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Original Article

Development of a physiologically relevant dripping analytical method using simulated nasal mucus for nasal spray formulation analysis ☆

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ABSTRACT

Current methods for nasal spray formulations have been elementary evaluating the dripping characteristics of a formulation and have not assessed the behavior of the nasal formulation in the presence of varying types of mucus depending on the indication or diseased state. This research investigated the effects of nasal mucus on the dripping behavior of nasal formulations and focused on developing an improved in vitro analytical test method that is more physiologically relevant in characterizing nasal formulation dripping behavior. Method development was performed using simulated nasal mucus preparations for both healthy and diseased states as coatings for the dripping experiment representing a wide range of viscosity. Factors evaluated during development of this in vitro test method included amount of mucus, application of mucus, drying times, and compatibility of the mucus on a C_{18} Thin Layer Chromatography (TLC) substrate. The dripping behavior of nasal formulations containing a range of 1% Avicel to 3.5% Avicel was assessed by actuating the nasal spray on a perpendicular TLC plate coated with either healthy or diseased simulated nasal mucus. After actuation of the nasal spray, the dripping of the formulation on the coated TLC plate was measured after the plate was repositioned vertically. The method that was developed generated reproducible results on the dripping behavior of nasal formulations and provided critical information about the compatibility of the formulation with the nasal mucus for different diseased states, aiding in nasal spray formulation development and physical characterization of the nasal spray.

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1. Introduction

Physiologically, the nasal mucosa naturally produces an abundance of nasal mucus when in a healthy state for purposes of protecting the nasal mucosa from drying out and trapping unwanted substances. Excessive nasal mucus may be secreted by patients suffering from allergic rhinitis, sinusitis and the common cold. Nasal mucus roughly consists of 95% water, 2.5% glycoproteins, 1%–2% electrolytes and other still incompletely defined components among which are lysozyme, lactoferrin, complement, and possible liquid fractions similar to surfactant [1–3]. The qualitative and quantitative features of the glycoproteins are primarily responsible for the rheological properties of the nasal secretions [4–6]. Important rheological features of mucus include viscosity, elasticity, adhesiveness, and the ability to be spun ("spinability") and poured ("pourability") [7].

Nasal spray is a unique drug delivery means that has been widely used to deliver medication to the intranasal cavity to treat numerous topical diseases such as allergic rhinitis, sinusitis, and nasal congestion for those suffering from the common cold. Other emerging applications of nasal sprays include vaccination delivery and the treatment for migraine via intranasal delivery. Formulation adherence to mucosa (e.g. residence effectiveness in the nasal cavity) and patient comfort are important factors often considered during nasal spray formulation development. A non-dripping form of a nasal spray formulation has been developed usually containing thixotropic agents such as microcrystalline cellulose to achieve the desired viscosity profile resulting in lower viscosity when shear stress is applied and increasing viscosity in its absence. Analytical methods assessing the dripping behavior of nasal spray formulations have not been commonly used for formulation development. A simple invitro method of employing a paper sheet as the spray substrate has been developed to assess the dripping behavior of nasal spray formulations and is also used to guide formulation development. However, this method hardly predicts or correlates with how the nasal spray formulation behaves inside the nasal cavity. Perhaps besides anatomical structure of the human nose, the most significant factor that should be considered is the interaction of the formulation with nasal mucus. Furthermore, mucus characteristics vary depending on the type and stage of

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diseases, ranging from watery and runny for healthy subjects and those exhibiting allergic rhinitis, to thick and viscous for a patient suffering from chronic sinusitis [8,9]. Current methods in the laboratory evaluating the nasal dripping characteristics of a formulation are elementary and do not assess the behavior of the nasal formulation in the presence of varying types of mucus depending on the indication or diseased state.

Therefore, the goal of this research was to investigate the effects of nasal mucus on the dripping behavior and physical properties of nasal formulations, and to develop an improved invitro analytical test method that is more physiologically relevant in characterizing nasal formulation dripping behavior generating reproducible results. The ultimate objective was to support formulation development by formulating a nasal spray for compatibility with the nasal mucus associated with a particular diseased state or indication for which the nasal spray is intended. To evaluate the interaction of formulation and nasal mucus, healthy simulated nasal mucus and diseased simulated nasal mucus were selected as coatings for the development of an analytical dripping method.

2. Experimental

2.1. Materials

Various types of dyes including allura red AC, methylene blue, alcian blue GX, congo red and crystal violet were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Nano Silica TLC plates, Cellulose Plastic TLC plates, and Cellulose Aluminum TLC plates were all sourced from Sigma-Aldrich (St. Louis, Missouri, USA). The microcrystalline cellulose (Avicel) was sourced internally from Merck MSD (Rahway, New Jersey, USA).

For the preparation of healthy simulated nasal mucus, porcine mucin type II, sodium chloride, and potassium chloride were all sourced from Sigma-Aldrich (St. Louis, Missouri, USA) and the calcium chloride dihydrate was sourced from Fisher Scientific (Fair Lawn, New Jersey, USA).

For diseased simulated nasal mucus, locust bean gum (LBG), saline solution, and sodium dodecyl sulfate (SDS) were sourced from Sigma-Aldrich (St. Louis, Missouri, USA), Bio-world (Dublin, Ohio, USA), and Invitrogen (Carlsbad, California, USA), respectively.

2.2. Instrument and characterization

A stainless steel actuation apparatus for nasal sprays was designed by Merck Engineering for this dripping study (Fig. 1). The apparatus was designed to seat a nasal spray device with the ability for manual actuation, taking into account stroke length for the nasal spray bottle. It also had a metal plate with an affixed TLC plate that can be positioned perpendicular to the nasal spray bottle during actuation and then repositioned 90 degrees vertically after actuation for evaluation of dripping behavior. The distance between the nasal spray tip and this metal plate was set at 3 cm. A digital camera was placed horizontally across from the stainless steel apparatus at a fixed distance and used to record the nasal formulation dripping time-elapse profile.

In addition, characterization of the simulated nasal mucus was performed by testing viscosity and surface tension. The surface tension was evaluated on a Kruss DSA-3 Surface Tension Analyzer in pendant drop mode (single drop measurement). The viscosity of each of the coatings and formulations were determined on a Brookfield Viscometer DV-II Pro. A 5 mL sample was transferred into the sample cup and equilibrated for 30 min in an undisturbed water bath at 37 °C. Rotations at 100 rpm were started after the 30 min and measurements were recorded at 0, 5 and 10 min. A

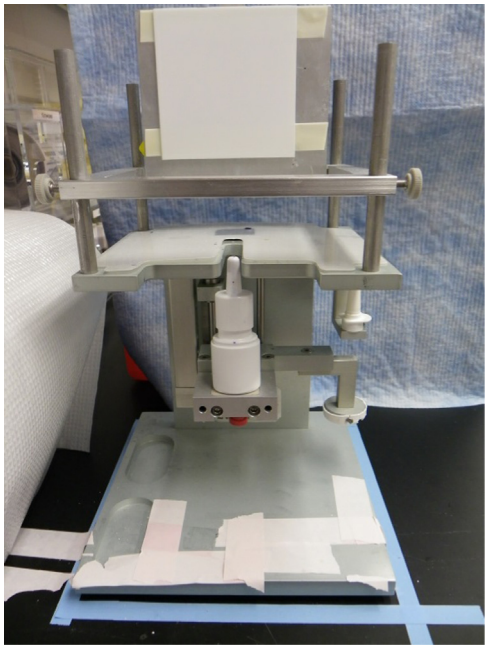

Fig. 1. Nasal spray apparatus.

Spraytec® laser diffraction system (Malvern Instrument Ltd., Westborough, MA) measured the droplet size distribution of the nasal sprays. The SprayView NSP system equipped with a high-speed camera (Proveris Scientific Corp., Westborough, MA) measured spray pattern of the nasal sprays.

2.3. Nasal formulation preparation

Six placebo formulations were prepared for this study containing varying amounts of Avicel (1%, 1.5%, 2%, 2.5%, 3% and 3.5% (m/m)). A stock solution was made by gradually charging 40 g of Avicel to 800 g of water in a steel compounding vessel (temperature 25 ± 5 °C) and continuously mixed at 350 rpm while recirculating through an in-line homogenizer (IKA Ultra Turrax T25) at a flow rate of 1 L/min for 30 min. After 30 min, 200 g of water was added to the compounding vessel and continued mixing for another 10 min. Variable amounts of stock solution and water were combined to achieve each of the desired concentrations of Avicel. Dye was added to each formulation at a concentration of 0.05% (m/m) followed by agitation once more at 350 rpm for 10 min. The final formulation was filled into a nasal spray bottle with a spray pump to deliver 100 μL per actuation.

2.4. Simulated mucus preparation and coating

Healthy nasal mucus was simulated by preparing a solution of porcine mucin in buffer exhibiting properties such as watery and non-viscous [10]. Conversely, a type of mucus that may exemplify a diseased state such as chronic sinusitis displaying highly viscous properties was simulated by a preparation of LBG and SDS in saline solution [11]. The healthy simulated nasal mucus was prepared by adding porcine mucin type II to a buffer solution consisting of 7.5 mg/mL of sodium chloride, 1.3 mg/mL of potassium chloride, and 0.3 mg/mL of calcium chloride dihydrate to attain an overall concentration of porcine mucin of 8% (m/m) in buffer. The diseased simulated nasal mucus was prepared by heating a beaker containing 100 mL of saline solution and SDS at a concentration of 6 mM to 80 °C. Once the solution reached a temperature higher than 70 °C, the LBG was slowly added while mixing until a final temperature of 80 °C was attained and the LBG was dissolved.

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