration when formulating for children, given that taste is one of the most important variables in ensuring adherence (13). In reality, most lollipops are formulated using sucrose and corn syrup, yet even though patients' acceptability might be ensured due to their sweet taste, concerns related not just to children dental health but also to long-term side effects linked to sugar consumption (e.g., overweight, cardiovascular diseases and diabetes) led to a growing need to formulate sugar-free dosage forms. Nonetheless, sugar-free confectionery, has advanced to goods that resemble their sugar equivalents to ensure taste acceptability (14,15). Sorbitol, mannitol, xylitol, maltitol, and isomalt, are examples of sugar replacers, used to produce sugar-free products.

One of the main reasons that led to the development of medicated lollipops was the fact that lollipops are supposed to be sucked and held in the mouth, avoiding the swallowability issues of conventional solid dosage forms, and enabling a local drug delivery in the buccal cavity (16,17). Perhaps, this advantage sums to the fact that the chosen API is meant to relieve mild cough symptoms, so a local and prolonged release of an API, such as citric acid, in the affected area is favourable to its effect, as it has a marked antioxidant effect that may reduce the inflammatory response involved in cough, summed to the demulcent effect of the polyols used in the formulation (6,10,18). Additionally, it is predictable that the lollipop sucking movements will increase saliva production, lubricating and so smoothing the mucosa, enabling a relief of other inflammation-related symptoms that might be present (e.g., sore throat) (19). Another good thing about formulating lollipops is that once a stable base (the main component of the lollipop formulation) is achieved, the inclusion of other excipients to the formulation, namely the API, sweetener agents, flavour and colour might be simplified, since the main component of the lollipop is its base. Still, the compatibility between excipients, as well as their stability throughout the manufacturing process and shelf-life, must be assessed.

In this work, a commercially available lollipop base – PCCA Sorbitol Lollipop^{TM} –, based on sorbitol and mannitol, was selected as the lollipop's matrix. Furthermore, isomalt was also used as a lollipop base. There are several reasons why sugar alcohols were chosen as the lollipop's base. Firstly, sorbitol, mannitol, and isomalt are nonfermentable and noncariogenic, both linked to tooth decay. Secondly, when compared to sucrose, sugar replacers have a pleasant cooling effect when dissolved in the mouth due to their high negative heat of solution and particle size. However, even though isomalt cooling effect is higher than sucrose, -5 cal/g

versus -4.3cal/g, respectively, it is quite low when compared to other polyols, namely, sorbitol (-26 cal/g). Thirdly, one can state that these polyols are chemically stable, as they are resistant to acidic conditions and stable to high temperatures, and do not undergo Maillard reactions. Finally, sugar replacers provide a low glycaemic, insulinemic and caloric response, being suitable for diabetic patients, unlike other conventional saccharides (20,21). Isomalt and sorbitol have a quite similar glycaemic response, but a slight difference can be seen, whereas isomalt presents a lower glycaemic index than sorbitol (22). Most bulk sweeteners are less sweet than sucrose, making it imperative to add stronger sweeteners to the formulation to make the lollipop taste desirable. Sorbitol's and isomalt's sweetness indexes are 0.5-0.6 and 0.4-0.5, respectively, when compared with sucrose (sweetness index =1). For that reason, sucralose (600 times sweeter than sucrose) was added some to the lollipop's formulation (23).

Unfortunately, given the sugar alcohol's slow absorption and incomplete digestion, laxative effects may appear due to osmotic effects. This side effect may differ depending on the type of sweetener used, and due to its gastrointestinal intolerance, it can be very harmful for children. Sorbitol and mannitol are two examples of bulk sweeteners present in confectionery products, highly associated to gastrointestinal side effects. Nevertheless, it is possible to formulate medicines avoiding the risk of excessive gastrointestinal side effects by using other bulk sweeteners, such as isomalt (24). Each polyol may have an acceptable daily intake threshold which must be considered in order to avoid these harmful side effects; for sorbitol the threshold is 140mg/kg/day and, although isomalt's threshold is not stated, it is known that 25g/day is an appropriate maximum limit (20,25).

Isomalt, a mixture of two stereoisomers, 6-O-α-D-glucopyranosyl-D-sorbitol and 1-O-α-D-glucopyranosyl-D-mannitol dihydrate (Figure 1), provides high-quality non-sticky sugar-free products with a low hygroscopicity, proving a longer shelf-life to products, when compared to sorbitol (20,26,27). Sorbitol can be found in nature in several types of fruits and leaves or be industrially synthetized by catalytic hydrogenation of dextrose or sucrose (25). Sorbitol and mannitol are isomeric (Figure 2), their main difference is their hygroscopicity (sorbitol is highly hygroscopic in opposition to mannitol, a non-hygroscopic material) (20,28,29).

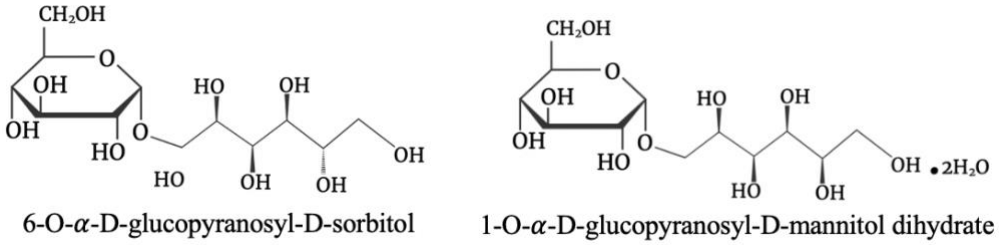

Figure 1. Structural Formula of Isomalt (Created with BioRender).

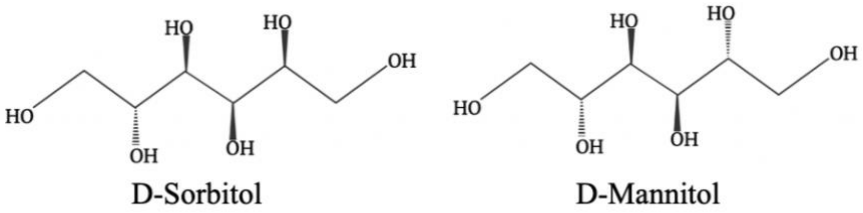

Figure 2. Structural Formula of Sorbitol and Mannitol (Created with BioRender).

Lollipops can be made by dissolving sugar alcohols in water at high temperatures, or by melting sugar alcohols to a high dry-matter concentration, followed by cooling and moulding. Depending on the type of polyol and manufacturing procedure, the temperature of manufacturing can range from 155 to 170ºC (30).

The lollipop's structure and texture can be significantly impacted by the fraction of water present. Indeed, even the low moisture content that happens to be found in hard candies might extraordinarily affect their stability and properties (31). Lollipops are molecularly amorphous solids, where the molecules are densely packed, that vitrify during a cooling step below their glass transition temperature (Tg), with some ability to absorb small molecules (e.g., water). Consequently, storage of lollipops at high relative humidity levels may affect their stability, with significant increase on stickiness and graining, that should be avoided. Depending on the polyol present in the lollipop matrix, different degrees of care should be considered, as there are polyols more hygroscopic than others requiring different storage conditions (32).

1.1 Hypothesis

Medicated lollipops can get beyond the obstacles that stand between children's safety and compliance.

1.2 Aim

This work aims at manufacturing lollipops containing citric acid, as the API, for the paediatric population (> 3 years old) intended to relief mild cough symptoms.

The choice of the API was based on the *Simple Linctus Paediatric BP* (British National Formulary for Children), a medicine licensed for use in the United Kingdom (UK), containing citric acid monohydrate (33). The process of manufacture of the lollipops was adapted from PCCA's suggested compounding procedure.

1.3 Structure

The structure of this project was designed to fulfil the purpose of developing medicated lollipops. For that, the project was divided into two main topics:

- Firstly, the main excipients of the lollipop were thermally analysed, providing knowledge about each material heat capacity and molecular behaviour. The purpose of this step was to understand how the manufacturing process and the excipients' inherent characteristics may affect the lollipop quality and stability.

- Secondly, the lollipops were a thoroughly characterised with regard to their appearance, taste, uniformity, and dissolution profile. This made it possible to gather information about the manufacturing process' effectiveness and efficiency, to predict the profile release of the API in the buccal cavity and assess the lollipop's quality.

2 Materials and Methods

2.1 Materials

The following excipients were used to produce lollipops: Citric Acid Anhydrous (NortemBio, Spain), Sucralose (Merck KGaA, Germany), Sorbitol (EMD Millipore Corp., Affiliate of Merck KGaA, Germany), Mannitol (Fisher Chemical, UK), PCCA Sorbitol Lollipop™ (PCCA, USA), Isomalt – GalenIQ 960 – (Beneo-Palatinit GmbH, Germany), Honey Flavour (LorAnn Oils, USA), Caramel Colour Powder E150d (Sethness Roquette, France), Olive oil (Waitrose and Partners, UK), and Type II Water (PURELAB Chorus 2, UK).

2.2 Methods

2.2.1 Preparation of Lollipops

Placebo and medicated lollipops (8g) with a spherical shape (22 mm diameter) were prepared based on the PCCA Sorbitol Lollipop™ Base General Formula and suggested procedure, and each batch consisted of 6 lollipops. The formulas of the lollipops – F1-9 – can be found in Table 1.

Table 1. Formulations of Prepared Lollipops[1]

	Formulation % (w/w)								
Excipient	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
PCCA Sorbitol Lollipop™	100	-	-	93.24	-	-	92.883	-	-
Isomalt	-	100	100	-	93.24	93.24	-	92.883	92.883
Sucralose	-	-	-	0.125	0.125	0.125	0.125	0.125	0.125
Honey Flavour	-	-	-	6.25	6.25	6.25	6.25	6.25	6.25
Caramel Colour Powder 150d	-	-	-	0.028	0.028	0.028	0.028	0.028	0.028
Citric Acid Anhydrous	-	-	-	0.357	0.357	0.357	0.714	0.714	0.714
Water[2]	-	-	25	-	-	25	-	-	25
Total	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**

[1] Weight of a lollipop – 8g

[2] Water was added as an intermediate in the preparation of isomalt syrup, as such, the amount added evaporated throughout the manufacturing process.

F1 – PCCA Sorbitol Lollipop™ Placebo Lollipop; F2 – Melted Isomalt Placebo Lollipop; F3 – Isomalt Syrup Placebo Lollipop; F4 – PCCA Sorbitol Lollipop™ Citric Acid Lollipop; F5 – Melted Isomalt Citric Acid Lollipop; F6 – Isomalt Syrup Citric Acid Lollipop; F7 - PCCA Sorbitol Lollipop™ Double Dose Citric Acid Lollipop; F8 – Melted Isomalt Double Dose Citric Acid Lollipop; F9 – Isomalt Syrup Double Dose Citric Acid Lollipop.

The *Simple Linctus Paediatric BP* was used as a guide to choose the API and consists of citric acid monohydrate 31.25 mg/5 mL, which is equivalent to 28.57 mg/5 mL of citric acid anhydrous, given with a posology for children of one or two 5 mL spoonfuls orally up to four times per day. Each single dose citric acid lollipop was made with the intention to have 28.57 mg of citric acid anhydrous and to be given 3 to 4 times per day. Double dose citric acid lollipops have twice the dose of single dose citric acid lollipops, that is, 57.14 mg of citric acid anhydrous.

2.2.1.1 PCCA Sorbitol Lollipop™ Placebo Lollipops

The lollipop base was prepared by slowly melting the PCCA Sorbitol Lollipop™ base and heating on a hot plate up to 160°C, in an appropriately sized beaker without stirring; if any lumps, they were removed with a spatula. The base was then allowed to cool down at room temperature to 90°C and syringed into the lubricated mould (greased with olive oil with the help of a cotton swab) – Figure 3 (34). The lollipops were left to rest overnight at room temperature, to guarantee complete solidification. To remove the lollipop from the mould, it was placed in a freezer (~15 min) and brought back to room temperature for 5 min before removing the lollipops, as per PCCA's suggested procedure. The lollipops were then wrapped in foil and stored at room temperature.

Figure 3. Example of the Lollipop Mould (34)

2.2.1.2 Isomalt Placebo Lollipops

Two types of isomalt placebo lollipop's base were prepared, one made of melted isomalt, and the other made by dissolving isomalt in water (4:1 proportion) – isomalt syrup.

Melted Isomalt Base: The procedure described in 2.2.1.1 was followed except that the base was heated and melted up to 165°C instead of 160°C, and cooled to 110-115°C instead of 90°C.

Isomalt Syrup Base: To prevent uncontrolled crystallization, isomalt was dissolved in previously heated water, and heated to 110ºC until a clear viscous syrup was obtained. The syrup obtained was then slowly heated up to 165°C and cooled to 110-115°C. The rest of the procedure was the same as the one cited in 2.2.1.1.

2.2.1.3 Medicated Lollipops – Citric Acid Lollipops

Citric acid lollipops were prepared with PCCA Sorbitol Lollipop™ base, Melted Isomalt base and Isomalt Syrup base. The mentioned procedures (2.2.1.1 and 2.2.1.2) were followed, except for the fact that extra ingredients, namely, the API (citric acid), sweetener (sucralose), and colourant excipient (Caramel Colour Powder), previously milled together in a glass mortar and pestle, were added to the melted lollipop base, cooled down to 90°C or 110-115°C, when using the PCCA base or the Isomalt base, respectively. Thorough mixing with a spatula was essential to remove lumps. Then, the honey flavour was added under continuous mixing. In case the base became too thick or too cold upon addition of the excipients, reheating the system was required. The final mixture was then poured into the lubricated mould and allowed to rest overnight at room temperature, and the rest of the procedure described above was followed.

2.2.2 Thermal Analysis

To characterise the PCCA Sorbitol Lollipop™ base, as well as each polyol, including sorbitol, mannitol, and isomalt, a thermal analysis was undertaken to assess the heat capacity of the specified excipients and their behaviour at various temperatures.

2.2.2.1 Melting Point Determination

The melting point determination was conducted using a Stuart® Digital Melting Point Apparatus – SPM10 (Philip Harris, UK).

2.2.2.2 Thermogravimetric Analysis (TGA)

The TGA analysis was performed in a TA Discovery TGA (TA Instruments, USA) by heating each material, such as Sorbitol, Mannitol, PCCA Sorbitol Lollipop™ and Isomalt, to 280, 350, 310, and 350°C, respectively, at 10°C/min.

2.2.2.3 Differential Scanning Calorimetry (DSC)

The DSC studies were performed in a Q2000 DSC (TA Instruments, USA) with the help of Zero Hermetic Lids and T_{zero} Pans (TA Instruments, USA), according to different cycles at 10°C/min. All samples were submitted to a first heating cycle (cycle 1), from 20°C to a temperature approximately 20°C above the expected melting point temperature, depending on the type of material being studied. Then all samples were submitted to a cooling step well below their melting temperature (-70°C), followed by a second heating cycle to 220°C (cycle 2), to confirm the Tg and cooling to room temperature (20°C). Data was analysed with Excel to extrapolate the plots that resulted from the DSC analysis, and with OriginPro 2021 (Academic) from OriginLab Corporation to integrate each thermogram melting event and extrapolate their enthalpies.

2.2.3 Lollipops Characterisation

The different lollipops were submitted to organoleptic characterisation, diameter and uniformity of mass determinations, and dissolution studies.

2.2.3.1 Organoleptic Characterisation

The evaluation of the lollipop's appearance was made by visual inspection based on its colour, transparency, and glossiness. Moreover, a honey colour grader, the Jack's Scale (Figure 4), was used to measure and compare the colour of the lollipops. Depending on the amount of caramel colour added, it is possible to obtain lollipops with different honey colour grades, thus, a defined amount of caramel colour was added so that a homogenous honey colour was achieved in between lollipops. The colour of the lollipops could range from water white (< 9 mm), extra white (9-17 mm), white (18-34 mm), extra light amber (35-50 mm), light amber (51-85 mm), amber (86-114 mm), to dark amber (> 114 mm) (35). But in order to select the proper colour, it was taken into consideration that the lollipops were meant to resemble honey and that they needed to be appealing, so lollipops too dark or too light could not be adequate.

Figure 4. Jack's Scale Honey Colour Grader (35)

Other parameters, such as the presence of bubbles and crystallized matter, and malleability and stickiness were also assessed, through self-visual and self-sensory methods, respectively.

The lollipop's taste and aroma were also evaluated – self-test. Together with the specific amount of a strong sweetener used to provide sweetness, plus the sweet effect of the polyol that makes up the base, it was possible to make neither too sweet nor too bitter lollipops. Moreover, honey flavour was added to provide the lollipop's aroma, so that the lollipops smell and taste like honey.

2.2.3.2 Diameter Determination

Diameter determination (n=3) was conducted by using a Vernier Calliper.

2.2.3.3 Uniformity of Mass

Lollipops of each formulation (n=3) were weighed individually on a precision balance, and their average weight was calculated. Moreover, to provide an index of weight variation between the lollipops, the Standard Deviation (SD) was determined.

2.2.3.4 Dissolution Studies

Lollipops from each formulation (n=3) were submitted to a dissolution test. Each lollipop was placed in a beaker covered with aluminium foil, containing 50 mL of Type II water at 37 $\pm$ 0.5°C, under gentle stirring (≈100 rpm) with a magnetic stirring bar. The temperature of the medium was monitored with a Standard ST-131 thermometer. To follow the release of citric acid, the pH of the solution was monitored using a benchtop pH meter. The measurement of the pH was performed before adding the lollipop to the water and every 15 min, until there was no visible mass left in the beaker. When no lollipop mass was left in the beaker, timing was stopped and registered.

3 Results and Discussion

3.1 Thermal Analysis

3.1.1 Melting Point Determination and TGA Analysis

PCCA Sorbitol Lollipop™ commercial base is described in its Material Safety Data Sheet (MSDS), as containing sorbitol, mannitol, and water, without specification of fractions and purity. Therefore, a melting point experiment and a TGA analysis were performed. Furthermore, the thermal analysis of the excipients was also intended to increase the knowledge about their water content and predict its effect on the lollipops' stability.

The melting point experiment revealed that the melting temperature of the commercial base is quite close (slightly lower) to the one of sorbitol alone (Table 2). Recent studies revealed that the presence of water, impurities, or other components, may cause a melting point decrease of sorbitol, the main component of the commercial base (36). As such, in comparison to sorbitol's melting point alone, it was expected that the presence of sorbitol, mannitol and water in the PCCA Sorbitol Lollipop™ formulation would result in a lower melting point than sorbitol alone (37).

Table 2. Melting Point and Percentage of Water Loss in each Raw Material

Excipient	Melting Point (°C)	Water Loss ≈100°C (%)[1]
PCCA Sorbitol Lollipop™	94-95	0.328
Sorbitol	97-98	0.298
Mannitol	166-167	0.189
Isomalt	144-147	1.006

[1]Extrapolated from the TGA experimental data.

The water loss by each raw material was extrapolated from the percentage of water loss, at approximately 100°C, observed in the TGA analysis. Thus, it can be mentioned that the water loss by each material (Table 2) was minimal (≤ 1%). The knowledge of the amount of water present in these materials was important, particularly of isomalt and the PCCA Sorbitol Lollipop™, as they served as the matrix for the lollipops and water may affect the lollipops' stability and quality. Regardless of the fact that it is expected that the water present in the lollipop base evaporates throughout the manufacturing process due to the high temperatures involved (160-165°C), the lollipop's final moisture content can vary from bellow 1 to 3%,

depending on the excipient used as the base (24,38). Although low moisture content prevents microbiological growth without the need of adding preservatives, the high hygroscopicity of sugar alcohols, may lead to physical instability, as the lollipop is prone to absorbing water from the environment (39,40). In fact, changes in the lollipops (e.g., loss of transparency and glossiness overtime) made of the PCCA Sorbitol Lollipop™ commercial base – F1, F4 and F7 – were seen, after storage at room temperature, covered in foil. Sorbitol, the main excipient of the commercial base used, is hygroscopic, absorbing water molecules from the air at the lollipop's surface, triggering changes on its appearance, likely due to a non-controlled crystallization of the lollipop's components. Indeed, after demoulding these lollipops, crystallized matter (crystal seeds) could be seen inside the lollipop, which could potentially enhance the lollipop's crystallization rate (41).

No changes were seen in lollipops made with either melted isomalt base or isomalt syrup-based lollipops after storage, this is consistent with the fact that due to its low hygroscopicity, isomalt provides products with greater stability against water absorption, with greater shelf-life and quality (26).

3.1.2 DSC Studies

The thermogravimetric analysis was useful to identify the temperature at which the polyols and the PCCA Sorbitol Lollipop™ base started to degrade and identify the highest temperature that samples could hold (< 220°C).

Calorimetric studies were designed with the purpose of understanding the molecular behaviour of the various bases and their heat capacity, the potential crystallization and recrystallization of the materials, and attempt to extrapolate the amount of sorbitol and mannitol in the PCCA Sorbitol Lollipop™ base.

During the first heating (cycle 1), the thermogram of mannitol revealed a sharp thermal event around 167°C, which was associated with its melting point (Figure 5). Upon cooling a shift from the baseline around 110°C can be seen, and when the material was reheated, no Tg was observed, yet another endotherm with onset around 168°C can be observed, emphasizing the crystalline state of the material upon cooling after melting (42). Moreover, when submitted to the final cooling, another exotherm was observed around 117°C, which might have been caused by crystallization (Figure 5).

D-mannitol is frequently used as an excipient in pharmaceutical formulations and may exist in both crystalline and amorphous forms. DSC data has shown that mannitol was crystalline (43).

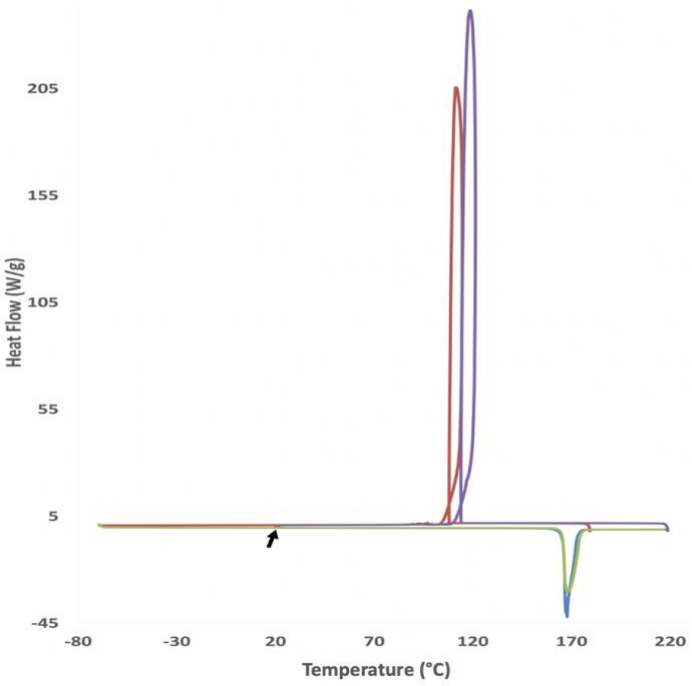

Figure 5. Thermogram of Mannitol

Note: Cycle 1 – Heating (blue), cooling (red); Cycle 2 – Heating (green), cooling (purple). The arrow represents the beginning of cycle 1 and end of cycle 2.

Sorbitol's thermogram (Figure 6-A) exhibited a sharp thermal event around 99°C (melting point temperature). Unlike mannitol, when submitted to cooling and reheating a Tg was observed close to 0°C, indicating that sorbitol was in an amorphous form that after cooling to a temperature quite below its melting point had changed from a hard glassy state to a rubber state (viscous) when the temperature was increased.

The thermogram for PCCA Sorbitol Lollipop™ (Figure 6-B) revealed a double endotherm (around 90 to 95°C), which was correlated with sorbitol's melting point. Overall, this thermogram was similar to the one observed for pure sorbitol. The differences observed – the lower melting point and the double thermal event – clearly suggest the mixture of two polyols, sorbitol and mannitol, which melted separately. Furthermore, upon cooling and

reheating it was possible to note a glass transition at about 0°C, which is comparable to sorbitol's Tg.

The thermogram for isomalt (Figure 6-C), has shown two thermal events, the first (around 97.4°C) was associated with dehydration and the second with its melting point (around 147°C) (44). Isomalt's thermogram showed a higher Tg (around 54°C) than Sorbitol and the PCCA Sorbitol Lollipop™.

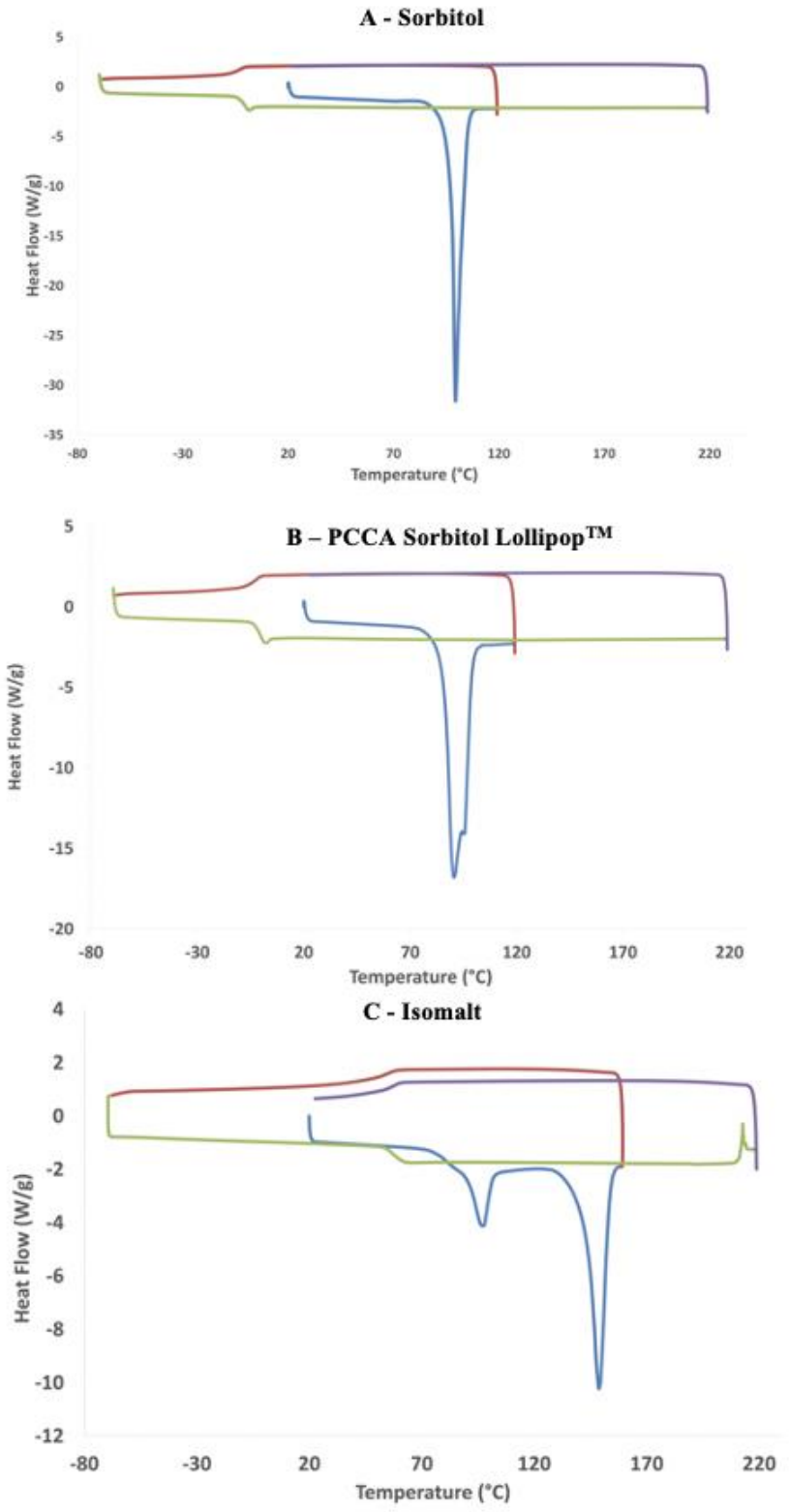

Figure 6. Thermograms of Sorbitol (A), PCCA Sorbitol Lollipop™ (B), Isomalt (C)

Note: Cycle 1 – Heating (blue), cooling (red); Cycle 2 – Heating (green), cooling (purple).

Despite the differences mentioned, it can be said that Sorbitol, PCCA Sorbitol Lollipop™, and Isomalt share similarities as suggested by the thermograms. After melting, these substances revealed to be in a viscous fluid-like rubber state, without undergoing crystallization, in contrast to mannitol, vitrifying randomly into a non-crystalline glass upon cooling (45). These findings suggest that sorbitol and isomalt can be used as the main excipients of a lollipop base, as hard candies have a glassy-like transparent structure typical of the glassy state of amorphous materials.

In general, the calorimetric studies confirmed the changes of the lollipop's characteristics overtime, in particular the ones made with the PCCA commercial base. Briefly, one can hypothesize that, the storage temperature of the lollipops can have an impact on their stability as these sugar alcohols may crystallize if cooled and stored at a higher temperature than their Tg. Thus, since the lollipops were cooled and kept at room temperature (20-25°C), and the PCCA Sorbitol Lollipop™ base has a Tg onset around 0°C, it is foreseeable that crystallization may occur over time, unlike lollipops made from isomalt, that were stable given that its glass transition temperature was above storage temperature (41).

The enthalpies related to the endotherms observed in the PCCA Sorbitol Lollipop™ thermogram were calculated by deconvolution of the thermal events (Table 3). Comparison between the enthalpies of pure sorbitol and mannitol has shown a correlation between the fractions of sorbitol and mannitol in the PCCA's commercial base: estimating 65% sorbitol for 24% mannitol.

Table 3. Thermogram Characteristics

Thermal Event		Temperature (ºC)	Enthalpy (J/g)
PCCA Sorbitol Lollipop™	Thermal Event 1	90.610	99.963
	Thermal Event 2	95.008	40.206
Sorbitol		99.416	154.164
Mannitol		167.744	169.480

It is common practice to use corn syrup to modulate crystallization in sucrose-based confectionery, whereas in sugar-free confectionery polyol blends are used to adjust the overall crystallization of the product. The PCCA Sorbitol Lollipop™ is one example on how polyols are used to modulate crystallization, in this case, mannitol must have been added to the formulation, most likely to modulate the extent and rate of sorbitol's crystallization over time,

even though little can be found about this topic in literature (46). Furthermore, despite mannitol's main role, the fraction added to the mixture can be crucial because it may crystallize and influence the overall crystallization of the lollipops (36). The choice of mannitol to control crystallization in the PCCA commercial base may be related to the fact that the two molecules (sorbitol and mannitol) are structurally related. Additionally, studies revealed that mannitol had a greater impact on preventing sorbitol crystallization, than other polyols (e.g., maltitol and glycerol) (46).

Sorbitol's gastrointestinal side effects can be harmful, especially to the paediatric population who are particularly sensitive to sorbitol. With the DSC studies it was possible to perform a safety risk assessment by comparing the estimated amount of sorbitol delivered in a lollipop to its acceptable daily intake (ADI) – 140mg/kg/day – stipulated by the European Medicines Agency (EMA) (47). Considering that F1, F4 and F7 contain more than 92% of PCCA's commercial base, if considered that the base is composed of approximately 65% of sorbitol, as estimated, children would be exposed to considerably higher amounts of sorbitol than what is accepted, that is, each lollipop – 8g – would contain at least 4.78g of sorbitol. Therefore, if a 3-year-old child is taken into account (≈14kg), the amount of sorbitol in one lollipop (> 341mg/kg) would be way above the acceptable limit, suggesting the need for an alternative (e.g., isomalt) (48,49).

Although Isomalt's ADI is not specified, it is stated that 25g/day might be a reasonable upper limit for children, allowing for the administration of three citric acid containing lollipops per day (50).

3.2 Lollipops Characterisation

3.2.1 Organoleptic Characterisation

When set side by side, lollipops made of isomalt syrup base were the ones that visually proved to be more appealing, with a clearer and glossier surface. None of the formulations originated lollipops with a sticky surface, which corroborates with the low moisture content after demoulding. The lollipops presented a light amber colour, around ≅70mm according to Jack's Scale, although the colour could have been adapted as per targeted honey colour, except for the placebo lollipops (F1, F4, and F7) since no colourant was added. Most lollipops made

of PCCA Sorbitol Lollipop™ have lost their glossiness after removal from the moulds and stored at room temperature wrapped in foil for a few days (Figure 7).

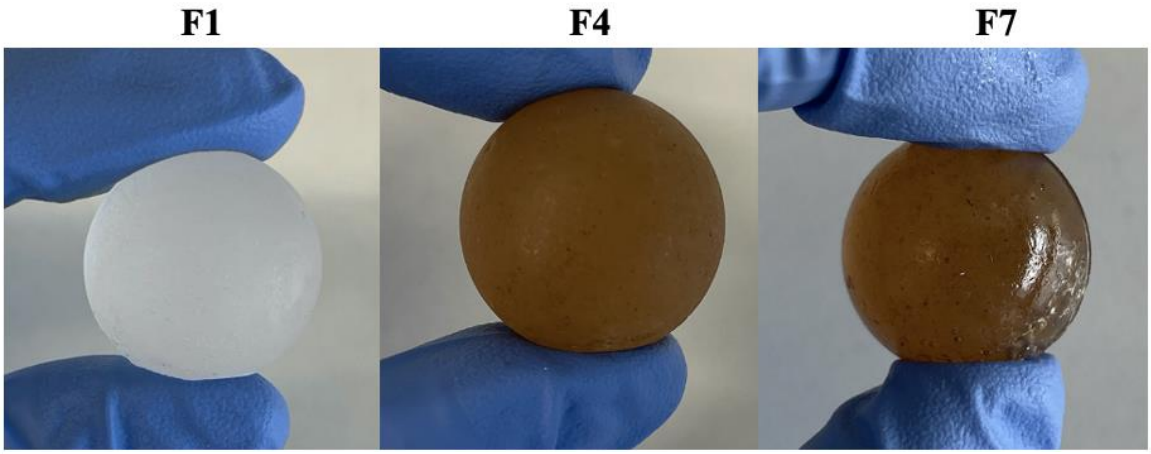

Figure 7. Examples of Lollipops made of PCCA Sorbitol Lollipop™.

F1 – PCCA Sorbitol Lollipop™ placebo lollipop; F4 – PCCA Sorbitol Lollipop™ citric acid lollipop; F7 – PCCA Sorbitol Lollipop™ double dose citric acid lollipop.

Furthermore, the lollipops made of either melted isomalt or isomalt syrup presented bubbles, whereas some of the lollipops made of PCCA Sorbitol Lollipop™ had some crystalline inclusions after demoulded. The key distinction between the lollipops prepared with melted isomalt and those made with isomalt syrup is that the former had a larger number of bubbles and irregularities in the surface (Figure 8), whereas the latter had fewer (Figure 9). Perhaps, due to its viscosity and the fact that it solidified quickly while being poured into the moulds, the melted isomalt is more difficult to work with, the reason why there was a higher bubble and irregularities formation, even though the lollipop mixture was reheated, as per PCCA's recommended procedure, to help pouring the molten blends into the moulds, by delaying hardening with the decrease in temperature. Despite that, these lollipops presented a glossy surface with no visible recrystallized matter, which remained upon storage (1 month), unlike the lollipops made of PCCA Sorbitol Lollipop™.

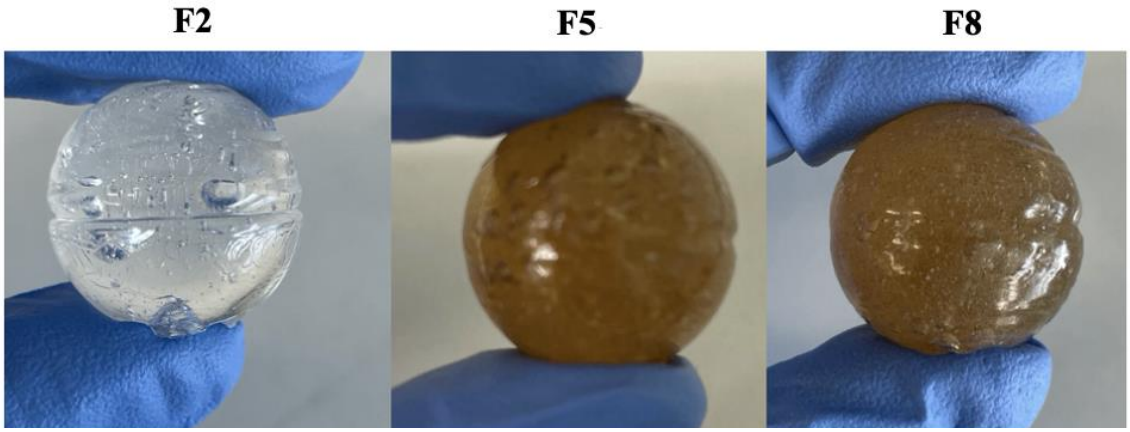

Figure 8. Examples of Lollipops made of Melted Isomalt.

F2 – Melted Isomalt Placebo Lollipop; F5 – Melted Isomalt Citric Acid Lollipop; F8 – Melted Isomalt Double Dose Citric Acid Lollipop.

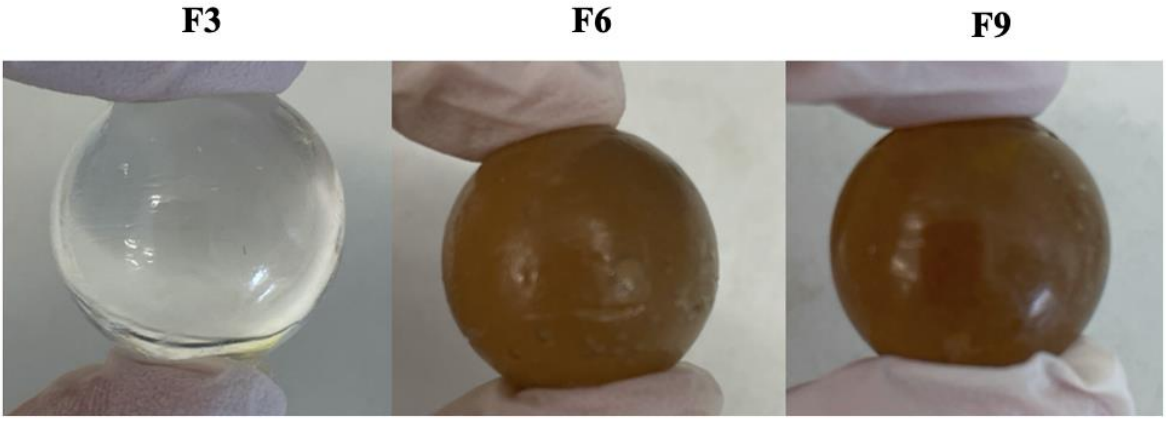

Figure 9. Examples of Lollipops made of Isomalt Syrup.

F3 – Isomalt Syrup Placebo Lollipop; F6 – Isomalt Syrup Citric Acid Lollipops; F9 – Isomalt Syrup Double Dose Citric Acid Lollipop.

Although the same fraction of honey flavour was added, F5, F6, F8 and F9 revealed a less intense aroma when compared to F4 and F7 lollipops, due to the addition of flavour to the first set at higher temperatures, causing some of the flavour to evaporate. Nonetheless, a self-taste test has shown that the lollipops had an excellent honey-like taste, in spite the fact that F1, F4 and F7 had a greater cooling effect in the mouth due to the presence of sorbitol, when compared with isomalt.

3.2.2 Diameter Determination and Uniformity of Mass

A weight variation (8.0 ± 0.4g) between the lollipops was deemed as acceptable considering the manual manufacture of the lollipops (Table 4). Indeed, the mass variation appeared to be related to the manufacturing process given the additional step of reheating the base, which might have affected the lollipops' volume. Moreover, the fact that the melted lollipop base would become extremely thick, making it difficult to manipulate, could have also affected the mass of each lollipop.

Table 4. Lollipop's Physical Parameters (n=3).

Parameter	Average Mass (g)	Diameter (mm)	Volume (cm^3)	Density (g/cm^3)
F1	8.05 ± 0.06	21.97 ± 0.06	5.55	1.450
F2	7.98 ± 0.09	21.90 ± 0.10	5.50	1.451
F3	8.36 ± 0.05	22.13 ± 0.15	5.68	1.473
F4	7.95 ± 0.04	21.93 ± 0.06	5.53	1.439
F5	8.06 ± 0.05	22.03 ± 0.06	5.60	1.439
F6	8.17 ± 0.11	22.10 ± 0.10	5.65	1.446
F7	7.97 ± 0.02	21.90 ± 0.06	5.52	1.443
F8	7.80 ± 0.04	21.87 ± 0.06	5.47	1.425
F9	8.04 ± 0.17	22,00 ± 0.10	5.58	1.442

The density of the lollipops slightly varied, even though differences in the poured volume were attempted to be minimised with the use of a syringe (Figure 10). The expected density of each lollipop was 1.435g/cm^3, considering the expected mass (8g) and diameter (22mm) of the lollipops, however, every formulation somewhat deviated from this value, highlighting the necessity of automating the manufacturing process, so that the same volume is poured into the moulds without the need to reheat the lollipop mixture.

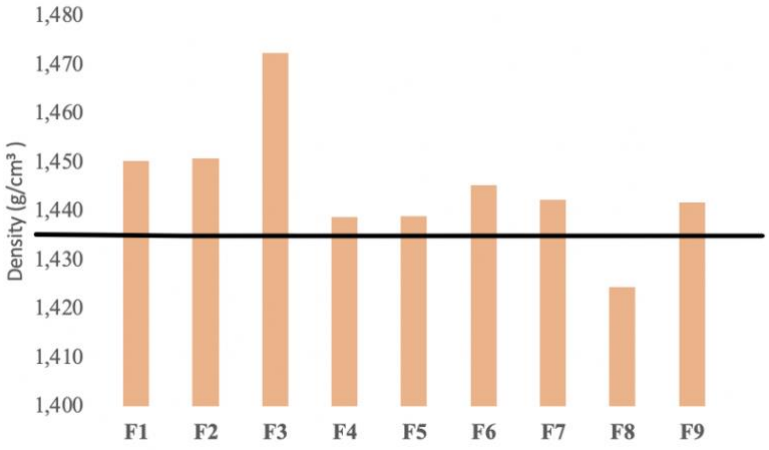

Figure 10. Density of the Studied Lollipops of each Formulation

3.2.3 Dissolution Studies

All formulations (F1-F9) were submitted to dissolution studies to determine citric acid's release from the lollipop in Type II water (37°C ± 5°C). Different lollipops based on the different formulations, namely placebo lollipops (A), single dose citric acid lollipops (B), and double dose citric acid lollipops (C) (Figure 11) were studied. Dissolution profiles from similar lollipops (e.g. placebo, single dose citric acid or double dose citric acid lollipops) were comparatively similar by opposition to the ones obtained for lollipops based on different formulations (A, without citric acid, with B and C, Figure 11). When citric acid was present in the lollipop (graphs B and C) a sharp pH drop in the first 15 min of the dissolution test was observed. Thus, the majority of citric acid was released from the lollipop within the first 15 min of the dissolution test, as the pH stabilized after. Furthermore, the amount of citric acid added to the formulation has affected the pH, higher the dose added, lower the pH value reached (double dose citric acid, Graph C, Figure 11). Aside from that, the two dissolution profiles, Figure 11 – B and C, are nearly identical. Additionally, a slight drop in the pH of medium was also predictable in the placebo lollipops, Figure 11 – Graph A, even though no citric acid was included in the formulation. This was associated with the presence of sugar alcohols in the formulation that may have reduced the pH of the solution (51). Lollipops based on formulations F1, F4 and F7 took about 33 to 38 minutes to dissolve completely, whereas F2, F5 and F8 lollipops took about 54 to 55 min and F3, F6 and F9 took 55 to 62 min (Figure 11), i.e., lollipops made of isomalt took longer than lollipops made of PCCA Sorbitol Lollipop™ to dissolve completely, particularly the ones made of isomalt syrup base.

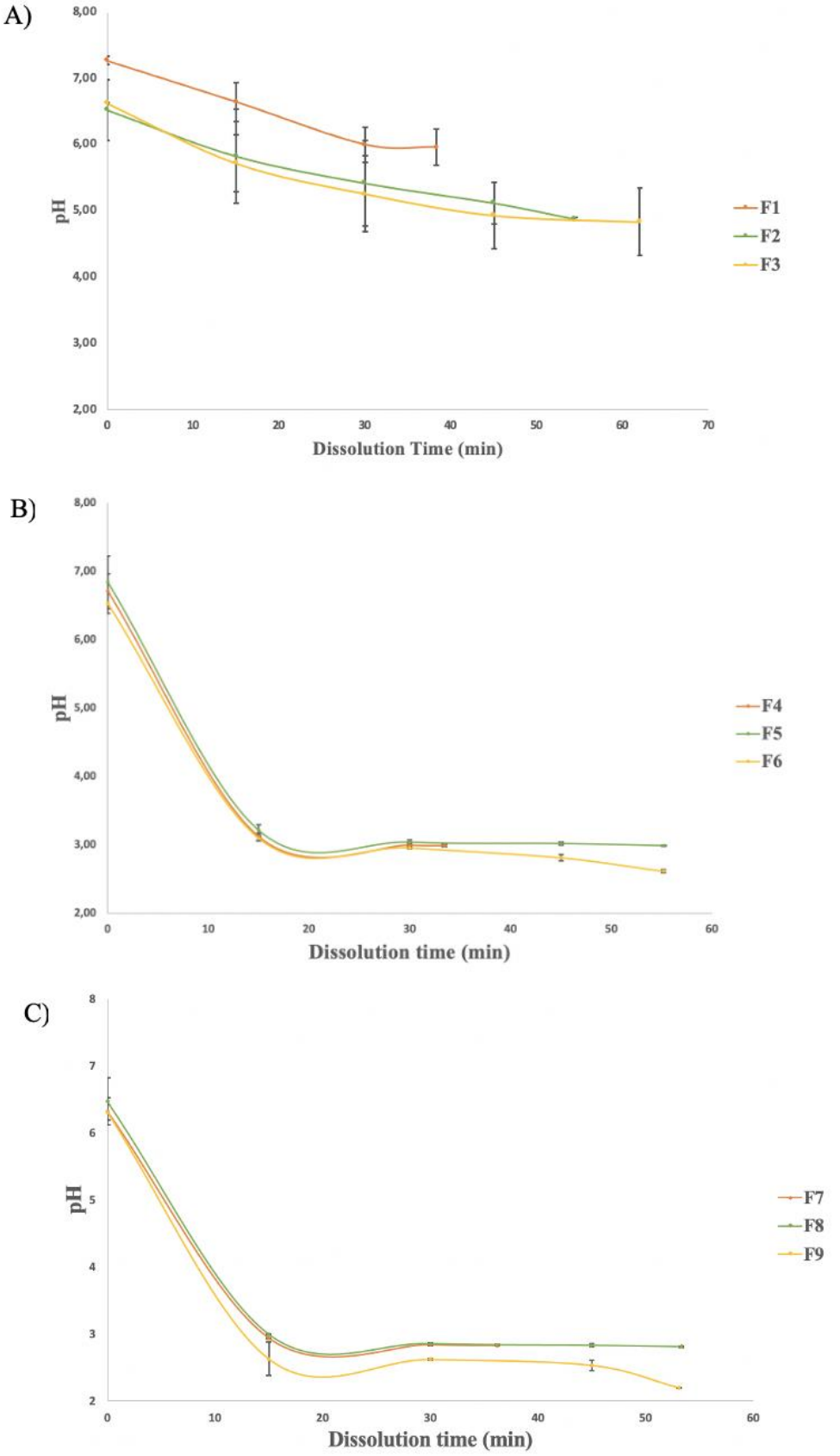

Figure 11. Dissolution profile of A) Placebo Lollipops, B) Single Dose Citric Acid Lollipops, and C) Double Dose Citric Acid Lollipops (n=3, mean±SD).

Taking into account that human saliva contains more than 99% of water, it is possible to anticipate that the longer the lollipop takes to dissolve in the mouth combined with the mouth sucking movements (mimicked with gentle stirring), the longer the API local effect will be. (52,53) Due to the fact that isomalt-based lollipops took longer to dissolve than the ones made of PCCA Sorbitol Lollipop™, it is expected that the first will have a better effect on symptoms relief, as the API will be in contact with the oropharyngeal mucosa for a longer period.

4 Conclusions

Sugar-free medicated lollipops are a promising dosage form for paediatric patients as alternative to the undesirable drawbacks of traditional dosage forms. Citric acid sugar-free lollipops were developed as a stable pharmaceutical dosage form suitable for the treatment of mild cough for paediatric patients, provided that the main excipient of the lollipop is carefully chosen, so that patient safety and quality is ensured. As such, this work showed that isomalt syrup revealed to be the better option to formulate sugar-free medicated lollipops.

Results show that isomalt adds value to the formulation of lollipops, when compared to the sorbitol-mannitol blend (PCCA Sorbitol Lollipop^{TM}), as it is safer, more stable to different environmental conditions, and provides lollipops with better organoleptic features. The lollipops presented a light amber colour that resembled honey. Isomalt-based lollipops had a less intense aroma than sorbitol-based ones, related to the high temperature involved in the manufacturing process. However, all the lollipops had a pleasant honey-like flavour. Because sorbitol has a stronger cooling effect than isomalt, lollipops manufactured with PCCA Sorbitol Lollipop^{TM} had a more refreshing sensation in the mouth than the ones made with isomalt. Regardless of the amount of API added to the formulation, the release profile from the lollipop was still relatively similar, despite the changes in the pH of the medium, enabling a prolonged release of the API in the buccal cavity.

Undesirable organoleptic changes observed in PCCA Sorbitol Lollipop^{TM} lollipops were related to the partial recrystallization of sorbitol which is highly hygroscopic. Furthermore, the temperature at which the lollipops were stored may have affected their stability, as these lollipops were stored at a higher temperature than the estimated Tg, enhancing crystallization, as opposed to isomalt-based lollipops. It was estimated that PCCA Sorbitol Lollipop^{TM} contains 65% of sorbitol. Following the *Simples Linctus Paediatric BP* suggested posology, the amount of sorbitol delivered in the PCCA Sorbitol Lollipop^{TM} based lollipops was over the permitted limit, revealing that these can be hazardous for children in terms of laxative effects, in opposition to isomalt-based lollipops. PCCA Sorbitol Lollipop^{TM} lollipops dissolved quicker, expecting to provide a shorter local effect of the API than when isomalt is used as the lollipop matrix, which might diminish the relief of symptoms.

The manufacturing process may have affected the mass uniformity and organoleptic characteristics of the lollipops. Melted isomalt-based lollipops would thicken and solidify quicker promoting the formation of more bubbles and surface imperfections than isomalt syrup-

based lollipops. Moreover, reheating the lollipop mixture may have led to the observed mass variation of the lollipops. Given the residues of water in the excipients of the lollipop matrix and the high temperatures involved in the process, lollipops had a low moisture content. None of the lollipops had a sticky surface after demoulding, confirming this feature.

5 Future Work

Further work should be performed to overcome several aspects that might affect the lollipops' quality, safety and stability.

The manufacturing process should be adapted and improved, through automating it and running it in a closed system, so that losses and chemical changes can be prevented throughout the process, and the mixture is not exposed to differences in temperature.

Vacuum could be applied to the system to reduce the high temperatures required in the manufacturing process.

The extent and rate of crystallization of the lollipops and their behaviour to moisture absorption should be accurately assessed. Rather than that, the final product water content and activity should also be assessed, as these parameters may influence shelf-life and texture.

The lollipops should be submitted to long-term stability studies, in order to determine their behaviour over a longer period of time, especially the isomalt-based lollipops.

The method used to perform the dissolution studies should be improved, to more accurately simulate the mouth sucking movements, and to measure the precise amount of citric acid released throughout the dissolution of the lollipop, thereby eliminating the other excipients' contribution on pH changes.

Children compliance to the organoleptic features of the lollipops, notably their appearance and taste, is also a factor that must be carefully studied.

Finally, the possibility of using these lollipops as a model for formulating with different APIs, especially those with an undesirable taste, due to their potential ability to mask undesirable flavours, should be assessed.

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