Iron delivery from liquid-core hydrogels within a therapeutic nipple shield

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\textbf{ABSTRACT}

To aid oral therapeutic administration to infants, a novel delivery technology, referred to as a Therapeutic Nipple Shield (TNS), was previously developed. It consists of a silicone nipple shield device and a dosage form containing a therapeutic (or Active Pharmaceutical Ingredient (API)) to enable delivery during breastfeeding. A range of dosage forms were investigated in past literature, but sufficient API release into human milk had not been achieved. The presented work illustrates the delivery of iron sulphate pentahydrate from liquid-core sodium alginate hydrogels, inserted into a commercially available ultra-thin silicone nipple shield into human milk during \textit{in-vitro} breastfeeding simulation. Release of iron was quantified employing absorbance measurements of a salicylic assay. An absolute recovery of 44.35 ± 5.43% of loaded iron(III) sulphate pentahydrate was obtained after 10.58 ± 0.09 g of human milk had passed through the nipple shield. This finding is superior to previous investigations involving the delivery of zinc from rapidly disintegrating tablets and non-woven fibres within a TNS. Due to their superior delivery properties, ease of fabrication and cost-efficiency, liquid-core sodium alginate hydrogels consequently represent a promising dosage form for use as part of the TNS. Further improvements can be made to enhance handling stability and shelf-life characteristics.

1. Introduction

There is a great need for innovations in infant therapeutic development and administration. The WHO estimates that access to affordable interventions, tailored for use in resource-constraint settings, could help to prevent a large percentage of the 5.9 million child deaths worldwide before the age of five (IGME, 2018; World Health Organization, 2007). Improved infant compliant technologies could also facilitate the process of infant oral administration in both high- and low-resource settings, easing the physical and emotional challenges experienced by many parents. While administration during feeding is recommended to improve acceptability (Helms and Quan, 2006), this is not a feasible approach for the 36% of exclusively breastfed infants aged 0–6 months (World Health Organization, 2017). A novel delivery technology, called Therapeutic Nipple Shield (TNS), could help to address this shortcoming. Designed to enable therapeutic delivery during breastfeeding, it consists of two components: a silicone nipple shield and a therapeutic dosage form contained within the nipple shield’s teat. The TNS is worn by the mother during breastfeeding, and enables therapeutic delivery to her sucking infant through the flow of human milk (see Fig. 1). \textit{In-vitro} testing of the TNS is performed using a breastfeeding simulation apparatus, capable of simulating the process of lactation and infant feeding (Gerrard et al., 2013). Past literature has investigated the use of a modified lip-containing nipple shield to enable drug placement, also referred to as the NSDS design, as well as the release of Sulforhodamine B from rapidly disintegrating tablets (Gerrard et al., 2012), and of zinc sulphate from both non-woven fibres and rapidly disintegrating tablets into human milk (Maier et al., 2018; Scheuerle et al., 2017a). Yet, in all cases, delivery of a full dose within the duration of an average breastfeed was not achieved (Gerrard et al., 2012; Maier et al., 2018; Scheuerle et al., 2017a), encouraging the investigation of liquid-core hydrogels as an alternative dosage form as part of the TNS.

Although iron is a biochemically essential element, involved in a range of metabolic processes and DNA synthesis (Camaschella, 2015), over two billion people are affected by iron deficiency, making it the most common single-nutrient deficiency worldwide (Lanzkowsky, 2016). Affected individuals experience a variety of nonspecific symptoms such a fatigue and weakness (Camaschella, 2015), as well as deficits in mental, behavioural, motor, and neurophysiological function (Agostoni et al., 2010; Berglund et al., 2015; Caglayan et al., 1993; Kazal, 2002; Lozoff et al., 2006). Although iron deficiency is particularly common in low-resource environments, as many as 26% of healthy toddlers aged 1 to 3 years were reported to be affected (Domelloef et al.,
Human milk alone, which contains only 0.2–0.4 mg l⁻¹ of available iron, cannot meet the increased iron requirements of preterm infants (Baker and Greer, 2010; De Alarcon and Werner, 2005), or due to premature birth, which results in significantly lower amounts of stored iron, resulting in deficiency already within the infants’ first months of age (Baker and Greer, 2010). Because the increased iron requirements of preterm infants cannot be met by human milk alone, which contains only 0.2–0.4 mg l⁻¹ of available iron (Ziegler et al., 2009)), supplementation is recommended (Baker and Greer, 2010). Guidelines suggest 2 mg of elemental iron per kg body weight per day, starting at the beginning of the infants’ fifth postnatal week until the end of their twelfth month of age (Rao and Georgieff, 2009). For developing countries with high prevalence of iron deficient anaemia (40% or higher), a condition in which the blood’s haemoglobin concentration is decreased and the red blood cell’s morphology affected, the World Health Organization recommends a daily dose of 10–12.5 mg of elemental iron for three consecutive months within a year (World Health Organization, 2016). Iron(II)sulphate, is the most commonly used form of iron supplementation, based on its availability, cost-effectiveness, and high bioavailability (Naude et al., 2000; Rao and Georgieff, 2009). It is included in both the WHO Model List of Essential Medicines and the WHO Model List of Essential Medicines for Children (World Health Organization, 2017, 2015), and can be found in fortified food, as well as in formulations of prophylactic and therapeutic purpose (eMC, 2018).

Taking into account the clear need for improved infant iron supplementation during breastfeeding, we embarked on developing an improved TNS system, employing a novel hydrogel based dosage form and a commercially available silicone nipple shield, which enhances its potential for translation from bench into clinical practice.

2. Materials and methods

2.1. Materials

Low viscosity alginic acid sodium salt in FCC grade (G:M ratio in the range of 61–65:39–35) was obtained from Alfa Aesar (Lancashire, UK), calcium lactate pentahydrate from Sigma Aldrich (Dorset, UK), salicylic acid and iron(III)sulphate pentahydrate from Fisher Scientific (Leicestershire, UK). Iron(III)sulphate was preferred over iron(II)sulphate to prevent potential competition with Ca²⁺ during crosslinking and to facilitate subsequent iron analysis. Human milk samples were provided by the Queen Charlotte’s and Chelsea Hospital Milk Bank (Imperial College Healthcare NHS Trust) and characterised to contain a lipid content of 43.52 g l⁻¹ and a protein content of 16.51 g l⁻¹ (Maier et al., 2018). These values align with previously reported literature (Emmett and Rogers, 1997; Kent et al., 2006; Maier et al., 2018; Saarela et al., 2005). The experimental use of human milk was approved by the Cambridge Human Biology Research Ethics Committee at the University of Cambridge.

2.2. Methods

2.2.1. Hydrogel fabrication

Liquid-core ferrisulphate hydrogels were prepared using the following procedure. Two solutions were prepared: i) A 0.5% sodium alginate solution of low viscosity alginic acid sodium salt in double deionized water (DDI), which was left to settle at 4 °C overnight to remove air bubbles, ii) a solution of 1% calcium lactate pentahydrate and 60 mg mL⁻¹ ferric sulphate pentahydrate in DDI water, of which 500 μL were pipetted into each of the hemispherical impressions of a food-grade silicone mould (impression measuring 2.5 cm in diameter and 1 cm in depth). The filled mould was transferred to −20 °C for at least 5 h. Gelation was achieved by exposing a frozen calcium lactate ferric sulphate hemisphere for 2.75 min to a 4 °C sodium alginate bath, following which access sodium alginate was rinsed off in a DDI water bath. All liquid-core hydrogels were prepared immediately before use in delivery or characterisation measurements.

2.2.2. Compression testing and visual characterisation

To assess the mechanical properties of manufactured liquid-core hydrogels, uniaxial compression testing was performed in octuplicate using a H5Ks electric screw machine (Tinius Olsen, Redhill/UK) fitted with a 5 N load cell. Hereby, each hydrogel was placed on a stationary flat surface, while a second flat plate applied vertical compression until the gel’s plastic region of formation was reached. An illustration of the setup is provided in Fig. 4a). The crosshead speed was set at 2 mm/min, and force displacement data recorded. Due to the complex nature of liquid-core hydrogels, other mechanical properties were not evaluated. Visual analysis of the gels’ rupture mechanism and morphology was performed by means of a bespoke optical system to enable real-time image analysis. It consisted of a high-speed camera (Basler, Ahrensburg/Germany) and a National Instruments card (NIC, National Instruments, Austin, TX/USA), controlled via a LabVIEW software programme. Calibration was performed by determining the number of pixels and the distance in mm between both the top and bottom compression plate. This relationship was used to evaluate the hydrogel’s average wall thickness, diameter, and height in quadruplicate using images taken before compression testing. Hereby, wall thickness measurements made use of the shell’s and core’s difference in colour strength when visualised via the LabVIEW programme, enabling to identify the solid core’s boundary.

2.2.3. Delivery of iron(III)sulphate during breastfeeding simulation experiments

Delivery of iron(III)sulphate was conducted in triplicate using the breastfeeding simulation apparatus by Gerrard et al. (2013), illustrated in Fig. 2. The apparatus transfers human milk within silicone tubing from a stirred reservoir to the fraction collector. Pump 1 enables human milk to reach a silicone breast mimic, on which the hydrogel-containing nipple shield is fixed in an angle of 30° downwards from the vertical axis, while pump 2 transports milk having passed the nipple shield to the fraction collector. Pump 3 is controlled by a computer system linked...
to a National Instruments Card, enabling temperature and pressure monitoring and the exertion of an oscillating suction pattern similar to those of breastfed infants. In accordance with breastfeeding physiology, an approximate flow rate of 5.0 mL min\(^{-1}\), a suction frequency of 1 suction sec\(^{-1}\), and a temperature range of 33.7–35.7°C, mimicking the temperature of human milk in the infant’s mouth, were used during breastfeeding simulation (Black et al., 1998; Geddes et al., 2008; Macias and Meneses, 2011; Moral et al., 2010). Prior to experimental procedures, the apparatus’ pumps were calibrated. To investigate the potential of hydrogel delivery for preterm infants, who commonly require use of ultrathin contact nipple shields to establish breastfeeding and increase milk transfer (Meier et al., 2000), the pressure values for breastfeeding simulation were adjusted in alignment with literature by Geddes et al. (2018, 2017). Mean peak vacuum values of \(-62.47 \pm 1.76\) mmHg, mean baseline vacuum values \(-0.92 \pm 0.37\) mmHg, and mean average vacuum values \(-38.30 \pm 9.71\) mmHg were recorded. Fractions, each collected for a duration of 10 s, were weighted before analysis, and recovery into approximately 10 g of human milk investigated.

### 2.2.4. Quantification of iron in human milk

Iron(III)sulphate pentahydrate in fractions collected during breastfeeding simulation as well as in prepared standards with known concentration was quantified as follows: In order to obtain transparent solutions, 1 M hydrochloric acid was added in a ratio of 1:8 to the sample to trigger the release of transferrin-bound iron and precipitate the human milk’s casein, with its isoelectric point at pH 4.7 (Broyard and Gaucheron, 2015; Phillips and Williams, 2011). All samples were mixed by vortexing and centrifuged for 7 min at 16,112 x \(g\). For each sample 20 \(\mu\)L of the supernatant was transferred to 180 \(\mu\)L of DDI water and 1700 \(\mu\)L of 0.1% salicylic acid solution added. Following mixing, absorbance of ferric salicylate in each sample was measured at room temperature at \(\lambda_{\text{max}} = 524\) nm. The wavelength of maximum absorbance was determined by means of absorbance scans of all calibration samples over the wavelength range of \(\lambda = 328–1000\) nm, and a calibration curve at ferric salicylate’s maximum absorbance in human milk generated (see Fig. A.1). A separate calibration curve was constructed in DDI water (see Fig. A.2) to determine the total amount of iron loaded within the liquid-core hydrogels. Frozen hemispheres were melted, weighted, diluted 1:1 in DDI water, and their concentration determined through absorbance measurements of ferric salicylate at \(\lambda_{\text{max}} = 524\) nm as described previously. Triplicate analysis indicated a total of 29.59 \(\pm 0.43\) mg ferric sulphate pentahydrate contained within manufactured liquid-core hydrogels, corresponding to 6.75 \(\pm 0.10\) g of elemental iron. Absorbance values obtained for fractions collected during breastfeeding simulation experiments were used to generate a release profile, i.e. the cumulative iron(III)sulphate pentahydrate recovery over time, represented as a percentage of the total amount encapsulated within the sodium alginate hydrogels. Hereby, the amount of iron(III)sulphate pentahydrate in each fraction was evaluated based on absorbance measurements at \(\lambda_{\text{max}} = 524\) nm using the calibration curve (Fig. A.1), and normalised to the total amount of ferric sulphate pentahydrate used for liquid-core hydrogel manufacture. A cumulative normalised release graph was obtained by summing up the resulting values of each new fraction with those of previous fractions.

### 3. Results and discussion

#### 3.1. Hydrogel preparation

Liquid-core hydrogels containing ferric sulphate were prepared by means of frozen reverse spherification, a method that originated from the molecular gastronomy (Barham et al., 2010; Caporaso and Formisano, 2016; Sen, 2017), and is nowadays also applied for formulation preparation and nutrient supplementation (Hudson and Noel,
The protocol was iteratively adapted, choosing frozen reverse spherification over reverse spherification due to the hydrogels' higher uniformity. Fabrication optimisation variables included the following: i) type of spherification technique used to obtain reproducibly uniform spheres, ii) ratio of iron(III)sulphate penta hydrate to calcium lactate pentahydrate with the objective to minimize precipitation of either compound, iii) duration of gelation to control wall thickness and liquid-core content available for delivery, iv) the gel size in order to maximize liquid load, but to also enable sufficient milk flow through the nipple shield's silicone teat. While the first two variables could be assessed visually, the optimal gel size and gelation time were evaluated by means of breastfeeding simulation experiments. Since wall thickness is a function of gelation time, increasing with prolonged gelation duration, fabrication optimisation procedures had the objective to provide sufficient stability for gel handling, while retaining the gel's mechanical sensitivity for rapid rupture. A range of gelation times between 1 min to 5 min were assessed and those stable enough for handling tested in the breastfeeding simulation apparatus. Less liquid to be encapsulated required shorter gelation times than larger amounts of liquid to achieve the same hydrogel stability. Aqueous solution of calcium lactate pentahydrate and iron(III)sulphate pentahydrate were pipetted into each of the hemispherical impressions of a food-grade silicone mould and subsequently frozen at −20°C. Gelation was achieved by exposing a frozen calcium lactate iron(III)sulphate hemisphere for 2.75 min to a 4°C sodium alginate bath (Fig. 3).

### 3.2. Compression testing and visual characterisation

Average values for wall thickness, diameter, and height of manufactured liquid-core hydrogels, as well as compression force required for gel rupture are summarised in Table 1. Values are compared to previously published data of i) rapidly disintegrating tablets for zinc delivery into human milk, ii) liquid-core alginate hydrogel beads by Tsai et al. (2017a, 2017b, 2017c). A typical force-displacement graph is illustrated in Fig. 4b). Two conclusions can be drawn: first, the larger diameter of fabricated liquid-core hydrogels, compared to rapidly disintegrating tablets, allows for central positioning of the gels within the nipple shield's teat, even without a lip for dosage form positioning, as studied previously (Gerrard et al., 2012; Maier et al., 2018; Scheuerle et al., 2017a), and increases the dosage form's surface area for human milk contact. Moreover, when comparing LHBS by Tsai et al. (2017a, 2017b) and liquid-core hydrogels, a five-fold lower compression force can be observed. This can likely be attributed to the comparatively large amount of liquid encapsulated within the manufactured hydrogels and its resulting diminished sphericity. Visual analysis data during compression testing, illustrated in Fig. 5, contributes towards this hypothesis, and reveals that the hydrogel's API-release mechanism merely entails the formation of a pinhole in the hydrogel's solid shell.

### 3.3. Release of iron from liquid-core hydrogels

Breastfeeding simulation data, illustrating the cumulative normalised proportion of iron sulphate pentahydrate released over time, can be found in Fig. 6. An absolute recovery of 44.35 ± 5.43% of loaded iron(III)sulphate pentahydrate was achieved after 10.58 ± 0.09 g of human milk had passed through the TNS, highlighting the liquid-core hydrogels' superior release properties compared to previously studied dosage forms. In comparison: Release of zinc sulphate from rapidly disintegrating tablets and non-woven fibres in approximately 10 g of human milk (equivalent to 2 min of breastfeeding simulation) resulted in only 3–5% and 29–31% recovery, respectively (Maier et al., 2018; Scheuerle et al., 2017a), and proofed even after an additional 18 min of breastfeeding simulation insufficient in delivering the full dose within the 76.0 ± 12.6 g human milk of an infants' average breastfeed (Kent et al., 2006). While the hydrogel's rapid release promises sufficient delivery even during short feeds, reduced mixing with human milk over time also necessitates that the therapeutic formulation is designed to possess adequate taste, aiming to prevent its impact on the infant's breastfeeding compliance. The potential to encapsulate commercially available paediatric liquid formulations and syrups, with their already optimised taste masking characteristics for the delivery by means of oral syringes or dosing spoons, provides a potential strategy to mitigate these risks. Although liquid-core hydrogels increase the ratio of API to human milk with a total of 38.16 ± 0.06% of iron sulphate released during the first minute of breastfeeding simulation, it has to be noted that human milk itself comprises taste masking properties (Bennett et al., 2012), and that breastfed infants are generally used to a wide range of different tastes as a result of the maternal diet (Bravi et al., 2016; Cosmi et al., 2017).

Despite their superior release properties, full release of the loaded dose within the approximately 2 min of breastfeeding simulation experiments was not achieved. The difference between the amount of iron (III)sulphate pentahydrate loaded into the hemispherical silicone mould as part of the hydrogels' fabrication process, and the amount recovered in human milk during breastfeeding simulation, can be explained by a combination of both iron retention within the hydrogel's core shell, as well as within the apparatus void space in form of iron-casein precipitates. The former is a direct result of the spherification process, whereby ferric sulphate is enclosed within the crosslinked alginate polymer chains, and the shell's remainder in the nipple shield teat following delivery of its liquid core. Iron-casein precipitates are caused by neutralization of the casein's negative charge following binding of Fe^{3+} to its Pser clusters (Gaucher, 2000), and can only be re-suspended in fractioned samples by adjusting the pH during pre-analysis processing. While in-vitro experiments yielded only insufficient delivery of the loaded dose, it has to be noted that therapeutic loss due to precipitate formation within the complex apparatus setup would not occur during in-vivo delivery and that the chosen experimental duration only assessed the hydrogel's rapid release properties within the first 2 min of breastfeeding simulation. A breastfed infant however would be directly latched onto the nipple shield containing the hydrogel, and...
breastfeeding for a seven times extended period of time (Kent et al., 2006).

In addition to their superior release characteristics, liquid-core hydrogels possess three distinct advantages, suggesting their preferred use as a dosage form as part of the TNS. Firstly, liquid-core hydrogels are the first dosage form studied for delivery into human milk that are characterised by a mechanically induced release mechanism, i.e. the rupture of the hydrogels' solid shells through suction force and milk flow. It thereby overcomes previous limitations of rapidly disintegrating tablets and non-woven fibres, which involved alteration of the dosage forms' release efficiency based on the milk's fat content, the milk's homogeneity, and the overall milk macromolecule composition (Gerrard et al., 2012). Hereby, the strong dependence of achievable release efficiency on human milk composition, which is known to vary among others based on the maternal diet and the stage of lactation (Vir, 2011), was perceived as particularly problematic for the exploration of suitable dosage forms and the formulation of widely applicable findings. The use of liquid-core hydrogels within a commercially available ultrathin contact nipple shield is also believed to enhance user acceptability through both, enabling use of the same nipple shield device for normal feeding and therapeutic administration, while at the same time reducing potential discomfort for mother and/or infant during breastfeeding based on the hydrogel's soft texture. Moreover, sodium alginate hydrogels manufactured via frozen reverse spherification enable the production of low-cost dosage forms, using both a biocompatible and non-toxic polymer, and calcium, one of the 21 essential elements of the human body (Preedy, 2016). While use of calcium lactate or calcium gluconate is beneficial due to its neutral taste (Pathomrungsriyongkul et al., 2010), sodium alginate is a common component of commercially available infant medication, e.g. ‘Gaviscon’ to treat gastric regurgitation in infants aged 1-2 years (Corvaglia et al., 2011b, 2011a; Dhillon and Ewer, 2004), as well as gastroesophageal reflux in preterm infants under medical supervision (Corvaglia et al., 2011b, 2011a; Dhillon and Ewer, 2004). As hydrogel manufacture goes without potentially harmful or problematic excipients used in other infant formulations, the liquid-core hydrogels presented in this study also respond to the consistently emphasized need for more appropriate paediatric formulations and their inclusion into pharmaceutical product portfolios (Lopez et al., 2015; Standing and Tuleu, 2005). Lastly, with regard to the therapeutic delivered as part of this study, the hydrogels’ rapid delivery properties as part of the TNS seem particularly suitable for iron release during breastfeeding, as prolonged exposure of iron to milk products over time, e.g. through supplementation in milk and yoghurt, results in an undesired change of odour and flavour, as well as the milk’s rancidity due to iron-induced lipid oxidation (Gaucheron, 2000).

Areas of further improvement include both the liquid-core hydrogel's stability and shelf life characteristics, as well as solubility considerations. According to Tsai et al., the hydrogels' mechanical stability for handling and storage purposes can be improved by means of a secondary gelation step (Tsai et al., 2017a, 2017b, 2017c), involving the introduction of crosslinked hydrogels into a Ca\(^{2+}\) solution to enable the ion's permeation into the previously unoccupied blocks within the hydrogels' core shell structure (Tsai et al., 2017c). This approach was shown to increase hardness and storage stability of LHBs produced by means of reverse spherification, while simultaneously decreasing the release rate of the encapsulated API (Tsai et al., 2017a, 2017b, 2017c). Due to the exposure of the TNS's hydrogels to repetitive mechanical stress during breastfeeding simulation, representing a significantly different environment than during experiments performed by Tsai et al. without agitation (Tsai et al., 2017a, 2017b, 2017c), it can however be hypothesized that a reduction in absolute recovery due to secondary gelation is not to be expected. In fact, findings by Scheuerle et al. give reason to expect an even enhanced API-recovery during in-vivo breastfeeding, as infant tongue peristalsis, shown to be an important driver for dosage form disintegration (Scheuerle et al., 2017b), cannot be mimicked using the breastfeeding simulation apparatus. Solubility considerations relate to the availability of calcium lactate pentahydrate for hydrogel gelation. Soluble calcium lactate might permanently precipitate during the spherification's freezing step, depending on both the characteristics and amount of dissolved therapeutic within the calcium lactate solution. As calcium ions are essential for gelation, it has to be noted that both crosslinking protocol and/or the concentration of calcium lactate pentahydrate used for hydrogel fabrication will need to be optimised.

In Table 1, an overview of wall thickness, diameter, height, and compression force of liquid-core hydrogels used for iron delivery into human milk can be found. The table includes data obtained by Scheuerle et al. and Tsai et al., using rapidly disintegrating tablets for zinc delivery into human milk (Scheuerle et al., 2017a), and liquid-core hydrogel beads for chlorogenic acid delivery into simulated intestinal fluid (Tsai et al., 2017a, 2017b), respectively.

<table>
<thead>
<tr>
<th>Description</th>
<th>Liquid-core hydrogels</th>
<th>Liquid-core alginate hydrogel beads (LHBs)</th>
<th>Rapidly disintegrating tablets (tablet type 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall thickness [mm]</td>
<td>0.44 ± 0.10(^{a})</td>
<td>Not provided</td>
<td>N/A</td>
</tr>
<tr>
<td>Diameter [mm]</td>
<td>14.28 ± 0.85(^{a})</td>
<td>Range: 4.17–5.84 (Tsai et al., 2017b)</td>
<td>8.093 ± 0.003</td>
</tr>
<tr>
<td>Height [mm]</td>
<td>4.91 ± 0.28(^{a})</td>
<td>1.26(^{a}) (Tsai et al., 2017a)</td>
<td>4.65 ± 0.03</td>
</tr>
<tr>
<td>Compression force [N]</td>
<td>0.245 ± 0.103(^{b})</td>
<td>22,000</td>
<td></td>
</tr>
</tbody>
</table>

\(^{a}\) Values were measured in quadruplicate.

\(^{b}\) Values were measured in octuplicate.

\(^{c}\) Values taken from Scheuerle et al. (2017a) referring to tablet type 2.

\(^{d}\) Reverse spherification using a single spherification step.
4. Conclusions

This study investigated the delivery of iron(III)sulphate pentahydrate from liquid-core hydrogels, comprised within the teat of a commercially available ultrathin contact nipple shield, into human milk by means of a breastfeeding simulation apparatus. A total recovery of 44.35 ± 5.43% was achieved after 10.58 ± 0.09 g human milk had passed through the shield. Compared to previous dosage forms used for delivery into human milk, liquid-core hydrogels within a commercial ultrathin silicone nipple shield were identified as the superior dosage form for delivery during in-vitro breastfeeding simulation. The hydrogel's delivery strategy, based on the rupture of the hydrogel's solid membrane, seems particularly feasible for administration during breastfeeding, as the release is not dependent on the complex and varying properties of human milk. Moreover, liquid-core hydrogels are characterised by their low cost, ease of fabrication, and high safety profile of used compounds, as well as their projected enhanced acceptability due to the hydrogel's soft texture and the possibility of using a commercially available nipple shield for both therapeutic delivery and normal feeding. Further research is required to enhance the hydrogel's stability characteristics for handling and storage purposes.

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Declarations of interest

None.
Fig. A.1. a) Absorbance scan for iron(III) sulphate pentahydrate samples of known concentration at λ = 328–1000 nm in human milk. The ferric salicylate’s maximum absorbance was measured at λ max = 524 nm. All samples were pre-processed by adding hydrochloric acid to the sample (1:8) to enable absorbance measurements following casein precipitation. Each data point represents the average of triplicate measurements.

Fig. A.2. a) Absorbance scan for iron(III) sulphate pentahydrate samples of known concentration at λ = 328–1000 nm in DDI water. The ferric salicylate’s maximum absorbance was measured at λ max = 524 nm. All samples were pre-processed by adding hydrochloric acid to the sample (1:8) to enable absorbance measurements following casein precipitation. Each data point represents the average of triplicate measurements.

References


