Use of Modified Ethylcellulose Lattices for Microporous Coating of Osmotic Tablets

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Commercially available lattices are often used to coat nonpareils or beads. Drug release occurs via diffusion through the polymer coating. Adequate release rates may be achieved with small particles because the surface area is large. However, tablets coated with unmodified lattices have exceedingly slow release rates. Therefore, a pore-forming agent, urea, was added to a commercially available ethyl cellulose latex, Aquacoat, to increase the release rate of drugs from coated osmotic tablets. Modified lattices were used to coat KCl and diltiazem · HCl tablets. Release of KCl and diltiazem into water or buffer solutions was determined in a standard U.S.P. dissolution apparatus. Rates varying from 1 to 100% release in 12 hr were obtained by varying the coating thickness, pore-former level, and plasticizer type and concentration. Scanning electron microscopy (SEM) showed that the urea was eluted from the coat in aqueous solution leaving a porous coating. Coat burst strengths were dependent on the coat thickness and the concentrations of pore former and plasticizer. Hence, modified lattices hold potential for use as coatings for controlled release osmotic formulations.

KEY WORDS: aqueous latex; osmotic pumps; ethyl cellulose; tablet coating.

INTRODUCTION

Due to the potential environmental safety and/or toxicity problems associated with some organic solvents, the pharmaceutical industry has been exploring alternatives to organic solvent-based tablet coating formulations (1–3). Several pharmaceutically useful polymers have been prepared as aqueous-based latex dispersions including ethyl cellulose (1–4), cellulose acetate (5–7), cellulose acetate phthalate (8), polymethacrylates (3,9), polylactic acid (10), polyglycolic acid (10), and styrene–butadiene copolymers (11). Two types of aqueous ethyl cellulose pseudolatex dispersions are commercially available for use in tablet coating: Aquacoat (12) and Surelease (13). Aquacoat is an ethyl cellulose dispersion stabilized by sodium lauryl sulfate and cetyl alcohol. When using Aquacoat a plasticizer must be added prior to coating.

The mechanism of drug release from tablets coated with Aquacoat is via diffusion through the hydrated polymer (2,12). This can be an exceedingly slow process unless formulations with a large surface area are utilized. Therefore, Aquacoat is often used to coat high-surface area nonpariels or beads.

In order to utilize Aquacoat to achieve osmotically controlled release of a drug from a tablet, it was necessary to modify the commercial formulation. In this work, plasticizers and a water-soluble pore-forming agent were added to Aquacoat. The release profiles of two model drugs (KCl and diltiazem · HCl) from tablets coated with several modified Aquacoat coatings were examined. The effects of plasticizer content, pore-former concentration, coating thickness, and the osmotic pressure differences across the coat were studied.

MATERIALS AND METHODS

Aquacoat was obtained courtesy of the FMC Corporation (Philadelphia, PA). Urea (reagent grade), dibutyl sebacate (DBS), and triethylcitrate (TEC) were used as received (Aldrich, Milwaukee, WI). Potassium chloride tablets (500 mg) were manufactured by direct compression of KCl crystals (Merck & Co., Rahway, NJ).

Diltiazem hydrochloride (Davos Chemical Corporation, Fort Lee, NJ), citric acid, magnesium stearate, and stearic acid (Fisher Scientific Company, Fairlawn, NJ), adipic acid (Eastman Kodak Company, Rochester, NY), sodium chloride (Mallinckrodt Inc., Paris, KY, and Morton Thiokol, Hutchinson, KS), and polyvinylpyrrolidone (Povidone 29-32 K, GAF Corp., Wayne, NJ) were used as received to manufacture the diltiazem · HCl cores. The diltiazem · HCl cores were manufactured from a granulation which contained (w/w%) 59.6% diltiazem · HCl, 14.1% adipic acid, 11.7% citric acid, 8.4% sodium chloride, 5.0% polyvinylpyrrolidone (29-32K), 1.0% stearic acid, and 0.2% magnesium stearate (14). The granulation was tableted on a single-station press (Stokes F-press, Warminster, PA) fitted with 7/16-in.-deep concave round tooling. The average tablet weight was 420 mg (250 mg diltiazem · HCl/tablet).

The coating formulation was prepared as follows: 250 ml of Aquacoat (75 g solids) was placed in a beaker and magnetically stirred. The plasticizer (either DBS or TEC) was slowly added over a period of 1–2 min to a final concentration based on the amount of solids in the latex dispersion (24–48% g/g Aquacoat solids). Urea (30–85% g/g Aquacoat solids) was then slowly added over 1–2 min to the plasticized Aquacoat. This mixture was magnetically stirred for 30 min to 1 hr before use to allow the coating formulation to reequilibrate to room temperature (urea dissolution is endothermic) prior to coating.

Coatings were applied in a side-vented pan coater (Freund HCT Mini Hicoater, Tokyo). Coating conditions were as follows: inlet air temperature, 80°C; air flow rate, 1.2 kg/cm^2; coating spray rate, 1 ml/min; and pan speed, 25 rpm. After coating to the appropriate thickness, devices were cured at 50°C for 3–5 days at a relative humidity <20%. The finished devices had smooth white coats with some evidence of small urea crystals on the surface in the coatings with >50% urea. The active agent and coating composition of each device type tested are given in Table I.

Release from coated KCl and diltiazem · HCl tablets was performed in a standard U.S.P. dissolution method No.

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Table I. Device Types

Device type	Active agent	Plasticizer	Urea content (%)
A	KCl	24% TEC	75
B	Diltiazem · HCl	24% TEC	75
C	KCl	24% TEC	30
D	KCl	24% TEC	50
E	KCl	24% TEC	60
F	KCl	24% TEC	68
G	KCl	24% TEC	70
H	KCl	24% TEC	85
I	KCl	30% TEC	75
J	KCl	36% TEC	75
K	KCl	42% TEC	75
L	KCl	48% TEC	75
M	KCl	24% DBS	75
N	KCl	30% DBS	75
O	KCl	36% DBS	75
P	KCl	42% DBS	75
Q	KCl	48% DBS	75

2 apparatus (VanKel Industries, Edison, NJ) in 900 ml of either deionized water, HCl buffer (isotonic, pH 1.25), or phosphate buffer (isotonic, pH 7.4, 0.05 *M* phosphate), at 37°C with constant stirring at 50 rpm. The release of KCl into deionized water was monitored by periodically placing a conductivity cell (Cole Parmer cell, Jenway PCM3 meter) in the dissolution medium. The standard conductivity curve was linear (r^2 = 0.9995) over a concentration range of 0–10 mg/ml. The release of diltiazem · HCl was determined by periodically withdrawing 1 ml of dissolution medium (volume replenished with fresh buffer), an aliquot of which was assayed for both diltiazem · HCl and the desacetyl hydrolysis product (desacetyl diltiazem) by HPLC (Shimadzu Corp., Kyoto, Japan). The mobile phase was 50:50 acetonitrile:water with 0.05% perchloric acid. Samples were injected in 20-μl aliquots and the flow rate was 2.5 ml/min. A C_8 reversed-phase column (10-cm RP-8 spheri 5, Brownlee Labs Inc., Santa Clara, CA) was used with UV detection and quantitation (peak areas) at 238 nm. The standard curve was linear (r^2 = 0.996) over a concentration range of 0–160 μg/ml.

In order to determine the mechanism of release, release from type A devices was performed in a U.S.P. dissolution method No. 2 apparatus in 900-ml volumes of aqueous urea solutions at 25°C with constant stirring at 160 rpm to prevent clumping of the tablets. The aqueous urea concentrations were 1.64, 3.42, and 7.06 molal. This experiment was performed at 25°C with these urea concentrations because osmotic pressure data were available from the literature (15) under these conditions and they encompassed a wide range of osmotic pressure. Three 900-ml vessels were used for each urea concentration. Six devices were placed in each vessel at time zero. Utilizing six tablets per vessel was not problematic because the solubility of KCl is ≥3.3 mg/ml (the maximum possible concentration in each vessel). One coated KCl tablet (device type A) was withdrawn from each of three vessels at each time point and sliced open, and the residual KCl was dissolved in 100 ml of deionized water and assayed conductimetrically.

Coat samples were prepared from devices before and after water exposure (leached and unleached devices) for observation by scanning electron microscopy (SEM; Hitachi S-570). Unleached coat samples were cut from devices which had never been placed in dissolution medium. Leached samples were prepared from fully core-depleted devices. All samples were oven-dried at 50°C for several hours, mounted on SEM stubs, gold-coated, and examined by SEM.

A tensile tester (Model 1130, Instron, Canton, MA) was utilized to measure the compression force required to burst the coat of leached devices. A 5-kg load cell was used with a cross head speed of 5 cm/min. The burst strengths of five hydrated fully depleted devices were analyzed and the averages are reported.

RESULTS AND DISCUSSION

Microporous latex coatings were formed by adding urea to a plasticized aqueous ethyl cellulose dispersion. Urea was chosen as a pore-forming agent because it is a small, readily water-soluble, uncharged molecule. The use of charged species in lattices may cause the polymeric dispersion to coagulate. Figure 1 shows scanning electron micrographs of the surface of both leached and unleached coats of device type A. The unleached coats appear to have urea crystals on the surface and embedded in the coat, but no pores are evident. The leached coat is free of surface crystals and clearly shows the presence of pores. These micrographs show that a microporous coating was formed by the elution of urea from the ethyl cellulose coating.

Figure 2 shows the release into water of KCl device type A. Greater than 75% of the KCl was released by zero-order kinetics (r^2 = 0.995) with a very short lag time (<5 min). Based on KCl solubility, release of 83% of a KCl core with zero-order kinetics is predicted (15).

Figure 3 shows the release of diltiazem · HCl (device type B) at pH 1.25 and pH 7.4. The steady-state release rates for diltiazem do not differ significantly at the two pH's, exhibiting the desired quality of pH independence. Diltiazem · HCl has a pH-dependent water solubility. At low pH's the drug is in its ionized form and is readily water soluble, while at higher pH's the nonionized form of the drug has limited solubility. Since release from an osmotic device

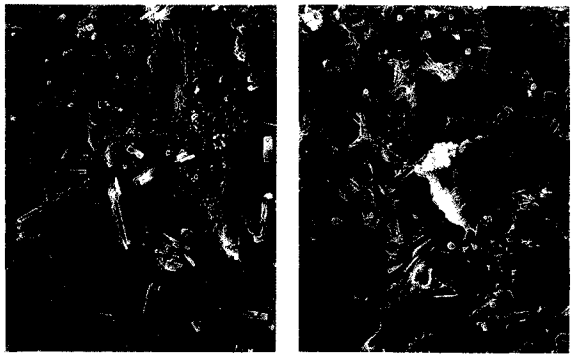

Fig. 1. Scanning electron micrographs of the surface of device type A coatings before and after exposure to water. ×1000; reduced 65% for reproduction.

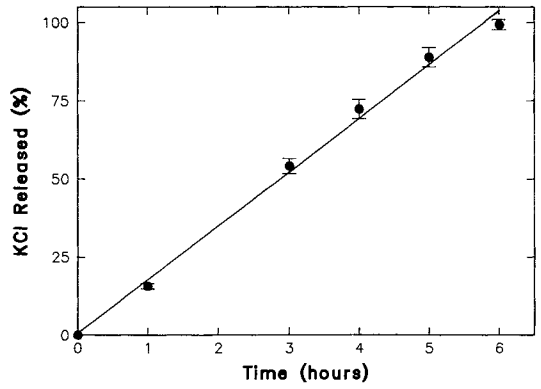

Fig. 2. Release profile of potassium chloride from device type A in water at 37°C (n = 3).

is dependent on the drug solubility (15), the pH-independent release of diltiazem · HCl indicates that the solubility within the core was constant (through the use of buffering agents). The release profiles shown in Figs. 2 and 3 demonstrate the potential utility of modified Aquacoat coatings for use with microporous coated osmotic devices.

The steady-state zero-order release rate (dm/dt) of a drug from an osmotic delivery device can be calculated using Eq. (1) (17).

$$\frac{dm}{dt} = \frac{AS}{h}L_p\sigma\Delta\pi + \frac{PAS}{h} = \text{osmotic pumping} + \text{diffusion} \quad (1)$$

where A is the device surface area, h is the coating thickness, S is the drug solubility, $L_p\sigma$ is the fluid permeability of the coat, P is the permeability coefficient of the drug through the coat, and $\Delta\pi$ is the osmotic pressure difference across the coat. The first term represents the osmotic pumping component and the second term is the contribution from simple Fickian diffusion (assuming sink conditions). Figure 4 shows steady-state zero-order release rates of KCl into various urea solutions plotted versus the calculated osmotic pressure difference across the coat (15). The linear relationship between release rate and $\Delta\pi$ confirms that osmotic pressure is the driving mechanism that controls the release of KCl (16). A least-squares linear regression yielded a slope of 0.26 mg/hr/atm and a y intercept of 3.66 mg/hr (r^2 = 0.96). The y intercept ($\Delta\pi$ = 0) is indicative of the contribution of the diffusive component of the overall release, which was small relative to the osmotic pumping component. Therefore, it was concluded that the release was primarily driven by an osmotic pumping mechanism.

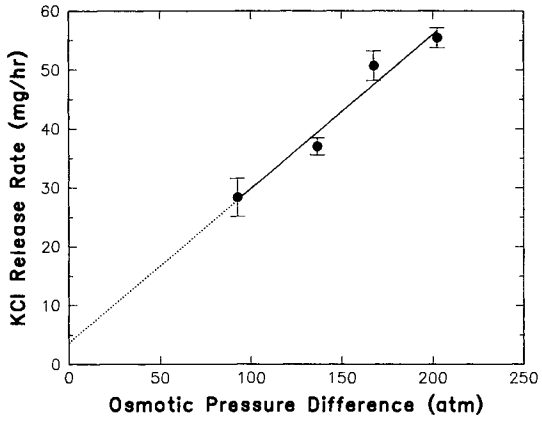

Fig. 4. Potassium chloride release rate from device type A at 25°C as a function of the osmotic pressure difference ($\Delta\pi$) across the coating (n = 3).

Figure 5 illustrates the relationship between the KCl release rate (device types A, C–H) and the percentage of urea pore former added to the Aquacoat latex. In all cases, the plasticizer was TEC (24% g/g Aquacoat solids) and all devices had coats of similar thickness (280 μm). The mean release rates increased with increasing pore-former concentrations. Previous work (18) showed that as pore-former concentration was increased, the number of "submicron voids" was also increased, resulting in a more porous, permeable structure. There also appears to be a critical point (50% urea) above which there is a near-linear (r^2 = 0.98) dependence of KCl release rate on urea content. It was also observed that devices with <50% urea swelled and became more spherical during the dissolution experiment, while devices coated with ≥50% urea coats did not swell and retained their character-

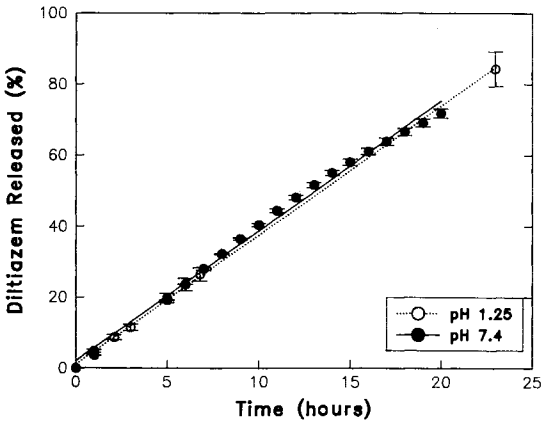

Fig. 3. Release profile of diltiazem · HCl from device type B in (●) pH 7.4 isotonic phosphate buffer at 37°C and (○) pH 1.25 isotonic citrate buffer at 37°C (n = 3).

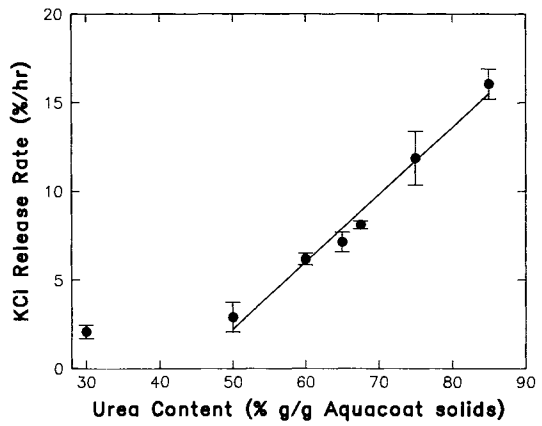

Fig. 5. Effect of urea concentration on the zero-order release rate of potassium chloride from device types A and C–H at 37°C in water (n = 3).

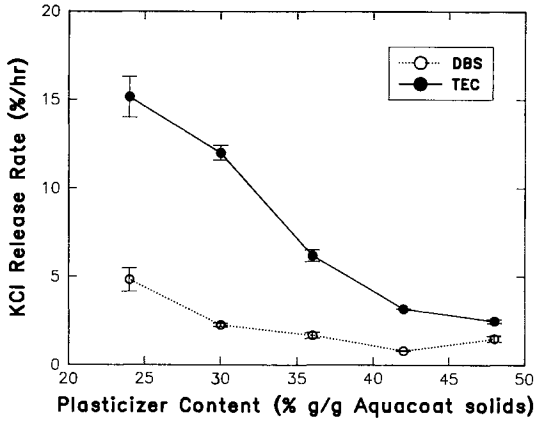

Fig. 6. Effect of plasticizer on the zero-order release rate of potassium chloride from device types A and I–Q at 37°C in water (n = 3).

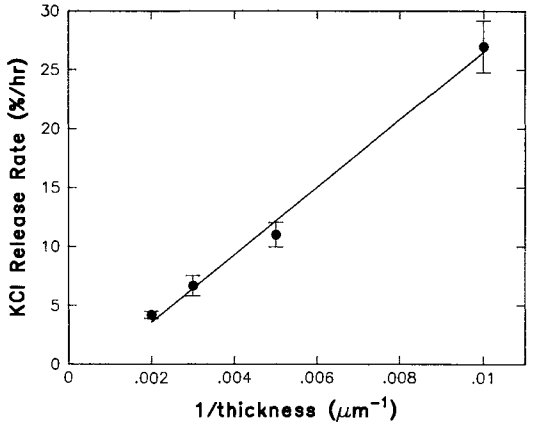

Fig. 8. Effect of coating thickness on the zero-order release rate of potassium chloride from device type A, at 37°C in water.

istic tablet shape. This suggests that at low urea concentrations many of the pores may not be continuous, however, at higher concentrations a proportionally greater fraction of the pores is continuous. These data show that the release rate can be controlled by adjusting the amount of urea in the latex coating.

The effect of plasticizer type and concentration on release from coated KCl tablets (device types A, I–Q) was determined in a series of experiments with the urea content of the coat and the coating thickness held constant (75% urea and 280 μm, respectively), while the percentage of plasticizer (DBS or TEC) was varied (24–48% g/g Aquacoat solids). The results are shown in Fig. 6. The KCl zero-order release rate decreased as the level of plasticizer increased, an effect consistent with previous observations (3,4). The release rates were more sensitive to changes in TEC concentration than DBS. In addition, higher rates were observed with TEC versus DBS at equal concentrations. This may be attributed to the difference in the plasticizer water solubilities. DBS is virtually water insoluble, while TEC has a water solubility of 6.5% (w/v) (2). Since DBS is more hydrophobic it would be expected to decrease the permeability of the coat to water and water-soluble agents more effectively. The dependence of the release rate on the type and level of plasticizer incorporated into the coat provides another method for tailoring the latex formulation to achieve a desired release profile.

The effects of coating thickness on KCl release and the burst strength of the depleted device coatings were examined by applying different amounts of Aquacoat to KCl tablets (device type A). Figure 7 illustrates that the KCl release rate decreases and the burst strength increases as the coating thickness increases. No bursting of the devices was observed in the *in vitro* dissolution experiments. A plot of the release rates versus inverse thickness was linear (r^2 = 0.997) (Fig. 8). This relationship is predicted theoretically from Eq. (1).

This research has demonstrated that modified Aquacoat lattices can be used to form microporous coats for controlled release from osmotic devices. Further, the release rates of drugs from these devices can be tailored by the appropriate combination of pore former content, plasticizer type and content, and coating thickness. The potential for minimizing environmental impact and increasing worker safety makes utilization of modified aqueous lattices an attractive alternative to traditional organic solvent-based coating.

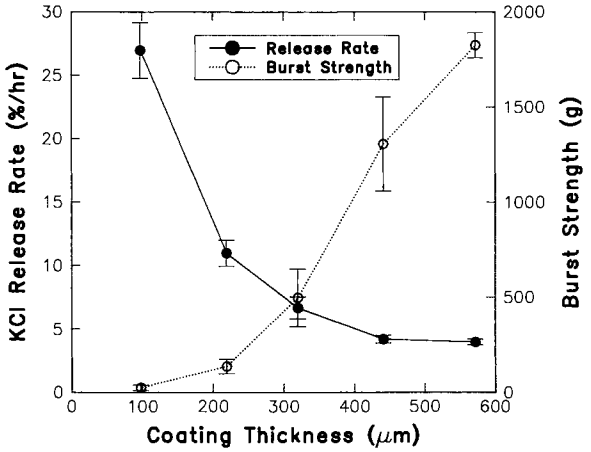

Fig. 7. Effect of coating thickness on the burst strength (n = 5) and the zero-order release rate of potassium chloride from device type A, at 37°C in water (n = 3).

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