Modeling the Physiological Factors That Affect Drug Delivery from a Nipple Shield Delivery System to Breastfeeding Infants

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ABSTRACT: An apparatus was designed to mimic lactation from a human breast. It was used to determine the influence of milk fat content and flow rate, and suction pulse rate of a breastfeeding infant upon the release of a model compound from a nipple shield delivery system (NSDS). The NSDS would be worn by a mother to deliver drugs and nutrients to her infant during breastfeeding. Sulforhodamine B dye (SB) was used as model compound and formulated as a dispersible tablet to be placed within the NSDS. Increasing suction pulse rate from 30 to 120 pulses/min clearly correlated with increased cumulative release of SB for the same volume of milk passed through the NSDS. No distinct correlation was found between flow rates (1, 5, and 8 mL/min) and SB release, possibly because of competing factors controlling release rate at different flow rates. A highly similar SB release rate into two fat content fluids (2.9 and 4.2 wt %) was observed for identical flow conditions. This proof of concept study outlines a novel method to mimic lactation from a breast, and future studies will lead to effective methods to identify key physiological factors that influence drug release from a NSDS. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:3773–3783, 2013

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INTRODUCTION

Difficulties in Infant Drug Delivery

New drug delivery systems are urgently needed for the treatment of pediatric diseases, especially in developing countries.[1,2] Each year more than 7.6 million children under 5 years die worldwide from diseases that could often have been prevented if they had access to appropriate forms of simple and affordable medicines.[3] Liquid formulations are typically the principal method for pediatric drug administration, but are often not practical in developing countries because of sterility issues, high cost, lack of access to refrigeration, and limited shelf life.[4–6] They may also be unpalatable and contain toxic preservatives and solvents. Solid oral dosage forms for infants are also often scaled down from adult doses, and there is currently a debate on the limitations of clinical work performed to demonstrate suitability of the dose to infant.[7,8] Dispersible tablets can also be used, but require sterile sources of water and administration devices.

Nipple Shield Delivery System

This paper outlines the development of experimental research to guide the design of a recently proposed novel drug and nutrient delivery system intended to be used for breastfeeding infants—a nipple shield delivery system (NSDS).[9,10] This thin disposable device adapted from an existing nipple shield breastfeeding aid is placed over the mother's breast just before infant feeding, and when milk passes through the device it releases the agent to be delivered to the infant via the breast milk. A wide-range of active pharmaceutical ingredients (APIs) could be delivered to infants using the NSDS such as antibiotics, antivirals, antimalarials, vitamins, nutrients, and probiotics while stored in a dry form. The NSDS has the potential to remove many of the issues related to maintaining sterility and stability of drugs delivered to infants in developing countries.

The NSDS would most likely be in a single-use form for low-resource settings, as there may be difficulties in ensuring sterile repeat use. The device will have to be designed to ensure dosage is attained well within all typical feeding behaviors. Future clinical studies will determine the most appropriate device design and technique for effective use to ensure no disruption to the infant's normal breastfeeding behavior. A color indicator, which is only apparent once a critical dose has been delivered, could be contained within the NSDS for the mother to identify when the critical dosage has been achieved.

Previously, the effective delivery of the anti-HIV microbicide sodium dodecyl sulfate from a nonwoven NSDS insert into simulated breastfeeding fluid flow conditions, as well as subsequent inactivation of HIV, has been demonstrated.[10] The potential of antiviral polycationic coatings in a NSDS for use in inactivating the free virus from milk has also been examined.[11]

In the present study, the delivery of a model drug mimic from a tablet placed within the NSDS has been examined using an apparatus that simulates the fluid dynamics of breastfeeding. To our knowledge, there are no previously published details of an apparatus of this form, that mimics the suction of the

Abbreviations: HNM, human nipple mimic; NSDS, nipple shield delivery system; SB, sulforhodamine B.

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infant, and the lactation of milk from a human nipple induced because of this suction. The influence of an infant's tongue during breastfeeding is also an important element to consider and is described in the discussion.

Physiological Factors Influencing Tablet Release from a NSDS

Many physiological factors vary during breastfeeding and between infants and their mothers that may influence the rate of delivery of a therapeutic from a NSDS to the feeding infant (i.e., they influence the dynamic behavior of milk contacting a NSDS tablet containing the drug). These include nipple size and duct structure,[12] feeding behavior allowed by the mother, suction pulse rate of the infant, flow of milk out of the breast,[13] and importantly the potential changes in feeding behavior of the infant in response to foreign tasting agents from the NSDS (which may support the addition of taste-masking excipients to increase acceptability).

This study focuses on the influence of fat content and flow rate of milk, and the suction pulse rate of the infant, three factors known to vary significantly between infants and during a single breastfeed.

Changes in Fat Composition

Human milk's main constituents are fat (triacylglycerol lipid globules with a phospholipid–protein membrane), protein (caseins and whey—including enzymes and immunoglobulins), and several forms of carbohydrates (primarily lactose).[14–16] The fat content in breast milk has been reported to increase up to threefold within a feed with typical ranges between 2 and 6 wt %.[17,18] Studies by Khan et al.[19,20] that collected the foremilk and hindmilk (the beginning and end of a breastfeed) from human breastfeeding also observed a significant increase in fat content between samples collected from individual donors, but no statistically different change in either protein (casein, whey, and skim milk) or lactose content during a feed. Also, within a single day, the average fat composition of milk has been shown to vary significantly depending on infant feeding behavior, whereas protein and lactose contents remained stable. It is also important to note that significant variations in milk contents between individual infant-mother pairs may occur at the same stage postpartum.[20] Over the first 30 days of life, the average total protein and lactose content significantly decreases and fat content increases, after which time all three compositions remain relatively stable.[21–24]

Suction Rate of Infant

Typical suction rates in breastfeeding upon the onset of nutritive sucking (i.e., significant flows of milk leaving the breast) have been reported to range typically between 40 and 120 suction pulses/min, although this can vary depending on the stage of the feed and infant.[13,25,26] A typical feed volume has been shown to be approximately 50 –80 g ingested over 7 – 10 min.[18,27,28]

Flow Rates of Milk from Breast

Flow rate also significantly changes depending on the infant and the phase of the feed. A previous review of breastfeeding behavior reports that volumes of milk intake can vary significantly between 0.01 and 0.14 mL/suction pulse, which when correlated against suction pulse rates of 40–120 pulses/min gives potential average flow rates of 0.4 –16.8 mL/min.[13]

Study Aims

The present proof of concept study investigated the effect of typically reported values of milk fat content and flow rate, and infant suction rate in breastfeeding upon the delivery of a model compound in a tablet placed inside an NSDS. This was performed using an apparatus that simulates the pressure conditions, average flow rate, fluid motion, and composition of milk as it leaves a nipple and passes through a NSDS.

MATERIALS AND METHODS

Adapting Nipple Shields to Contain Tablets

Nipple shield delivery system prototypes were made by adapting an existing commercial nipple shield to hold a tablet. A nipple shield (Maternity Silicone Nipple Shields, Boots, Cambridge, UK) had a 15-mm outer diameter O-ring (3.9 mm thick, 9.5 mm inner diameter) with a fiberglass mesh (1.4 mm square spacing with 0.4 mm fiber diameter) sealed inside the nipple shield using silicone (Platsil Gel 00, Mouldlife, Suffolk, UK) at 9 mm from the inside tip of the nipple. The mesh was placed on the side of the O-ring nearest to the inside of the nipple shield in order to allow a tablet to sit within the O-ring in the shield. This allowed tablets to be accurately positioned in the same location for experiments. The nipple shield had four evenly spaced 1 mm holes around the nipple to allow milk to pass out of the device. An additional eight evenly spaced holes of the same diameter to the existing holes were added 5 mm further down the nipple to increase the release of the disintegrated tablet from the device (see Fig. 1). Preliminary experiments indicated that without these additional holes a build up of fragmented tablet within the shield reservoir occurred.

NSDS Tablets Used

Round-faced tablets (0.33 g, 8 mm diameter) were formulated by direct compression using a Manesty F3 tablet press (Manesty, Liverpool, UK) and a biconcave punch and die set (Holland, Nottingham, UK) with a crushing strength of 80 N. A dispersible formulation was used to maximize the likelihood of API delivery well within a typical breastfeed (up to ~80 g).[18] Sulforhodamine B (SB) (Sigma–Aldrich, Dorset, UK), a highly soluble red dye monosodium salt, was used as a model API. The dye was found to be accurately detected in milk using a spectroscopic assay without additional sample manipulation, with a peak absorbance at 554 nm. Tablet excipients used were based on typical pharmaceutical requirements for a fast disintegrating tablet using direct compression.[29] Tables 1 and 2 outline the composition, excipient role, and the results of standard European Pharmacopeia physical testing performed on the tablets.

Simulation of Milk Flow from a Human Nipple

A silicone human nipple mimic (HNM) was constructed with ducts to simulate the flow of milk leaving a breast induced from an infant's suction. The silicone nipple shape was formed out of a polyurethane mold from epoxy modeling board (constructed using a computer-aided design high-pressure waterjet). This produced a hemisphere with a 12-mm diameter based on a typical size of a nipple.[12] A square grid of 25 equally spaced stainless steel needles held apart using a plastic mesh was also placed into the mold when the silicone (Platsil Gel 00; Mouldlife) was poured in. The needle number, size, and spacing were based on