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Local delivery of clotrimazole chitosan films and gels for oral candidiasis

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Topical delivery of antimicrobial agents is the most widely accepted approach aimed at prolonging active drug concentrations at mucosal layer in oral cavity. As most antifungals do not posses an inherent ability to bind to the oral mucosa, this is best achieved through improved formulations. Chitosan, a partially deacetylated chitin, which is a biologically safe biopolymer, prolongs the adhesion time of oral gels and drug release from them. Chitosan also inhibits the adhesion of *Candida albicans* to human buccal cells and has antifungal activity. The antifungal agent, clotrimazole (CLZ), also reduces *C. albicans* adhesion to oral mucosal cells. The aim of this study was to design a formulation containing chitosan film and gel for local delivery of CLZ to the oral cavity. Chitosan films and gels (1 and 2% concentration) containing 0.1, 0.2 and 0.4 % of CLZ were prepared. Chitosan was allowed to swell in lactic acid 1% to form gel. Medicated and non-medicated films of chitosan were prepared by casting mixture of chitosan gel and 5% glycerine (plasticizer). Prepared films were crosslinked with 0.1% TPP. The prepared films and gels studied for film thickness, water absorption capacity, viscosity, in-vitro drug release and antifungal activity. The films were found to have high water absorption capacity and gels exhibit pseudoplastic flow with drug incorporation does not have significant effect. Increasing the chitosan concentration from 1 to 2% resulted in an decrease in CLZ release in chitosan gel. Release of CLZ from gels was maintained for 4 h. The amount of CLZ released was decreased with cross-linking in chitosan films. When 0.2% CLZ was incorporated into films, the percent released from free and crosslinked films was 40 and 22%, respectively. A prolonged release was observed with film formulation. No lag-time was observed in release either from gels or films. The antifungal activity of CLZ increased with increasing concentration of chitosan in the gels and films. The highest antifungal activity was obtained with 2% chitosan gel containing 0.2% CLZ. It is concluded that film formulations gave prolonged release with films remaining intact up to 4 h, which might be advantageous for periodontal therapy in future with lower concentrations of antimicrobial agents.

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Alginate-chitosan beads: determining the influence of processing parameters on bead formation

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Both alginate and chitosan based carriers have been used medically in drug delivery systems and wound dressings. In this project, gel beads composed of an alginate-chitosan polyelectrolyte complex intended for controlled drug release were prepared. To control the release of an encapsulated drug for optimal therapeutic effects, control of the size and shape of the beads is critical. To establish the influence of processing parameters on bead size and shape, a series of experiments were devised using experimental design techniques. The effects of these parameters were assessed by both optical microscopy and mathematical modelling. Following the bead preparation protocol outlined by Anal & Stevens (2005), experimental parameters which in theory could influence the size and shape of the beads produced were established. Using the software package 'Statistica' a series of experiments were designed in which each of these parameters were varied. The analysis was carried out on coded variables, in which all the values were between −1 and 1. The products resulting from each of the experiments fell into one of four categories described by the following 'shape numbers': (1) spherical beads, (2) irregular shaped beads, (3) gel clumps and (4) stringy gel. The sizes of the beads produced varied from between 640 μm to 1668 μm. The sizes of the subset of the spherical beads produced was found to fit a theoretical 2nd order polynomial equation ($R^2 = 0.992$), developed using surface analysis methodology, in which predicted bead sizes and the significance of the processing parameters were determined mathematically. It was found that the trend observed experimentally for the processing parameters correlated well with the predicted results. For instance, an increase in flow rate was seen to reduce bead size, which was also seen for the predicted coefficient values where a negative result was acquired. This relationship holds for the other parameters, with the exception of combination effects (for example tip distance and flow rate, needle gauge and flow rate) in which no obvious correlation between the experimental data and the predicted bead sizes was observed. Both experimental design and polynomial modelling assisted in the determination of the processing parameters that influenced bead formation, shape and size. The data used in polynomial model development was limited due to the inability to quantify the non-spherical bead formations. The work presented will include additional experimental work included to refine the model developed.

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Particle aggregation of salmeterol xinafoate (SX) in HFA134a high pressure suspensions

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The optimum aerodynamic size range of particles for the topical treatment of pulmonary disease is generally accepted as being 2.5–6 μm (Pritchard 2001).

Particles of this size range are usually produced by air-jet milling, a high-energy process that can produce disturbances in crystallinity (amorphous regions) as well as polymorphic conversion. The occurrence of either phenomenon is likely to affect product performance. An alternative strategy might be to directly crystallize the drug, restricting crystal growth to the micron range, since this would provide the opportunity to avoid potential crystal modification during processing (Murnane et al 2005). The aim of this work was to assess the aerodynamic performance of a pressurized metered dose inhaler of SX produced by micronization and crystallization from an aqueous phase. The particle size distributions of micronized SX (a gift from GlaxoSmithKline, UK), and SX microcrystals (produced as previously reported by Murnane et al (2005)), were determined by laser diffraction using the Malvern Mastersizer X. SX (0.096% w/w) suspensions in 1,1,1,2,-tetrafluoroethane (HFA 134a; Solvay, Germany) were prepared in aluminum or PET canisters sealed with either DF31/63 RCU CS or continuous 20 mm valves (Valois, UK). SX was weighed into the canisters, which were filled under pressure after crimping to final weight with HFA 134a using a propellant filling unit (Pamasol, Switzerland). The particle size distribution of the SX suspensions was determined using a Malvern Mastersizer X and a pressure cell system engineered in-house to allow continuous recirculation at varying shear rates (Jones et al 2005). The in vitro aerosol performance was assessed using a twin stage impinger (TSI) coupled with HPLC analysis. Powder density was determined by helium pycnometry (Accupyc, Micromeritics, UK). Differential scanning calorimetry (DSC 2920; TA Instruments, UK), determined by heating hermetically sealed samples at 2°C min^{-1} showed the crystallized material to have improved polymorphic purity compared to the micronized material. There was no significant difference ($P > 0.117$; t-test) between the median diameters ($D_{(v, 0.5)}$) of the micronized and crystallized material (Table 1). However there was a significant difference in the cumulative 90% undersize ($D_{(v, 0.9)}$) indicating that the size distribution of the crystallized material tailed towards larger particle sizes. This was confirmed by the smaller fraction of crystallized SX particles calculated as having an aerodynamic diameter below 6.4 μm. The median diameters of the SX/HFA suspensions indicated that the primary particles for both the micronized and crystallized material aggregated in suspension (Table 2). However, there was no significant difference between the resultant median diameter or between the % <6.4 μm calculated from laser diffraction data, for either inhaler. Nevertheless, TSI results indicated a higher fine particle fraction (% < 6.4 μm) was obtained from the suspended micronized particles than when crystallized SX was employed. The aggregation of salmeterol xinafoate particles in HFA-based pMDIs and de-aggregation upon actuation appeared to be a key determinant of respirable fraction. Although the crystallized material displayed the higher polymorphic purity, the tailing size distribution appeared to be the source of the decreased fine particle fraction.

Table 1 Particle size distribution and density of micronized and crystallized salmeterol xinafoate

Raw material	$D_{(v, 0.5)}$ (μm)	$D_{(v, 90)}$ (μm)	Density (gcm^{-3})	% < 6.4 μm (calc.)
Micronized	1.13 ± 0.12	3.69 ± 0.23	1.239 ± 0.058	97.7 ± 0.5
Crystallized	1.23 ± 0.06	8.72 ± 0.22	1.308 ± 0.017	76.8 ± 1.1

Data are means ± s.d., n = 5.

Table 2 Particle size characterization and aerodynamic assessment of HFA-based suspension inhalers of salmeterol xinafoate

Inhalers	$D_{(v, 0.5)}$ (μm)	% < 6.4 μm (calc.)	% < 6.4 μm (TSI)*
Micronized	6.69 ± 1.44	42.6 ± 11.6	45.74 ± 2.28
Crystallized	8.98 ± 1.32	32.0 ± 5.5	26.26 ± 2.37

Data are means ± s.d., n = 3, *n = 4.

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Adjustment of drug release kinetics from ethylcellulose-coated pellets

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Polymeric film coatings are frequently used to control the release rate of a drug out of a pharmaceutical dosage form. Showing good oral biocompatibility and film forming properties, ethylcellulose is a suitable polymer for this purpose. However, continuous ethylcellulose films are poorly permeable for many drugs (Siepmann et al 1999), resulting in low release rates. To overcome this restriction, hydroxypropylmethylcellulose (HPMC) has been proposed as a pore former accelerating drug release (Frohoff-Huelsmann et al 1999) but relatively high quantities are required and the presence of HPMC in the coating dispersions causes coagulation. The major objectives of this study were: to effectively adjust desired drug release patterns from ethylcellulose-coated pellets by adding small amounts of a water-soluble polymer, without affecting the stability of the coating dispersions; and to study the effects of different curing conditions (temperatures, time periods and relative humidities) on the resulting drug release kinetics. Theophylline-loaded matrix cores were coated in a fluidized bed coater with aqueous dispersions of ethylcellulose (Aquacoat ECD, plasticized with 25% triethylcitrate), with or without adding small amounts of a poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer (Kollicoat IR). The pellets were cured for 24/48 h at 60°C and ambient relative humidity (RH); or for 24/48 h at 60°C and 75% RH (followed by 24 h at 60°C and ambient RH). In vitro drug release was measured in 0.1 M HCl and phosphate buffer pH 7.4 at 37°C in a USP paddle apparatus. Importantly, the addition of only small amounts of the poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer to ethylcellulose-based film coatings significantly accelerated drug release from the coated pellets, irrespective of the pH of the release medium. For instance, 0, 2, 11, 64 and 96% theophylline were released after 4 h exposure to phosphate buffer pH 7.4 from pellets coated with ethylcellulose-based films containing 0, 5, 10, 15 and 20% of the poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer (coating level: 10%, curing conditions: 24 h at 60°C and ambient RH). This can be attributed to a significant increase in the water uptake of the film coatings and to the leaching of the water-soluble polymer out of the films into the bulk fluid. Both effects result in increased permeabilities of the coatings for the drug. In contrast to the addition of HPMC, the presence of the poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer did not affect the stability of the coating dispersions. Interestingly, the type of investigated curing conditions did not significantly alter the resulting release patterns. For example, 60 (± 3)% theophylline was released after 8 h exposure to 0.1 M HCl from pellets coated with ethylcellulose-based films containing 15% poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer (coating level = 20%) upon curing for 24 or 48 h at 60°C and ambient RH or 75% RH. This can serve as an indicator that stable polymeric films were formed and that high humidity curing is not needed. Interestingly, drug release did not depend on the pH of the release medium. In conclusion, desired drug release profiles from ethylcellulose-coated pellets can effectively be adjusted by adding only small amounts of a poly(vinylalcohol)-poly(ethyleneglycol)-graft-copolymer. Importantly, the stability of the coatings dispersions is not affected and stable film coatings seem to be achieved after appropriate curing.

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Carrageenan as an efficient modulator for the properties of ethylcellulose-based films

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Ethylcellulose-based films are frequently used to coat solid dosage forms, e.g. to control the release rate of a drug. However, continuous ethylcellulose-based coatings are poorly permeable for most drugs, resulting in low release rates (Lecomte et al 2004). To overcome this restriction, hydroxypropyl methylcellulose (HPMC) has been proposed as a pore former accelerating drug release (Frohoff-Huelsmann et al 1999). However, relatively high quantities are required and the presence of HPMC in the coating dispersions causes coagulation. Due to its chemical structure carrageenan is a promising candidate to render ethylcellulose-based films more hydrophilic and, thus, more permeable for many drugs. The major objectives of this study were: to evaluate the potential of carrageenan as an effective modulator for the properties of ethylcellulose-based films; and to quantitatively describe the observed water uptake and drug release kinetics of/from

ethylcellulose-based films using Fick's second law of diffusion. Thin films were prepared by casting aqueous dispersions of ethylcellulose (Aquacoat ECD, plasticized with 25% triethylcitrate) and carrageenan (Viscarin GP 209) onto Teflon plates and controlled drying. Drug-containing films were prepared accordingly, adding theophylline to the aqueous dispersions. The drug loading was below the solubility of theophylline in the polymeric systems (monolithic solutions). The water uptake and dry weight loss kinetics of the films were measured gravimetrically upon exposure to 0.1 M HCl and phosphate buffer pH 7.4. In vitro drug release was monitored in the same media (37°C, UV drug detection). The apparent diffusion coefficients of water and theophylline in the polymeric systems were determined by fitting an analytical solution of Fick's second law of diffusion to the experimentally measured water uptake and drug release kinetics. Importantly, the addition of only 2.5% carrageenan to the ethylcellulose-based films resulted in a 4-fold increase in the extent of water uptake upon exposure to 0.1 M HCl. This renders the films much more permeable for the drug. Interestingly, the water penetration kinetics could be quantitatively described using Fick's second law of diffusion. The apparent diffusion coefficients of water were determined to be 1.5, 5.3, 7.8 and 9.2×10^{-8} cm^2/s for films containing 0, 2.5, 5 and 10% carrageenan. In addition, the presence of carrageenan in the systems significantly increased the extent and rate of the dry weight loss of the films upon exposure to 0.1 M HCl and phosphate buffer pH 7.4. Both, the increased water content as well as dry weight loss resulted in a tremendous increase in the permeability of the films for the drug: for instance, the apparent diffusion coefficient of theophylline increased from 0.3 to 2.5, 3.6 and 5.1×10^{-8} cm^2/s when adding 2.5, 5 and 10% carrageenan (upon exposure to phosphate buffer pH 7.4). Importantly, and in contrast to HPMC, the aqueous ethylcellulose dispersions were stable in the presence of carrageenan. As the addition of only small amounts of carrageenan significantly alters the properties of ethylcellulose-based film coatings and at the same time provides stable coating dispersions, it is a very promising modulator for the release kinetics from ethylcellulose-coated dosage forms.

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Temperature dependency of vapour sorption behaviour of mannitol polymorphs

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Mannitol exists in three polymorphic crystalline forms that have been well characterised and reported in the Literature (Walter-Levy 1968; Burger et al 1999). A number of techniques may be employed to differentiate between polymorphic forms. These include microscopy, spectroscopy, crystallography and thermal analysis. More recently the use of vapour sorption to probe the behaviour of crystal polymorphs has been reported by Carvahal & Staniforth (2006). Consequently it was decided to determine the vapour sorption behaviour of two polymorphic forms of mannitol over a range of temperatures. Powder *X*-ray diffraction was recorded with a Bruker D8 diffractometer (wavelength of *X*-rays 0.154 nm Cu source, Voltage 40kV, filament emission 40 mA). Samples were scanned from 5–45° (2θ) using a 0.01° step width and a 1 second time count. The receiving slit was 1° and the scatter slit 0.2°. Moisture sorption experiments were carried out using an IGAsorp moisture sorption analyser incorporating a real time processor (Hiden Isochemica, UK). Samples (50–60 mg) were placed in stainless steel sample baskets. The sequence of isothermal steps incorporated drying the samples to 0% RH until constant weight was achieved. The RH was then increased in increments of 10% to a maximum of 95% RH. The results show that beta mannitol is more hygroscopic than the delta form at all three temperatures. The profiles of delta mannitol at 25°C and 40°C show minimal weight gain prior to approximately 75% RH when a sudden increase in weight is visible. The vapour sorption profile of delta mannitol at 60°C shows a decrease in weight immediately before the increase in weight at 75% RH. This indicates that moisture induced polymorphic conversion may have occurred. XRPD analysis confirmed that complete polymorphic conversion had occurred in the sample. XRPD of delta mannitol run at 25°C showed an incomplete polymorphic conversion. Polymorphic conversion can impact product quality and functionality and the moisture sorption technique can readily assess any temperature dependency of moisture induced polymorphic transition potential during manufacturing. Table 1 shows the water uptake of the two polymorphs at different temperatures.

Table 1 Water uptake (%) in samples

Mannitol polymorph	**% Water uptake**		
	25°C	40°C	60°C
Beta	4.3 ± 0.08	6.6 ± 0.04	11.9 ± 0.35
Delta	1.2 ± 0.09	3.3 ± 0.53	7.5 ± 0.69

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