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European Journal of Pharmaceutics and Biopharmaceutics 63 (2006) 310–319
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

# Parameters affecting the drug release from in situ gelling nasal inserts

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Received 18 July 2005; accepted in revised form 28 November 2005
Available online 2 March 2006

**Abstract**

The purpose of the study was to investigate the influence of physicochemical drug properties, drug loading, and composition of the release medium on the drug release from in situ gelling nasal inserts. Sponge-like nasal inserts of carrageenan and HPMC K15M with the model drugs oxymetazoline HCl, diprophyllin, and acetaminophen (APAP) were prepared by lyophilization. Drug release studies at different drug loadings were performed in various release media. Raman analysis, DSC, and SEM were conducted to analyze the physical state of the drugs in the inserts. All drugs were dissolved in the solid HPMC inserts and were released at similar rates at all investigated loadings except for the least soluble APAP. APAP concentrations in the hydrating HPMC K15M inserts in excess of its solubility limit resulted in reduced relative release rates at higher drug loadings. Drug–polymer interactions (formation of less soluble drug–polymer salts) resulted in a slower release of oxymetazoline HCl from carrageenan inserts than from HPMC K15M inserts. Changes in the composition of the release medium affected the water uptake of carrageenan but not of HPMC K15M inserts. Oxymetazoline release from carrageenan inserts increased with higher $Na^+$-content of the medium because of ion exchange and at low (pH 2) as well as at high pH (pH 10). The osmolality of the release medium had no effect. The solubility of the drug, its physical state in the polymer matrix, and drug–polymer interactions governed the drug release from nasal inserts. The release from inserts prepared with oppositely charged polymers and drugs was influenced by electrostatic drug–polymer interactions and by the composition of the release medium.


*Keywords:* Carrageenan; Drug–polymer interaction; Extended drug release; HPMC; Inserts; Nasal drug delivery; Release medium

## 1. Introduction

Nasal inserts have previously been described as a promising drug delivery system [1–3]. This solid dosage form, which is prepared by lyophilization, consists of a sponge-like hydrophilic polymer matrix, in which the drug is embedded. It allows easy dosing with a high potential for systemic administration under circumvention of the harsh conditions of the gastrointestinal tract and the hepatic first pass metabolism [4]. Once in contact with the highly vascularized nasal mucosa, the polymer sponge takes up water and rapidly forms a gel from which the pharmaceutically active ingredient is released in a controlled fashion. The use of bioadhesive polymers ensures a prolonged nasal residence time for extended release application.

Although the nasal mucosa allows the delivery of higher molecular weight drugs, such as proteins and DNA [5–8] low molecular weight model drugs were used in the present study to elucidate the embedding of the drug in the polymer matrix, possible drug–polymer interactions, and the release mechanism.

Besides the properties of the drug and the delivery system, the physiological conditions of the nasal cavity can also influence the performance of the system. The pH of the nasal fluid is normally around 5.5–6.5 but depends on air temperature, sleep, emotions, and food ingestion [9,10]. An increase in pH to 7–9 during acute and allergic rhinitis, rhinirhea, and chronic and acute sinusitis was observed [11,9]. Also diabetes mellitus influences the nasal

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doi:10.1016/j.ejpb.2005.11.008

pH [12]. Inhalation of cold, dry air can act as a physical stimulus to induce symptoms of rhinitis that are associated with an increase in osmolality from 280 to 290 to ≈310 mosm/kg [13]. Stimulation of the nasal gland secretion with chilli powder was reported by [14] to reduce the osmolality to approximately 238 mosmol/L. The same authors also found changes in the sodium and potassium ion content of the nasal secretion. Pathological conditions also affect the viscosity and viscoelasticity of the nasal mucus as well as the ciliary beat frequency [15,16].

The variability in the composition and properties of the nasal fluid can greatly influence the performance of a nasally administered drug delivery system [4,17].

Besides the effect of the drug properties (molecular weight, solubility, and drug–polymer interaction) and drug loading, this study also investigated the influence of the release medium (osmolality, sodium ion content, and pH) on water uptake and drug release properties of in situ gelling nasal inserts.

## 2. Materials and methods

### 2.1. Materials

Model drugs: oxymetazoline hydrochloride (Procter & Gamble Pharmaceuticals Germany, Weiterstadt, Germany); diprophyllin (Knoll AG, Ludwigshafen, Germany); acetaminophen (APAP, Synopharm GmbH, Barsbüttel, Germany). Polymers: ι-carrageenan (Genuvisco carrageenan type TPH-1, Copenhagen Pectin A/S, Lille Skensved, Denmark); hydroxypropyl methylcellulose (HPMC, Methocel K15M, Colorcon Ltd., Dartford, UK). All other excipients were of pharmaceutical grade. Purified water was used as a solvent if not otherwise stated.

### 2.2. Insert preparation

Polymers (2% w/w) and drug (5%, 10%, 20%, 30%, 40%, 50%, 60%, and 100% on polymer mass, w/w) were dissolved in purified water. Aliquots ($V = 1.5$ or 0.1 ml) were placed into blister molds and frozen at −25 °C for 1 h. The samples were then freeze-dried (0.25 mbar for 24 h with increasing shelf temperature −15 to 0 °C and a final drying for 2 h at +15 °C and 0.01 mbar) (Gamma 2-20, Martin Christ Gefriertrocknungsanlagen GmbH, Osterode am Harz, Germany). The inserts were stored in a desiccator until use.

### 2.3. Water uptake

A sponge (5 cm × 6.5 cm × 3 cm, Santex household sponge, Santex GmbH, Wald-Michelbach, Germany) was fully soaked in the hydration medium (phosphate buffer, pH 6.0, USP XXVII) and placed in a petri dish filled with the same buffer to a height of 1 cm in order to keep the sponge soaked during the experiment. Round filter paper ($d = 55$ mm, Schleicher & Schuell GmbH, Dassel, Germany) was also soaked in the medium and positioned on top of the sponge. This experimental set-up was equilibrated for 30 min. Accurately weighed inserts ($V = 1.5$ ml) were then placed on the filter paper and the water uptake was determined as weight increase of the insert (weight of hydrated insert and filter paper minus weight of wet filter paper) over time normalized to the initial dry insert weight ($n = 3$).

Different buffers were used as medium. For the investigation of the effects of medium composition, phosphate buffer, pH 6.0 (USP XXVII), was adjusted to the chosen osmolality by addition of sorbitol (Osmomat 030, Gonotec Gesellschaft für Meß- und Regeltechnik mbH, Berlin, Germany). Sodium ion content was adjusted by addition of sodium chloride. Alkaline borate buffer, pH 10 (USP XXVII), and hydrochloric acid buffer, pH 2 (USP XXVII), were used with the necessary adjustments of osmolality and sodium ion content. The potassium ion content was constant at 0.05 mol/L in all buffers and no other positively charged ions were present.

### 2.4. In vitro drug release

A self-made diffusion cell was used for drug release studies mimicking the humidity properties of nasal mucosa. It consisted of a release medium container (20–80 ml phosphate buffer, pH 6.0, USP XXVII) into which a tube of 3.5 cm inner diameter was inserted. The lower end of the tube was closed with a tightly stretched, thin sponge and adjusted exactly to the height of the release medium surface so that the sponge was wetted but not submersed. Inserts ($V = 1.5$ ml) were placed on the thin sponge and the whole system was closed with Parafilm® "M" sealing film (American National Can Company, Chicago, IL, USA) to avoid evaporation of release medium and to allow the establishment of a constant relative humidity around the insert. The experiments were performed in a horizontal shaker with 75 rpm and at 37 °C. Samples of 2 ml were taken at predetermined time points and replaced by fresh medium. The drug content of the samples was analyzed by UV spectrophotometry (oxymetazoline HCl: $\lambda = 280.0$ nm, diprophyllin: $\lambda = 273.5$ nm, and APAP: $\lambda = 243.6$ nm, UV-2101 PC, Shimadzu Deutschland GmbH, Duisburg, Germany). Drug-free inserts were also subjected to the drug release test to quantify the contribution of the polymers to the UV-absorption. At each time point this value was subtracted from the value of the drug-loaded inserts. The actual drug loading of the inserts was determined by complete dissolution of inserts in phosphate buffer, pH 6.0 (USP XXVII), followed by UV analysis. The contribution of the polymers to the UV-absorption was substracted. All drug release experiments were performed in triplicate (mean ± SD) and under sink conditions ($c_{\max \text{ in medium}} < 10\%\ c_{\text{saturation}}$).

### 2.5. Raman spectroscopy

Carrageenan and oxymetazoline HCL powders were analyzed in a capillary while the inserts (carrageenan 2%