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*Graphical Abstract*
A Nipple Shield Delivery System for Oral Drug Delivery to Breastfeeding Infants: Microbicide Delivery to Inactivate HIV

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ABSTRACT

A new drug delivery method for infants is presented which incorporates an active pharmaceutical ingredient (API)-loaded insert into a Nipple Shield Delivery System (NSDS). The API is released directly into milk during breastfeeding. This study investigates the feasibility of using the NSDS to deliver the microbicide sodium dodecyl sulfate (SDS), with the goal of preventing mother-to-child transmission (MTCT) of HIV during breastfeeding in low-resource settings, when there is no safer alternative for the infant but to breastfeed. SDS has been previously shown to effectively inactivate HIV in human milk. An apparatus was developed to simulate milk flow through and drug release from a NSDS. Using this apparatus, milk was pulsed through a prototype device containing a non-woven insert impregnated with SDS. The total SDS release from the insert ranged from 70-100% of the average 0.07 g load within 50 ml (the volume of a typical breastfeed). Human milk spiked with H9/HIVIIIB cells was also passed through the same set-up. Greater than 99% reduction of cell-associated HIV infectivity was achieved in the first 10 ml of milk. This proof of concept study demonstrates efficient drug delivery to breastfeeding infants is achievable using the NSDS.

KEYWORDS

Breastfeeding, Microbicide, Pediatric drug delivery, HIV, Mother-to-child transmission, MTCT, Sodium dodecyl sulfate, SDS, Breast milk

ABBREVIATIONS

MTCT, Mother-to-child transmission

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1. INTRODUCTION

There is no single suitable drug and nutrient delivery method available for infants or young children (Kearns et al., 2003). In developing countries where medical infrastructure is often scarce, pediatric drug and nutrient delivery systems face numerous challenges in supply, stability, sterility, distribution, and dosing (Knoppert, 2009; WHO, 2010c). Liquid formulations are often the principal method of pediatric drug delivery, but are ill-adapted due to high cost and lack of access to refrigeration or potable water for reconstitution (UNICEF and WHO, 2010). When liquid formulations are not available, a solid dosage form can be used. However, when replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected mothers is recommended. This condition is often not met, and breastfeeding in low-resource settings has been shown to significantly increase infant survival (Brahmbhatt and Gray, 2003). In light of this, recent WHO guidelines recommend the continued use of oral anti-retroviral (ARV) drugs by the mother and/or the infant to prevent HIV transmission through breastfeeding (WHO, 2010a). However, widespread distribution of ARVs does not yet exist in Sub-Saharan Africa, and ARVs can lead to side effects and resistant strains of the virus. Therefore, there is a need for alternatives to the current methods of delivering ARVs.

Given the dearth of oral delivery methods, new strategies for delivery may be effective means of reducing viral load in milk through the prevention of mother-to-child transmission (MTCT) of HIV. We propose a method to deliver ARVs during breastfeeding that also overcomes many of the general challenges associated with frequent drug delivery to infants. The concept is to incorporate a drug-impregnated insert into a nipple shield worn by a mother during breastfeeding (Fig. 1), where during suckling, a drug is released directly into the milk (Gerrard, 2011; Sokal et al., 2009). Nipple shields, typically a single molding of silicone, are available at low cost and are breast feeding aids that have been studied for their potential to improve milk transfer efficiency in human lactation (Hartmann et al., 2006a). Sodium dodecyl (or lauryl) sulfate (SDS), an anionic surfactant, is a candidate for use as an edible microbicide with anti-HIV activity in human milk. It has been demonstrated that 0.1–1 wt% SDS rapidly kills sexually transmitted pathogens, including HIV in media (Howett et al., 2000, 1999; Krebs et al., 2000, 1999). A concentration of 0.1 wt% SDS has been demonstrated to rapidly inactivate cell-free and cell-associated HIV in human milk at 37°C (Hartmann et al., 2005; Tuaillon et al., 2009). This concentration is safe for infant use, based on a maximum acceptable infant oral exposure to SDS of 1 g/kg (of infant)/day (Hartmann et al., 2006a, 2006b). Another benefit of SDS is its broad antiviral activity by solubilizing lipid membranes; therefore, unlike many anti-viral compounds, SDS is strain independent and unlikely to drive HIV mutation to a resistant form (Hartmann et al., 2006b).

Given that delivery of SDS during breastfeeding may be an effective method of reducing viral load in milk through the prevention of MTCT of HIV, we propose a method to deliver ARVs during breastfeeding that also overcomes many of the general challenges associated with frequent drug delivery to infants. The concept is to incorporate a drug-impregnated insert into a nipple shield worn by a mother during breastfeeding, where during suckling, a drug is released directly into the milk (Gerrard, 2011; Sokal et al., 2009). Nipple shields, typically a single molding of silicone, are available at low cost and are breast feeding aids that have been studied for their potential to improve milk transfer efficiency in human lactation (Hartmann et al., 2006a). Sodium dodecyl (or lauryl) sulfate (SDS), an anionic surfactant, is a candidate for use as an edible microbicide with anti-HIV activity in human milk. It has been demonstrated that 0.1–1 wt% SDS rapidly kills sexually transmitted pathogens, including HIV in media (Howett et al., 2000, 1999; Krebs et al., 2000, 1999). A concentration of 0.1 wt% SDS has been demonstrated to rapidly inactivate cell-free and cell-associated HIV in human milk at 37°C (Hartmann et al., 2005; Tuaillon et al., 2009). This concentration is safe for infant use, based on a maximum acceptable infant oral exposure to SDS of 1 g/kg (of infant)/day and an biochemical analysis of the effect of SDS on milk content (Hartmann et al., 2006a, 2006b). Another benefit of SDS is its broad antiviral activity by solubilizing lipid membranes; therefore, unlike many anti-viral compounds, SDS is strain independent and unlikely to drive HIV mutation to a resistant form (Hartmann et al., 2006b).
This study had two aims: firstly to determine the kinetics of drug release into milk from a NSDS insert during a pulsed flow that mimics breastfeeding; and secondly to establish whether the release of SDS from a NSDS into human milk can inactivate HIV within the fluid.

2. MATERIALS AND METHODS

2.1 Formulation of non-woven fiber inserts with SDS

To make the NSDS inserts, 10 mm diameter discs of a medical grade non-woven cellulosic (viscose) and polyester based fiber matrix with a 2.75 mm thickness and area density of 300 g/m² (Bathfelt, Texel, Québec, Canada) were soaked in a 30 wt% SDS (Reagent Plus > 98.5% purity, Sigma Aldrich, UK) solution at 60 °C for 10 seconds. They were then air dried at room temperature for 72 hours. Their final weight gain was 0.07 g (standard deviation 0.01 g, n = 13). This fiber grade was chosen because it is non-toxic, suitable for flow with low back pressure, and it is easy to load a compound such as SDS onto it.

2.2 Kinetics of SDS release into milk in simulated breastfeeding conditions

To simulate use of a NSDS to deliver SDS during breastfeeding, loaded inserts were placed in an O-ring (BS012 Viton™ O-ring, 3/8" ID, UK) to seal them into a Sinnex filter holder (Millipore, MA, USA) (Fig. 1). Sample fluids were heated to 37 °C by passing through tubing in a water bath held at 42 °C, and then delivered through the SDS loaded device. Around 50 1 ml fractions per test were collected from the flow-through using a SuperFrac™ fraction collector (GE Healthcare Sciences, UK) to reflect typical volumes of milk consumed in a feed (Kent et al., 2006). The milk reservoir was continuously stirred to prevent fat accumulating at the top inlet. Individual fractions were assayed in triplicate for SDS concentration using a colorimetric assay described below.

SDS concentration in milk fractions was measured using an adapted stains-all colorimetric assay (Rusconi et al., 2001). The assay relies on the shift in absorbance at 438 nm when the reagent dye, stains-all, is mixed with SDS. The stains-all reagent underwent a spectral shift when mixed with milk alone without SDS, presumably caused by interactions with lipids, proteins or components with surfactant-like properties in milk. However, a highly reproducible further spectral shift was seen when SDS was added. This shift, together with the absorbance at 438 nm from milk without SDS, allowed SDS concentration in samples to be calculated. Samples were treated with SDS to ensure SDS concentration was measured in its non-reducing form as a sodium dodecyl sulfate (SDS) micelle, which is not directly proportional to SDS concentration in milk.

To make an assay solution sufficient to analyze 250 samples, 20 mg stains-all dye (Sigma-Aldrich, UK) was dissolved in 1 ml isopropanol, followed by the addition of 19 ml of 1:1 isopropanol:water. Triplicate 25 μl samples of each diluted fraction were mixed with 1000 μl stains-all stock solution followed by measurement of absorbance at 438 nm. Triplicate standards were measured to ensure a linear calibration curve was achieved. Samples were then assayed in triplicate, for which absorbance was measured at 438 nm.

To compare the SDS concentration in milk with that in standard SDS solutions, calibration curves were measured. Fluids used were: cow's milk, either pasteurized but not homogenized (Taste the Difference Jersey Milk, 5.2% fat, J.S. Sainsbury's, UK) or unpasteurized non-homogenized full-fat goat's milk (4% fat, Wobbly Bottom Farm, Hampshire, UK).

2.3 Formulation of non-woven fiber inserts with SDS and homogenized with SDS

To determine the difference between milk samples and SDS, milk solutions were prepared with SDS and without SDS, and their absorbances at 438 nm were measured. A spectral shift was seen when SDS was added, but no shift was seen when SDS was not added. This indicates that SDS is not reduced in milk, allowing SDS concentration to be measured in milk. To compare the SDS concentration in milk with that in standard SDS solutions, calibration curves were measured. Fluids used were: cow's milk, either pasteurized but not homogenized (Taste the Difference Jersey Milk, 5.2% fat, J.S. Sainsbury's, UK) or unpasteurized non-homogenized full-fat goat's milk (4% fat, Wobbly Bottom Farm, Hitchin, Hertfordshire, UK).

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2.3 Inactivating HIV in human milk with an SDS-loaded NSDS insert

To determine inactivation of cell-associated HIV by SDS released from the NSDS, human milk was spiked with H9/HIVIIIB cells (provided by the NIH AIDS reagent program Cat. No. 400) to a final concentration of 2.6 x 10^5 cells/ml and was pumped through SDS impregnated NSDS inserts using a near identical setup to that used to measure SDS release kinetics, see section 2.2 (fraction collector: BioRad Model 2110, USA). Human milk samples were provided by the Mothers’ Milk Bank, Valley Medical Centre (San Jose, California, USA). H9/HIVIIIB cells are self-replicating cells that express HIV (type-1 IIIB), and have been previously used to model cell-associated HIV (Lara et al., 2011; Yamaguchi et al., 2007). The cell content spiked in milk was based on previously reported concentrations of between 1 to 3255 infected cells per 10^4 in milk with typical total cell concentrations in the first few days of life to be 10^6 cells/ml (Nduati et al., 1995; Rousseau et al., 2004). Prior to being spiked in milk, the cells were centrifuged at 1500 RPM for 5 minutes and re-suspended in cell culture media to remove free virus. 5 ml milk fractions were assayed for HIV-infectivity using TZM-bl cells in triplicate (provided by the NIH AIDS reagent program Cat. No. 8129). TZM-bl cells are HeLa clones genetically engineered to express CCR5 and CD4 receptors and indicate HIV infectivity via a luciferase reporter (Montefiori, 2005). Infectivity values were calculated by comparing them with standard samples of known infectivity for concentrations of H9/HIVIIIB cells in the same milk (Fig. 6a). The concentrations of SDS released into early milk fractions, and the human milk itself, were both found to disrupt the TZM-bl reporter cells, preventing direct measurement of HIV infectivity in the fractions. Therefore, for all collected fractions, SDS and milk were separated from H9/HIVIIIB cells 20 minutes after fraction collection, by 3 rounds of centrifugation and washing in cell culture medium and phosphate buffered saline (PBS). Preliminary experiments demonstrated this method removed sufficient human milk and SDS at all release concentrations to prevent direct disruption of TZM-bl cells with the donor milk used (data not shown). This protocol also prevented HIV inactivation by SDS following NSDS treatment, during subsequent sample incubation with TZM-bl cells, which would not be representative of the conditions encountered by cell-associated HIV passing through the NSDS in physiological breastfeeding simulation conditions.

100-150 μL samples of milk fractions were diluted 1:10 (vol.) in cell culture media in a 96-well round bottomed plate (# 3799, Corning, USA), centrifuged (1500 RPM for 5 minutes at 15°C) and washed twice in PBS, followed by centrifugation and re-suspension of washed H9/HIVIIIB cells in 100 μL culture medium (DMEM and 15% fetal bovine serum). After washing, 25 μL of culture medium, 25 μL washed sample and 50 μL TZM-bl cells at 2 x 10^5 cells/ ml were added to flat bottomed 96-well plates and incubated for 2 days at 36.5°C and 5% CO2 (incubator: Sanyo, USA). Samples were re-suspended in culture medium and DEAE Dextran (30 µg/ml) was added to TZM-bl cells just prior to sample addition at 2 µL per 1 x 10^5 cells/ ml. A D-Luciferin potassium salt (Thermo Scientific, USA) reagent mixture was added and luminescence read using a GloMax® 96 Microplate Luminometer (Promega, USA).

3. RESULTS

3.1 Release of the edible microbicide SDS from NSDS inserts

The release of SDS from a NSDS insert in a mimicked breastfeeding simulation environment was studied using the apparatus outlined in section 2.2 and Fig. 2d. This was performed to provide evidence of the influence of the physiological variables within breastfeeding that could influence drug release from a NSDS. Preliminary experiments determined a suitable apparatus to mimic drug release from a drug-loaded NSDS insert. Conditions of milk flow through an NSDS insert resembling breastfeeding were achieved by maintaining the milk at 37°C and using a peristaltic pump to produce pulses to flow similar to the suction minimizing the milk at 2°C. The release of a passive and effective amount of drug from the simulation environment was expected by measuring the concentration of SDS inset in situ by an NSDS insert, which then allowed the calculation of potential NSDS performance during breastfeeding. The milk samples were spiked with H9/HIVIIIB cells. The milk samples were collected 2.6 x 10^5 cells/ml and were pumped through SDS impregnated NSDS inserts in a near identical setup to that used to measure SDS release kinetics. A final concentration of 100 μL milk samples were provided by the Mothers’ Milk Bank, Valley Medical Centre (San Jose, California, USA). To determine inactivation of cell-associated HIV by SDS released from the NSDS, human milk was spiked with H9/HIVIIIB cells (provided by the NIH AIDS reagent program Cat. No. 400)
The influence of milk composition on release kinetics

3.2. Effect of flow conditions and temperature and insert form on release kinetics

The initial focus was to identify the principal release behavior of SDS from the non-woven fiber over a range of flow conditions. This was intended to examine the basic influence of fluid kinetics on release behavior, which may vary significantly from a feeding infant using the NSDS.

The effect of milk temperature upon release behavior was studied to provide evidence of the importance of fluid temperature for future laboratory studies. The release of SDS from the non-woven fiber insert into homogenized, pasteurized cow’s milk at 16°C (laboratory temperature), was similar to that detected at 37°C (temperature of human milk) into homogenized, pasteurized cow’s milk (Fig. 4a and b). Around 70-100% release was detected after 30 ml in all tests. This suggests that milk temperature is not a significant factor affecting SDS release from the non-woven fiber insert.

The influence of two types of flow conditions were compared between tests: the pulse rate (how quick the infant sucks) and the pulse volume (how much milk is extracted from the breast per suck); these were controlled by altering the size of tubing used by the peristaltic pump and the operating speed. Two test sets were run using non-homogenized pasteurized cow’s milk: (1) maintaining the pulse rate at 60 pulses/min and varying pulse volume at 0.02, 0.07 and 0.45 ml/pulse and (2) maintaining the pulse volume at 0.07 ml/pulse and varying the pulse rate to 40, 60 and 80 pulses/min. The release results demonstrated that SDS was released into non-homogenized cow’s milk at similar rates for all these flow rate conditions, with >50% of release of the disc’s load after 20 ml for all conditions.

The influence of the non-woven fiber on SDS release was determined by comparison to SDS powder placed into the insert holder. 0.1 g of SDS powder was used per test. Similar release patterns were seen in all conditions.

3.3. Effect of milk composition on release kinetics

The influence on release behavior due to milk composition was studied, using milk from different animal sources and with varying pasteurization and homogenization. Analysis of initial release behavior provided a suitable marker for the effect of different fluid types. In all conditions used, the majority (70%–100%) of SDS was released from non-woven fiber inserts within 50 ml. A common release pattern was observed in all conditions, with SDS being released at a constant rate over time. SDS concentrations of above 0.1 wt% SDS (previously reported to be highly anti-viral) were seen for the tests in the first 20 ml of milk that passed through the non-woven fiber insert.

The influence of milk composition and insert form on release kinetics

This work has extended the understanding of SDS release from the NSDS, providing evidence of the importance of fluid temperature and flow conditions in affecting SDS release. Further studies are needed to explore the impact of milk composition on release kinetics, with the aim of optimizing the design of the NSDS for use in different milk sources.
milk and 30-60% into the non-homogenized pasteurized form, suggesting a progressively slower release into these respective fluids (Fig. 5). The mean volume needed for 50% release of the SDS from the non-woven disc insert between these 3 fluids was also compared, and goat's milk (average 1.4 ml) induced significantly more rapid release than both homogenized pasteurized (5.1 ml) (p < 0.05) and non-homogenized pasteurized (16.3 ml) (p < 0.1) cow's milk (using unpaired two tailed t-tests). The difference in volume to 50% release into homogenized compared to non-homogenized cow's milk was not significant (p > 0.05). The observed difference in cow's and goat's milk release behavior indicates that milk composition significantly influences release kinetics.

3.4 Modeling release behavior

For an initial model it was proposed that total drug release was dependent on the fraction of SDS released for fixed flow and temperature conditions.

\[
q_t = k_1 q_t \exp(k_2 q_t)
\]

Integrating from the start of the test until a volume, \(q\), has passed through the insert gives Eq. (2):

\[
\int_{0}^{q} \frac{1}{k_2(q - q_0)} dq = k_1 t
\]

Using Eq. (2) for each release test \(k_1\) and \(k_2\) were varied to optimize the least squares value using a computational non-linear regression analysis optimization algorithm (Tables 1 and 2). Software: Mathematica - Wolfram, IL USA).

The 1st order release kinetics model presented \(R^2 > 0.969\) for all tests apart from one with the highest flow rates, with \(R^2\) at 0.933 (Table 1.). This indicates that for most flow conditions the release behavior is well modeled by 1st order release kinetics. For non-woven fiber tests under the same flow conditions (Table 2.) the constant \(k_2\) was noticeably higher in goat's milk (0.416-0.522) compared to non-homogenized cow's milk (0.141-0.181) to homogenized cow's milk (0.036-0.069). The mean \(k_2\) values for each fluid were statistically different between all fluids (p < 0.05) using unpaired, two tailed t-tests. \(k_2\), which indicates rate of release, was highest for the goat's milk, where SDS release was most rapid. 1st order kinetics was significantly more rapid than any conditions with 1st order release behavior, which, while not significant, suggest that the same apparatus and test conditions at the release speeds, when using human milk, given for the fluid element of this proof of concept study the reduction of cell-associtated HIV by SDS was

3.5 HIV inactivation by a SDS loaded NSDS insert

For the final element of this proof of concept study the reduction of cell-associated HIV by SDS was studied using the same apparatus and test conditions as the release studies, but using human milk. Given the anti-viral concentrations of SDS found to release into various milk types in early fractions, it was predicted that similar release would be detected in human milk. However, SDS release was most rapid, indicating a high SDS content in early fractions. It was predicted that similar release would be detected in human milk, but this was not observed. The observed difference in cow's and goat's milk release behavior indicates that milk composition significantly influences release kinetics.

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HIV inactivation by a SDS loaded NSDS insert
There was a high inactivation of cell-associated virus in early fractions (0-10 ml) of human milk passed through the NSDS SDS-insert (>99%), followed by a much smaller reduction in later fractions. The first-order cumulative release model presented here observed data well, and the constants derived in the fitting provided good agreement with the observed data.

Discrepancies in the fit of data to the first-order model were likely due to biological variations in milk from different sources, as well as the theoretical assumptions of the model. Further work is needed to refine the model and better understand the factors influencing the release of APIs from the NSDS.

**DISCUSSION**

### 4.1 Drug release into milk from the NSDS

Parameters that are expected to influence release kinetics of APIs from the NSDS include drug form, support material/excipients, flow conditions and solvent type. For this study, where flow conditions and milk type were changed, the greatest variation in release behavior was seen between the differing milk types, with goat's milk producing the most rapid SDS release rate.

Understanding in detail the effect of milk composition on release kinetics will be important for controlled release into human milk, which is known to have highly variable composition; for example, during a typical feed, the fat content can increase by up to 3-fold (Daly et al., 1993).

In order to obtain consistent drug release from mothers despite their varying milk content, it may be necessary to produce an insert formulation that allows for flow rate-independent release kinetics for various milk compositions possible in feeding. Further formulation methods should be considered for SDS and other APIs. They could include modifying or changing the current soaking impregnation method onto the fiber or using a different support material such as a rapidly disintegrating tablet or a soluble polymer film. Preliminary tests demonstrated that addition of hydroxyl methyl cellulose into the SDS insert during formulation may result in slower SDS release into milk and reduce the initial high release seen in earlier studies.

The first-order cumulative release model fitted our observed data well, and the constants derived in the fitting provided good agreement with the observed data. However, this simple model may not encompass all the factors influencing release from the NSDS, especially at higher flow rates where the model fitted least well. Further work is required to refine the model. We postulate that a combination of dissolution phenomena and particulate release govern SDS release from fibers.
This suggests that the initial high release behavior of SDS observed in goat's milk may also have occurred with human milk and therefore goat's milk may be a suitable mimic for use in NSDS release studies. Further work is needed to understand what components affect SDS release and dissolution, and how milk composition affects release kinetics before a suitability-of-use analysis can be made.

The importance of the release kinetics of SDS into HIV infected milk for prevention of MTCT can only be speculated about at this point. MTCT of HIV in breastfeeding is complex and incompletely understood. Transmission may occur either through the free virus or cell-associated virus, with sites of transmission including the mucosal surfaces of the tonsils and gut (Cavarelli and Scarlatti, 2011). Thus the SDS release rate into milk may alter transmission rates depending on where anti-viral concentrations of SDS in the digestive system reside during the feed. The proof of concept data in this paper should provide an indication of how cell-associated HIV could be inactivated by SDS in a physiological environment. Further study will be required to better predict the effectiveness of a given NSDS microbicidal surface in preventing transmission to recipients who are exposed to infection.

In vivo SDS may act on both free virus and infected cells during their passage through the digestive system, and SDS released into early fractions may subsequently mix with infected milk consumed later in the feed. This would lead to a higher level of HIV inactivation under such circumstances and a reduced risk of transmission to recipients who are exposed to infection. In addition, any cell-free virus released into the milk may be exposed to the high anti-viral concentrations of SDS in the digestive system at multiple points in the feed. The results of this study suggest that the NSDS may be a viable consideration for preventing MTCT of HIV specifically by inactivating virus during passage through the NSDS. This could be combined with microbicide release to potentially increase viral inactivation within the NSDS, improving the effectiveness of the device in preventing transmission.

4.3 Future uses of the NSDS

The acceptability of a NSDS to breastfeeding mothers must be carefully assessed prior to use. For its specific use in preventing MTCT of HIV during breastfeeding a study was conducted in Kenya. Mothers and stakeholders involved in deciding infant feeding practices were questioned, and gave positive feedback about the potential use of a NSDS to prevent HIV transmission in feeding (Israel-Ballard et al., 2010). For any specific application, careful consideration will be needed to determine if a disposable single use device or a re-useable one, with a replaceable drug-loaded insert, would be most suitable. Alternative APIs and formulations could be considered.

Potential increases in viral inactivation using a NSDS breastfeeding device (Borkow et al., 2011, 2008). This could be combined with other NSDSs to target other opportunistic infections, such as malaria or tuberculosis. The acceptability of a NSDS for the specific use in preventing MTCT of HIV may also be a viable consideration. For example, vitamin A could be delivered to infants using the NSDS, helping to prevent vitamin A deficiency, which is a major risk factor for HIV infection. Similar inserts could be incorporated into modified bottle teats, allowing equally effective drug delivery to infants fed with formula or expressed milk via a bottle.

Using a NSDS to deliver drugs with formulas or expressed milk via a bottle, effective drug delivery seems more feasible than intravenous administration. Further study will be required to better predict the effectiveness of a given NSDS microbicidal surface in preventing transmission to recipients who are exposed to infection. In addition, any cell-free virus released into the milk may be exposed to the high anti-viral concentrations of SDS in the digestive system at multiple points in the feed. The results of this study suggest that the NSDS may be a viable consideration for preventing MTCT of HIV specifically by inactivating virus during passage through the NSDS. This could be combined with microbicide release to potentially increase viral inactivation within the NSDS, improving the effectiveness of the device in preventing transmission.
formulation offers improved stability over liquid formulations. Drug administration during breastfeeding may also increase the bioavailability of some drugs (Charkoftaki et al., 2010).

Additional benefits of the NSDS in low-resource healthcare settings include simplicity, low cost production, a low level of training needed for correct dosing, potential for a single-use disposable device avoiding requirement for sterilization, and a robust dry formulation for thermostable distribution. Most importantly, with reducing MTCT of HIV, the NSDS is designed to be compatible with breastfeeding, which is often the safest method of infant feeding even when the mother is infected (Brahmbhatt and Gray, 2003).

5. CONCLUSION

A sustained release of the edible microbicide SDS into HIV infected milk during breastfeeding from a NSDS placed over the mother’s breast, is proposed to be an effective method for oral delivery of microbicides to prevent MTCT of HIV. This study has demonstrated that a NSDS can deliver SDS into human milk. The NSDS is especially valuable for use in developing countries where no safer alternative to breastfeeding exists. Future work is needed to fully understand the effects of milk composition on the release of drugs from the NSDS. Modifying the non-woven fiber composition, the addition of cellulose based compounds onto the fiber, or the addition of microbicides and cellulose in fiber construction, may enable controlled release patterns. With better understanding of the sites of transmission in breastfeeding these methods could be adapted to prevent MTCT of HIV.

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Summary of SDS release experiments using cow's, and goat's, milk for constant flow conditions.

**Table 1.**

<table>
<thead>
<tr>
<th>Fluid Type</th>
<th>Pasteurized</th>
<th>Homogenized</th>
<th>Temp (°C)</th>
<th>Pulse Rate</th>
<th>Pulse Volume (ml/pulse)</th>
<th>Total Release (ml)</th>
<th>Initial Load (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow</td>
<td>696.0</td>
<td>0.07</td>
<td>0.042</td>
<td>1.02</td>
<td>1.4</td>
<td>0.030</td>
<td>696.0</td>
</tr>
<tr>
<td>Cow</td>
<td>686.0</td>
<td>0.07</td>
<td>0.032</td>
<td>1.14</td>
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**Table 2.**

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Cross sectional diagram of milk leaving breast passing through nipple shield delivery system insert.
REFERENCES


Figure 2a
Click here to download high resolution image
SDS concentration in milk (wt%)

1 in 10 milk dilution
0.03 to 0.5 wt%

1 in 100 milk dilution
0.5 to 5.0 wt%

Figure 3 - SDS in water

Absorbance 438 nm

0 to 3.0 wt%
1 in 100 milk dilution
0.5 to 5.0 wt%
1 in 10 milk dilution
0 to 3.0 wt%

Figure 3 - Resubmission
Fig. 4.

Cumulative SDS release fraction of input SDS in each fraction (wt%)

ai) SDS insert at 16 ºC
bi) SDS insert at 37 ºC

do) SDS insert at 37 ºC

ei) SDS powders,

milk temperature at:

16 ºC
37 ºC

- 60 pulses/min
- 0.02 ml/pulse
- 0.07 ml/pulse
- 0.45 ml/pulse

Flow rate:

- 2.9 ml/min
- 4.3 ml/min
- 6.0 ml/min

Pulse volume:

- 0.07 ml/pulse

Total volume passed through SDS insert (ml)
Cumulative SDS release fraction of input [SDS] in each fraction (wt%)

(a) Non-homogenized unpasteurized goat's milk 37 ºC

(b) Homogenized pasteurized cow's milk 37 ºC

(c) Non-homogenized pasteurized cow's milk 37 ºC
Fig. 6. Correlated infected H9/HIV-IIIb cellular content (cells/ml x 10⁴) with volume of human milk passed through SDS insert (ml). Lower limit of detection: ND - not detected.