Formulation and Optimization of a Modified Microporous Cellulose Acetate Latex Coating for Osmotic Pumps

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A cellulose acetate (CA) latex was modified for use as a microporous coating for osmotic devices. Potassium chloride core tablets were coated with a CA latex formulation containing a plasticizer (triacetin) and a pore-forming agent (urea). To promote the coalescence of the cellulose acetate latex beads into a film on the surface of the tablet, it was necessary to cure the coated tablets, hereafter referred to as devices, at elevated temperatures. The objectives were to determine the effect of four formulation variables (plasticizer level, pore former level, cure time, and cure temperature) on the *in vitro* KCl release rate and coat burst strength using a full 2^4 factorial experimental design. Burst strength was measured as the number of grams force a depleted device could support before bursting. The results indicated that urea content was the most important variable, followed by triacetin content and cure time. Cure temperature did not influence the results. Response surfaces generated with the experimental values were used to predict a formulation which would have both a high release rate and a high burst strength. This formulation was prepared and tested both *in vitro* and *in vivo* in dogs. The *in vitro* release rate and burst strength results agreed with those predicted by the model. The *in vitro* and *in vivo* release rates were not statistically significantly different as determined by ALQ analysis.

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

INTRODUCTION

The use of controlled-release microporous osmotic pumps fabricated by coating osmotically active cores with organic-based polymer solutions has been well documented (1,2). Usage of aqueous-based polymeric dispersions has increased in the last decade as the pharmaceutical industry attempts to reduce solvent emissions. Aqueous polymeric dispersions have been utilized in tablet coating applications (3,4) including microporous osmotic pumps (5,6). In this work, a cellulose acetate (CA) latex was modified for use as a microporous coating for an osmotic core. The objectives of this research were to determine the relative importance of coating formulation and processing variables and to determine which combination of variables would yield a device with both a high release rate and a high coat burst strength (>1 kg). A full 2^4 factorial experiment was employed, examining each of four variables (plasticizer content, pore former content, cure time, and cure temperature) at two levels.

MATERIALS AND METHODS

Cellulose acetate latex was obtained courtesy of the FMC Corporation (Newark, DE). Urea (reagent grade) and triacetin were used as received (Aldrich, Milwaukee, WI), Potassium chloride tablets (500 mg) were manufactured by direct compression of KCl crystals (Merck & Co., Rahway, NJ).

The coating formulation was prepared as follows: 250 ml of CA latex (75 g solids) was placed in a beaker and magnetically stirred. The triacetin was slowly added over a period of 1–2 min to a final concentration based on the amount of solids in the latex dispersion (50–100 g triacetin/100 g CA latex solids). Urea (25–100 g/100 g CA latex solids) was then slowly added over 1–2 min to the plasticized CA latex. 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 pancoater (Freund HCT Mini Hicoater, Tokyo). Coating conditions were as follows: inlet air temperature, 80°C; air pressure, 1.2 kg/cm^2; coating spray rate, 1 ml/min; and pan speed, 25 rpm. After coating the devices were cured in ovens at 60 or 80°C for 1 or 72 hr. All coating thicknesses were 250 ± 45 μm.

In vitro release testing from coated KCl devices was performed in a standard USP dissolution method 2 apparatus (VanKel Industries, Edison, NJ) in 900 ml of deionized water at 37°C with constant stirring at 50 rpm. The release was monitored by periodically placing a conductivity cell (Cole Parmer cell, Jenway PCM3 meter) into the dissolution medium. The standard conductivity curve was linear (r^2 = 0.9995) over a concentration range of 0–10 mg/ml. Three devices of each composition/processing history were tested. Burst strengths were determined by compressing depleted devices (n = 10) with the thumb on a top-loading balance and recording the burst strength in grams at the point of rupture. Experiments were performed in random order to minimize systematic bias.

In vivo studies were conducted using KCl tablets coated with CA latex/85% triacetin/100% urea which had been cured for 72 hr at 60°C. Three beagles were fasted for 24 hr and then fed 1 hr before the start of dosing. Each dog was given one tablet orally (all tablets were uniquely marked) every hour for 7 hr. One hour after administration of the last tablet the dogs were sacrificed and the devices were retrieved. The coats of retrieved tablets were sliced open with a scalpel and the residual KCl was dissolved in water and quantified conductimetrically.

RESULTS AND DISCUSSION

The experiment was designed and evaluated using a commercial software package (RS/1, BBN Software Products, Cambridge, MA). Table I gives the level and definition of each variable for each run and the results from dissolution

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and burst strength testing (mean and standard deviation). Both the actual run order and the Yates order (order necessary to evaluate the data using an algorithm) are given. In order to evaluate the data all the x variables were transformed to z variables such that the low value corresponded to -1 and the high value corresponded to $+1$ [Eqs. (1)–(4)].

$$z_1 = \frac{x_1 - 75}{25} \tag{1}$$

$$z_2 = \frac{x_2 - 62.5}{37.5} \tag{2}$$

$$z_3 = \frac{x_3 - 36.5}{35.5} \tag{3}$$

$$z_4 = \frac{x_4 - 70}{10} \tag{4}$$

Using the Yates algorithm (7), the response data were used to calculate coefficients. These coefficients describe the effects of the variables on the release rate and the burst strength. The results were used to generate Eqs. (5) and (6), which relate the release rate (y_1) and burst strength (y_2) responses to the transformed formulation/processing variables.

$$y_1 = 6.33 - 1.03z_1 + 4.54z_2 + 0.99z_3 - 1.03z_1z_2 + 0.72z_1z_3 + 0.56z_2z_3 \tag{5}$$

$$y_2 = 1934 + 749z_1 - 1055z_2 + 168z_4 - 167z_1z_2 - 163z_2z_4 \tag{6}$$

These equations indicate the relative importance of the individual formulation parameters and show that there are important interaction terms (i.e., the effect of one variable is dependent on another variable). Since the high and low levels were coded $+1$ and -1, respectively, the results are normalized and can be compared directly. Larger coefficients reflect the more influential terms. If a coefficient was more than an order of magnitude less than the highest coefficient, the corresponding term was considered insignificant and was not included in the equation. The level of urea (z_2) in the formulation was the most important variable affecting the release rate followed by the triacetin (z_1) level. The cure time also affected the release rate as indicated by the coefficient (0.99). Also, several second-order interaction effects (z_1z_2, z_1z_3, etc.) had contributions to the release rate response, indicating that the variables cannot be considered separately. The effect of urea concentration on the release rate, however, was >4.5 times that of any other variable or interaction.

The major variables which affected the burst strength were the urea and triacetin concentrations, with urea approximately 1.5 times more influential. The negative sign for the urea coefficient indicates that increases in urea concentration result in lower burst strengths. The cure temperature and some two variable interaction terms also affected the burst strength to a much lesser extent.

The strong effect of urea on both responses was expected. Urea is a highly water soluble compound, which crystallizes as the coatings dry and is leached from the coating in an aqueous environment. With increases in urea concentration, the coating becomes more porous upon exposure to water, thereby increasing the release rate and decreasing the coat strength. The triacetin effect was more complicated, showing a clear time dependence that became evident when the data were analyzed as two 2^3 designs (analysis not shown): one for the 1-hr cure times and one for the 72-hr cure times. At 1-hr cure times the triacetin coefficient for the release rate was 2.3 times smaller than the urea coefficient, indicating that triacetin content made a significant contribution to the release rate. At 72-hr cure times the triacetin coefficient was 16.9 times smaller than the urea coefficient, which means that triacetin had little effect on the release rate. Physically, this is probably accounted for by the loss of the triacetin while curing. Other researchers (8) have noted the loss of plasticizers during drying. The triacetin may also leach from the coating during dissolution. This would result in the triacetin behaving as a pore-forming agent. This was

Table I. Experimental Design[a]

Yates run no.	Run order	Triacetin x_1	Urea x_2	Cure time x_3	Cure temp. x_4	*In vitro* rate (%/hr)	Burst strength (g)
1	6	−	−	−	−	1.88 (0.07)	1847 (691)
2	1	+	−	−	−	1.01 (0.74)	3619 (1501)
3	5	−	+	−	−	12.43 (1.42)	244 (145)
4	14	+	+	−	−	6.64 (1.63)	1748 (193)
5	7	−	−	+	−	1.90 (0.42)	1758 (821)
6	2	+	−	+	−	2.29 (0.36)	3403 (982)
7	12	−	+	+	−	13.60 (1.22)	201 (84)
8	10	+	+	+	−	9.79 (2.61)	1305 (409)
9	11	−	−	−	+	1.73 (0.08)	2210 (513)
10	16	+	−	−	+	0.82 (0.72)	4522 (1157)
11	3	−	+	−	+	12.32 (2.76)	365 (198)
12	4	+	+	−	+	5.89 (1.98)	1566 (357)
13	15	−	−	+	+	1.62 (0.12)	2473 (482)
14	9	+	−	+	+	3.01 (0.05)	4075 (479)
15	8	−	+	+	+	13.33 (1.15)	376 (176)
16	13	+	+	+	+	12.94 (1.06)	1225 (236)

[a] The − or + symbol denotes the low or high values for the variable. Triacetin (x_1): − = 50 g/100 g solids; + = 100 g/100 g solids. Urea (x_2): − = 25 g/100 g solids; + = 100 g/100 g solids. Cure time (x_3): − = 1 hr; + = 72 hr. Cure temperature (x_4): − = 60°C; + = 80°C.

not observed. The sign in front of z_1 in Eq. (5) is negative, indicating that increases in triacetin level result in a decrease in KCl release rate. Thus, the leaching of triacetin from the coating did not appear to significantly affect the results. The effect of cure temperature appeared negligible (<10 times the largest coefficient) for release rate and very small for the burst strength response. Therefore, further studies were done using the low cure temperature (60°C). With KCl cores thermal degradation of the cores is not an issue, however, since this technology might be applied to other drugs which may be thermally sensitive, it was better to use a lower cure temperature.

Figure 1 shows the contour plots for both burst strength and release rate. This figure was generated using Eqs. (5) and (6), holding cure time and cure temperature fixed at $+1$ (72 hr) and -1 (60°C), respectively. The triacetin and urea levels were allowed to vary between -1 and $+1$ and lines of constant release rate and burst strength were calculated. The triacetin content had little effect on rates (dashed lines) between 4 and 10%/hr. However, at higher and lower rates the triacetin effect became significant. For devices with slow release rates (i.e., <4%/hr), increases in triacetin content decrease the release rate, while for devices with fast release rates (i.e., >10%/hr) an increase in triacetin concentration increased the release rate. The burst strength response (solid line) was highly dependent on both urea and triacetin content. Devices became weaker by increasing urea and decreasing triacetin.

Frequently the pharmaceutical scientist must formulate a device which releases quickly and yet has a burst strength sufficiently high to prevent premature rupture and the attendant dose dumping in the gastrointestinal tract. This is a challenging objective because, in general, fast release is accompanied by low coat strength. However, based on the contour plots a formulation with 85% triacetin and 100% urea cured for 72 hr at 60°C was predicted to satisfy both the high release rate and the high burst strength (i.e., >1 kg) criteria. It was predicted that this formulation would release 11.80%/hr within a 95% confidence interval of 10.80 and 12.88%/hr and have a burst strength between 900 and 1360 g. This formulation was prepared and tested. The experimentally measured release rate (14.62 ± 0.87%/hr) exceeded the prediction but was within 5.0% of the predicted range. The measured burst strength (1290 ± 371 g) was in agreement with the burst strength prediction.

These devices were also administered to dogs to determine the *in vivo* release performance. In all dogs a majority of the tablets was retrieved from the stomach, and all devices were intact (no burst coatings). The amount of KCl released was determined by assuming that any KCl not in the recovered tablet had been released. Figure 2 shows that the *in vitro* and *in vivo* release profiles were very similar. The *in vivo* release rate was 12.04 ± 1.18%/hr, and the *in vitro* release rate was 14.62 ± 0.87%/hr. An ALQ (average, linear, and quadratic) analysis (9) was performed on the first 5 hr of both the *in vitro* and the *in vivo* release profiles. No statistically significant difference in the release profiles was found; *P* values for the three summary measures were 0.2, 0.1, and 0.4 for the average, linear, and quadratic, respectively. The release performance of the devices was not expected to be affected by residence in the stomach since the release of KCl is not pH dependent (1). The retention of devices in the stomach was attributed to the relatively large (⅜-in. std. concave) tablet size.

These results demonstrated the utility of factorial experimental design in the facile optimization of a controlled-release formulation and/or process. This approach yielded data which were readily interpreted in a quantitative manner and led to the definition of important factors which would not be readily discerned using a nonstatistical approach to experimental design. In addition, it was demonstrated that CA latex/urea/triacetin coatings may be applied to tablets to

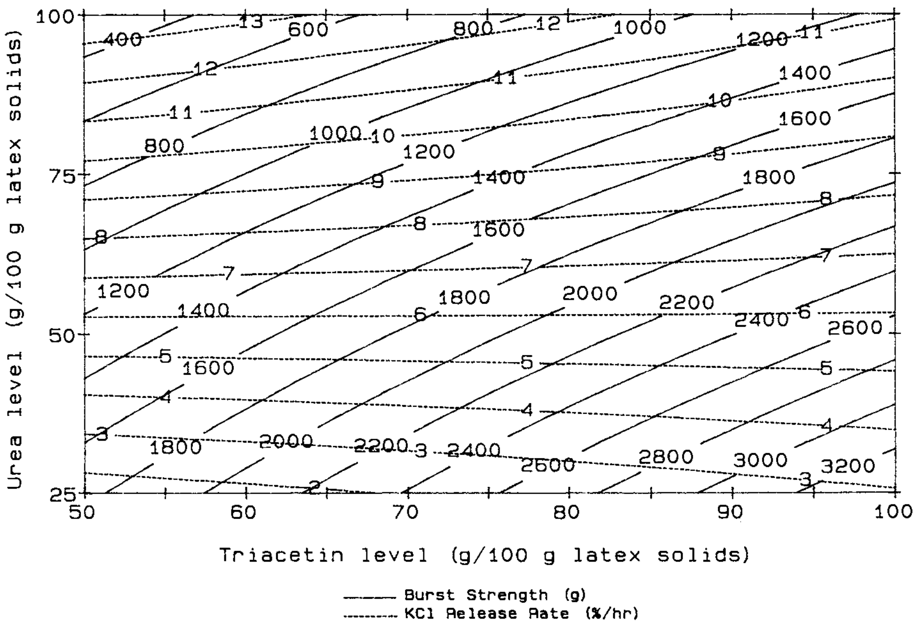

Fig. 1. Contour plot showing the effect of urea and triacetin on device release rate (dashed lines) and burst strength (solid lines).

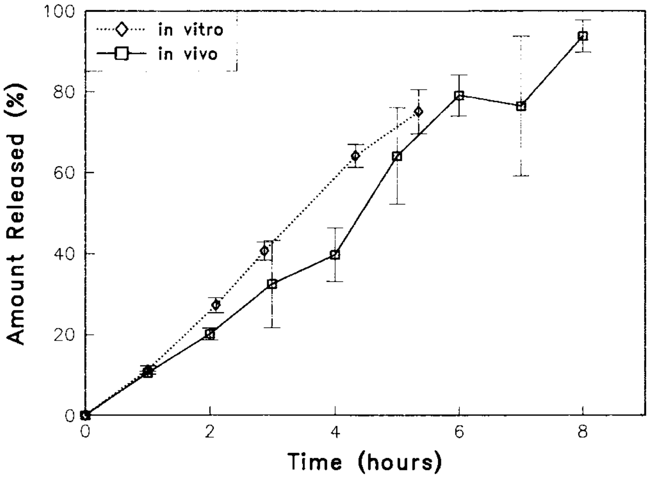

Fig. 2. Comparison of *in vitro* (dashed lines) and *in vivo* (solid lines) release profiles.

generate a wide range of *in vitro* release performance, and in the case examined in this work good agreement between *in vitro* and *in vivo* performance was observed.

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