Changes in the Mucoadhesion of Powder Formulations after Drug Application Investigated with a Simplified Method

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ABSTRACT: The residence time in the nasal cavity can be prolonged by dry particles that absorb water and subsequently increase the viscosity of the mucus layer. A novel nasal drug delivery system based on interactive mixtures has previously been developed, where fine particles of the active component are adhered to the surface of mucoadhesive carrier particles by dry mixing. The surface coverage may alter the original mucoadhesiveness of the carrier particles and to investigate this, a simplified tensile strength method was developed and evaluated. Reliable results were obtained with a plastic coated absorbent paper covered by a mucin solution as a substitution for porcine nasal mucosa and should also be applicable to other dry particle systems. The method showed that the swelling of sodium starch glycolate particles was slightly delayed, corresponding to the degree of hydrophobic surface coverage. Carrier particles of partly pregelatinized maize starch were not influenced by the addition of a hydrophobic substance, probably because of the rough particle shape that inhibited a complete surface coverage. It was concluded that the surface coverage of carrier particles in interactive mixtures only could cause a short delay in water absorption that should not affect their mucoadhesive characteristics *in vivo*. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:3855–3864, 2008

Keywords: mucosal drug delivery; nasal drug delivery; powder technology; in vitro models; residence time; microparticles; mucoadhesion; texture analyzer

INTRODUCTION

The struggle to achieve improved bioavailability and/or prolonged residence time has led to an increased interest in mucoadhesion during the past decades. The nasal route of administration is well suited for mucoadhesive delivery systems since the nasal mucosa has an air interface, which gives the opportunity to combine mucoadhesive characteristics with an increased viscosity that will slow down the mucociliary clearance;[1,2] comparatively simple mucoadhesive systems comprising of dry and swellable particles can thereby be used. The nasal mucus layer is otherwise transported to the nasopharynx at a speed of approximately 6 mm/min, resulting in a residence time of about 20 min.[3] Transfer across the nasal respiratory epithelium leads to systemic absorption without hepatic first-pass metabolism and a decelerated clearance to the throat and stomach could thus increase the drug bioavailability significantly.

The mechanisms behind mucoadhesion have been widely discussed and are better described elsewhere, see, for example, the review by Smart.[4] For a dry powder system, the hydration of the formulation by water movement from the mucosa seems to be the predominant cause of mucoadhesion.[5] Several methods have been developed to

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evaluate the mucoadhesiveness of pharmaceutical formulations;[6] perhaps the most common technique is based on detachment measurements, where the force needed to detach the formulation from the mucosa is determined. The results will reflect the weakest point of the system, which can be one of three possibilities: the mucus layer, the formulation or the interfacial region between the mucus layer and the formulation. A tensile strength method for measuring the mucoadhesion of polymer gels using porcine nasal mucosa has previously been developed and extensively evaluated in our research group.[7,8] The method may be further simplified for measurements on dry particles, as it has been shown that the mucosa is of minor importance for the immediate mucoadhesive characteristics of swelling particle systems.[9,10]

A novel dry particle system for nasal drug delivery, which consists of interactive mixtures with a fine particulate mucoadhesive carrier, has been developed.[11] Sodium starch glycolate (SSG) was used as carrier particles owing to its excellent capacity for absorbing water and its good flowability, which enables the formation of interactive units even in a size range suitable for nasal administration, that is, down to 30 μm. The interactive units are formed when micronized particles adhere to the surface of the coarser carrier particles during dry mixing. This technique has previously been used to add micronized mucoadhesive particles to the surface of inert tablet excipients such as mannitol[12] and it was shown that the mucoadhesion of the interactive units increased until the carrier was completely covered with mucoadhesive material. As the present delivery system consists of a mucoadhesive carrier covered by inert particles, it may result in the opposite relationship between surface coverage and mucoadhesion.

The duration of mucoadhesion could be benefited by a powder formulation with a slow fluid absorption.[13] However, such a powder would also be more sensitive to surface coverage and to investigate this effect, partly pregelatinized maize starch (PPS) was included in the study as a plausible mucoadhesive carrier with a less extensive capacity for absorbing fluids.

A straightforward *in vitro* technique with a well defined mucosal substitute to give a decreased variability would be of substantial use when evaluating changes in the mucoadhesive characteristics after addition of a drug. The aims of this study were thus to develop a simplified tensile strength method for screening the immediate mucoadhesion of dry particle systems of different swellability and evaluate it by comparing the results with measurements on porcine nasal mucosa. The final objective was to investigate the effect of surface coverage on the mucoadhesive characteristics of SSG and PPS.

MATERIALS AND METHODS

Materials

Sodium starch glycolate (SSG, Primojel®, DMV International GmbH, Veghel, The Netherlands) and partly pregelatinized maize starch (PPS, Starch 1500®, Colorcon, Kent, UK) were used as mucoadhesive materials. Sodium salicylate (Sigma–Aldrich, Stockholm, Sweden) and oxazepam (Wyeth, Münster, Germany) were used as model substances for freely and poorly soluble drugs, respectively, and magnesium stearate (Kebo, Huddinge, Sweden) was chosen to create a complete hydrophobic surface coverage as a theoretical worst case scenario.

Krebs Ringer Bicarbonate buffer (KRB) from Sigma–Aldrich was supplemented with 15 mM $NaHCO_3$, 1.2 mM $CaCl_2$ and 138 mM NaCl. Porcine gastric mucin type II (PgmII) was purchased from Sigma and was dispersed in KRB to different concentrations (w/w). All chemical substances were of analytical grade.

Preparation and Characterization of Test Materials

The SSG was dry sieved between 45 and 32 μm (Retsch, Haan, Germany) and the corresponding size fraction of PPS was obtained with an air classifier (100 MZR, Alpine, Ausburg, Germany). The particle sizes were measured with laser diffraction analysis (LS 230, Coulter, Miami, FL, USA). The specific surface area of SSG was determined using steady state permeametry[14,15] and calculated according to Eriksson et al.[16] The theoretical surface coverage was calculated as the ratio of projected external surface area of the micronized substance to the total external surface area of SSG, according to Nyström et al.[17] Glass beads were dry sieved between 63 and 45 μm to obtain a negative standard in approximately the same particle size.

Oxazepam was milled in a pin disc mill (Alpine, 63 C) and sodium salicylate in a mortar grinder (Retsch). The finest fractions of the two materials