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COMMUNICATIONS

IN VITRO RELEASE OF DISOPYRAMIDE FROM CELLULOSE ACETATE BUTYRATE MICROSPHERES

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ABSTRACT

Disopyramide was microencapsulated with cellulose acetate butyrate (CAB) using an emulsion-solvent evaporation process. Drug dissolution from microcapsules was studied in both simulated gastric (SGF) and intestinal fluids (SIF) under sink conditions using the USP paddle method. There was no significant difference between drug release into SIF and SGF. As the CAB to drug ratio decreased from 3:1 to 2:1 at constant polymer mass, the drug release rate increased and the $T_{50\%}$ decreased from 2.3 hr to 0.3 hr for 303 μm particles. Dissolution $T_{50\%}$ increased from 0.4 hr to 2 hr when the mean microcapsule size was increased from 153 to 428 μm (26% drug loading). The addition of acetone to the external phase during preparation shifted the size distribution toward larger particles, but resulted in a higher drug dissolution rate for a given particle size range. A shift to smaller particles was obtained upon increasing the concentration of surfactant. The dissolution profiles were described by the Higuchi and Baker-Lonsdale equations for drug release from spherical matrices up to 90% of the drug release.

INTRODUCTION

Disopyramide is a widely prescribed antiarrhythmic drug with proven efficacy in the management of both ventricular and supraventricular arrhythmias (1-6). Disopyramide has a half-life of 7 hours in normal subjects and a narrow therapeutic range of 3-5 mg/L (7-8). The conventional tablet preparation is usually dosed four times daily to maintain peak and trough concentrations within the therapeutic range.

Poorly water-soluble polymers have been used to prepare sustained release microspheres of various water-soluble drugs (9). A sustained release formulation of

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disopyramide microspheres was developed using cellulose acetate butyrate as a coating polymer. This investigation was undertaken to design and evaluate a sustained release solid oral drug delivery system for disopyramide.

EXPERIMENTAL

Materials: Disopyramide phosphate, G.D. Searle lot numbers P-4095, P-4097, and P-226 was donated by the G.D. Searle Company. Cellulose acetate butyrate was from Scientific Polymer and heavy mineral oil and Sorbitan monooleate were from the Ruger Chemical Co., Inc. Solvents used were purchased from the J.T. Baker Chemical Co. All chemicals were used without further purification.

Preparation of Microspheres: Disopyramide microspheres were prepared by the emulsion-solvent evaporation method (10). Cellulose acetate butyrate (CAB) was dissolved in acetone to form a 10-15% solution, in which the drug powder was dispersed. The dispersion was then emulsified in 125 mL of heavy mineral oil containing sorbitan monooleate and magnesium stearate with continuous stirring at 420 rpm until all the acetone had evaporated, usually within 7 hours. The microspheres were separated from the oil by centrifugation at 1500 rpm for 5 min, and then washed with 150 mL of hexane three times to remove the oil. The microspheres were recovered by filtration, and dried under vacuum for at least 12 hr at room temperature.

The dried microspheres were weighed and sized with a tarred nest of standard sieves. The mass of microspheres retained on each sieve was obtained by the difference in weights after 10 min on a sonic sifter. The mean size of the microspheres was assigned as the sieve size through which they passed. Interbatch variation was maintained below 10% for all batches prepared in this study.

Standard calibration curves ($r>0.999$ for all plots) for disopyramide were constructed by plotting the absorbance maxima (λ_{max}) values at 260.2, 261, and 259.1 nm against known concentrations (1-100 μg/mL) of drug in methylene chloride:methanol (50:50 v/v), simulated gastric fluid (SGF, pH 1.2), and simulated intestinal fluid (SIF, pH 7.4).

To determine drug content in microspheres exactly 10 mg of microspheres were weighed, placed in 100 mL of methylene chloride:methanol (50:50 v/v) in a volumetric flask and sonicated for 10 min to dissolve the CAB and drug. The drug concentration was determined spectrophotometrically at 260.2 nm. It was determined that CAB did not interfere with the assay. Triplicate samples were measured for each batch with an intrabatch variation of not more than 5%. The Student's *t*-test was used to determine statistical significant differences ($p < 0.05$) in disopyramide content and release rate.

Drug Release Rate: Drug release was evaluated using the USP XX paddle stirrer dissolution apparatus rotated at 100 rpm. The dissolution media (1 L of either SGF or SIF) was maintained at 37°C.

An accurately weighed portion (100 mg) of microspheres was suspended in the dissolution media, samples were withdrawn at successive intervals and assayed

spectrophotometrically for drug content. Immediately after measuring the absorbance, the samples were returned to the dissolution vessels. For each duplicate batch of microspheres, triplicate samples were tested. When intrabatch and interbatch variation was greater than 5%, the batch was rejected.

RESULTS AND DISCUSSION

The emulsion-solvent evaporation microencapsulation technique with continuous stirring produces droplets of varying size depending on the processing conditions. The droplet size is influenced by the viscosity of the internal and external phases, the stirring speed, the phase volume ratio, and the concentration of surfactants.

Disopyramide CAB microspheres had a size range of 77 μm to 428 nm with a small percentage ≥ 500 μm.

The surface of CAB microspheres were examined under a scanning electron microscope. The spherical matrices of disopyramide revealed a relatively smooth surface, which texture was affected by the evaporation rate of acetone during microencapsulation. The faster the evaporation rate, the rougher the resulting surface. Furthermore, the larger and more concentrated the disopyramide particles, the rougher was the surface.

Analysis of drug content was performed on four different sizes of microspheres from two different formulations. The formulations differed by either adding or not adding 10% v/v of acetone. Without acetone the mean disopyramide content was 24% ± 1.5 %, but with acetone it was 28% ± 0.5 for both microspheres with 26% v/v initial disopyramide in the formulation. The increased disopyramide in the acetone-containing formulation is evidence for loss of polymer.

The effect of formulation on microsphere yield and disopyramide loss was studied in five different formulations (Table 1). Formulations 1, 4 and 5 represent initial disopyramide contents of 26%, 30.4%, and 19.4%, respectively. Formulations 2 and 3 represent initial acetone contents of 5% and 10% v/v, respectively. The formulations in which acetone was included had the lowest drug loss among all the formulations.

The dissolution profile of unencapsulated disopyramide indicated that it dissolved within 30 min, and was stable under the experimental conditions. Microsphere sizes of 428, 303 and 215 μm were tested for in-vitro dissolution in SGF and SIF. Figure 1 represents the release profile of disopyramide in SIF. Dissolution studies of the microspheres in SGF and SIF showed no significant difference in the release rates of the drug in SIF and SGF that indicates drug release is pH independent.

The release rates were inversely related to the microsphere size because of the increased surface area, decreased diffusion path length, and in the case of the smaller sizes, some exposed (uncoated) drug particles. In all cases, the rate of release was nonlinear, and showed more rapid initial phase. The initial rapid release may be attributed to some exposed drug particles at the surface of the microspheres.

Previously reported studies (9) have established that as the drug:polymer ratio decreases, the release rate of the drug from the microspheres also decreases. This was also the case with disopyramide release from CAB microspheres as shown in Figure 2.

From microspheres with a drug loading of 19.4%, only 57% of the drug was released within 4 hr. When the drug loading was increased to 30.4%, 90% of the drug was

TABLE 1

The Effect of Formulation on the Yield and Drug Loss.

Parameter	Formulation Number 1	2[c]	3[d]	4	5
Initial Drug Content (%)	26.0	26.0	26.0	30.4	19.5
Yield[a] (%)	90.4	91.0	95.5	85.0	84.4
Drug[b] Loss (%)	17.7	3.0	0.5	14.2	16.7

a $$\%\ \text{Yield} = \frac{\text{Mass of recovered microspheres}}{\text{(Initial mass of disopyramide + CAB)}} \times 100$$

b $$\%\ \text{Drug Loss} = 1 - \frac{\text{(Assayed drug concentration} \times \text{Mass of recovered microspheres)}}{\text{Initial amount of disopyramide}} \times 100$$

c Acetone concentration was 5% v/v in the external phase prior emulsification

d Acetone concentration was 10% v/v in the external phase prior emulsification

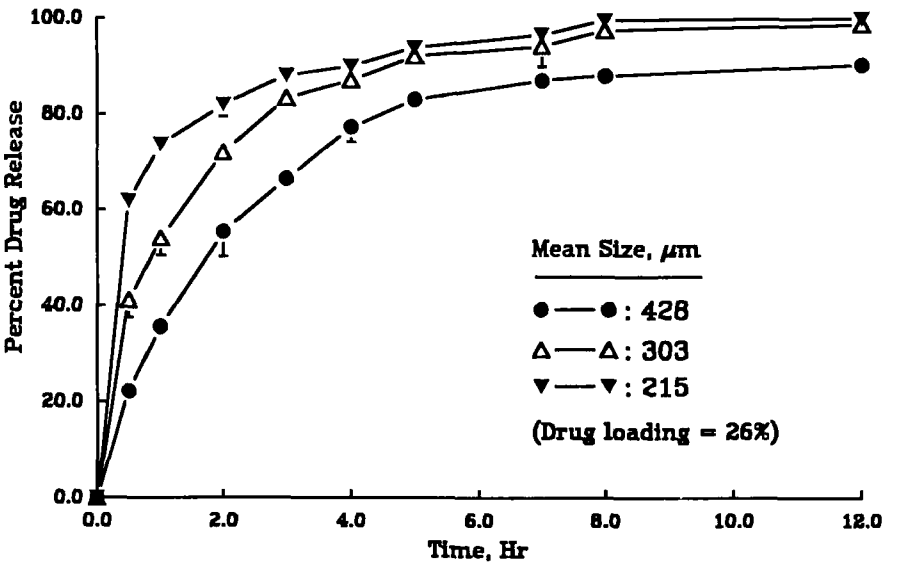

FIGURE 1

Effect of Mean Size of CAB Microspheres Containing 26% w/w Disopyramide on Drug Release in Simulated Intestinal Fluid at 37°C

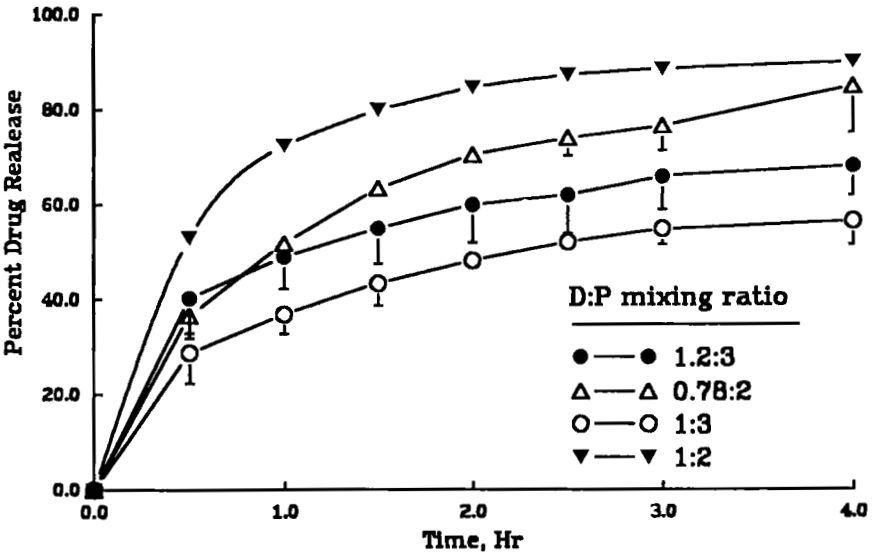

FIGURE 2

Effect of Disopyramide to CAB Mixing Ratio on Disopyramide Release from 303 μm Microspheres in SGF at 37°C

released within 4 hr. These results suggest that the sustained release characteristics of this microsphere system was dependent on the drug:polymer ratio. An increase in drug loading for microspheres of a given size distribution not only increases the porosity of the system as the drug dissolves, but also reduces the relative amount of polymer material as a diffusional barrier.

Kitajema *et al.* (11) proposed that the addition of acetone to the external phase prior to emulsification would retard the initial extraction of acetone from the internal phase into the external phase by mineral oil, which would improve coating of the drug with the polymer. If this were the case, the release of the drug from such microspheres should be lower than microspheres with no acetone added to the mineral oil. However, the CAB microspheres consistently showed an increased release rate of the drug with increasing amount of acetone added.

Since the evaporation of acetone, and, hence, solidification of the microspheres with acetone extended the time during which the emulsion droplets remained in a fluid state, a larger proportion of polymer was sheared away from the drug particles. This resulted in microspheres with lower polymer content. These effects were significant with microspheres prepared with 10% acetone added to the external phase (Figure 3).

The effect of sorbitan monooleate concentration on the release of disopyramide from 215 μm microspheres with a 26% w/w content was also investigated. The initial

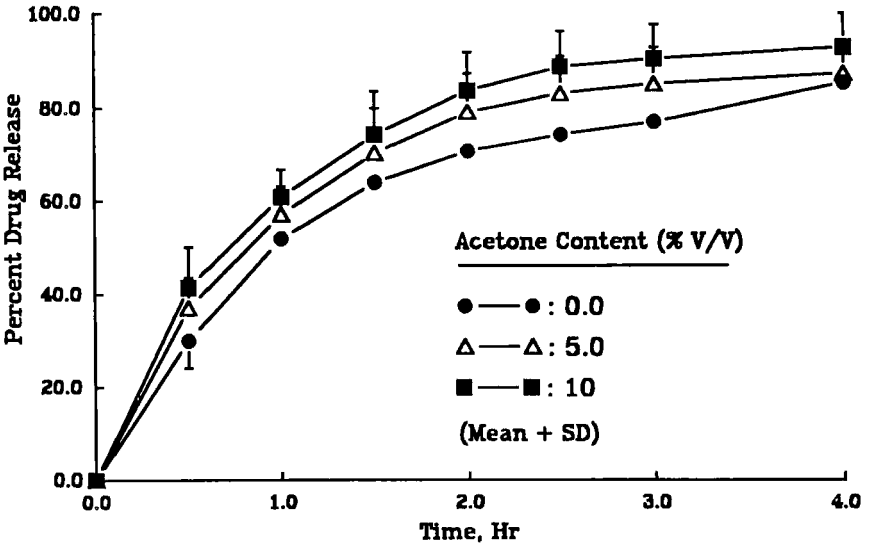

FIGURE 3

Effect of Acetone Concentration in the External Phase on Disopyramide Release from 303 μm Cellulose Acetate Butyrate Microspheres Containing 26% w/w Disopyramide into SGF at 37°C (Mean of % Drug Released + SD)

release of the drug increased as the concentration of sorbitan monooleate increased. The effect of sorbitan monooleate was insignificant during the slower release stage of the drug release in the dissolution medium.

The release curves for disopyramide show a nonlinear drug dissolution pattern (Figures 1-3). Those dissolution data also gave linear plots using Eq. 1, the spherical matrix model proposed by Higuchi (12). This model involves the diffusion of drug dissolving in the penetrating solvent within the polymeric matrix. It is suited to systems in which drug particles are: 1) small relative to the diffusional distance and 2) are uniformly distributed throughout the matrix.

These microspheres contained relatively large drug crystals in relation to the size of the microspheres, which may be regarded as a granular matrix system. The Higuchi model applied to drug release from microspheres is suited to evaluating factors that influence the rate of drug release (Figure 4). The equation can be written as follows:

$1 + 2(F) - 3(F)^{2/3} = Kt$ (Eq. 1)

$F = [a/a_o]^3$ = fraction of drug remaining or undissolved

a_o = radius of the whole microsphere

a = radius of that part of the microsphere still holding drug

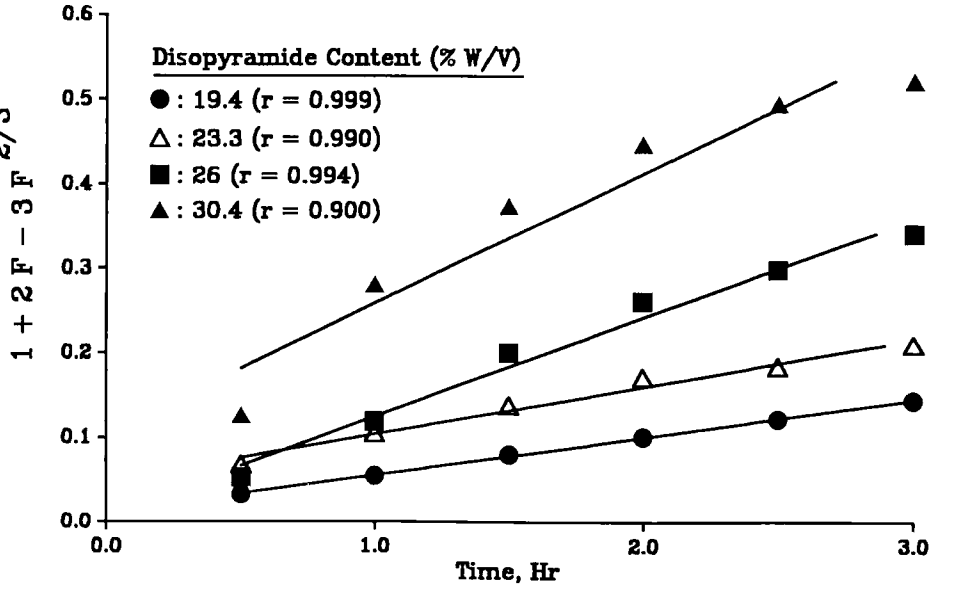

FIGURE 4

Effect of Disopyramide Content on Drug Release from 303 μm Cellulose Acetate Butyrate Microspheres into SGF at 37°C According to Equation 1

t = time

$$K = \frac{6 D k C_s}{A a_o^2}$$ = a constant for a spherical pellet of a homogenous matrix

or

$$K = \frac{6 D k C_s}{\tau a_o^2}$$ = a constant for a spherical pellet of a granular matrix

C_s = drug solubility in the dissolution medium

D = drug diffusivity

k = specific volume of the drug

A = initial drug content per unit volume of the matrix (drug loading)

τ = tortuosity factor of the pore structure

The results show that the release of disopyramide from relatively monodisperse sieve fractions of particles, after an initial surge from exposed drug crystals or aggregates of smaller particles, follows kinetics described by the spherical matrix model. Also, the microsphere size affected the rate of disopyramide release consistent with that predicted by Eq. 1 (Table 2). The CAB microspheres consistently showed an increase release rate with

TABLE 2

Effect of Mean Microsphere Size on the Slopes of the Dissolution Plots According to Eq 1.

Dissolution Medium	Disopyramide Content (%)	Slope of Equation 1[a] of Microsphere Size 153	215	303	428 (μm)
SIF[b]	26		0.132	0.111	0.070
SIF	30.4		0.140	0.120	0.109
SGF[c]	26	0.141	0.133	0.112	0.106

[a] slope = K [b] Simulated intestinal fluid, USP [c] Simulated gastric fluid, USP

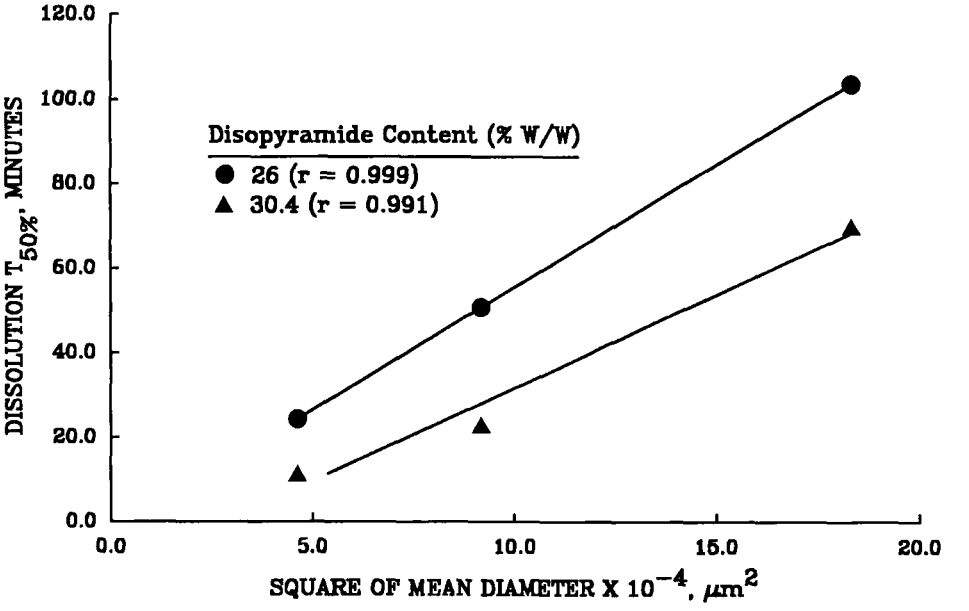

FIGURE 5

Relationship Between the Time for 50% Dissolution ($T_{50\%}$) of the Disopyramide Content and the Square of the Mean Diameter of CAB Microspheres in Simulated Intestinal Fluid at 37°C

increasing disopyramide content. This can be attributed to decreased tortuosity in the diffusion path of the drug. The τ factor would decrease as drug loading increases; thus, predicting shorter $T_{50\%}$ values. The release rate curves of some microsphere sizes or drug loading exhibited a biphasic pattern. This can be attributed to the dissolution of a small fraction of uncoated drug particles located on the surface of the microsphere, or possibly, aggregates of very small microspheres. If diameter (d) is substituted for a_o (radius) in the Higuchi equation (11), then the following adaptation results:

$$1 + 2(F) - 3(F)^{2/3} = \frac{6\,D\,k\,C_s}{\tau\,a_o^2}\,t = \frac{24\,D\,k\,C_s}{\tau\,d^2}\,t \qquad \text{(Eq. 2)}$$

d = diameter of the microsphere = $2\,a_o$

Considering the situation where 50% of drug has been dissolved, or F = 0.5, then the following is obtained:

$$T_{50\%} = K'\,d^2 \qquad \text{(Eq. 3)}$$

$$K' = \frac{0.00459\,\tau}{D\,k\,C_s}$$

Plotting the dissolution $T_{50\%}$ versus the square of the mean diameter, according to Eq. 3, should yield a straight line with a slope equal to K' (Figure 5). There was a better correlation for 26% drug loading (r = 0.999 and 0.999 for SGF and SIF, respectively) than for 30.4% drug loading (r = 0.991 in both media). This is attributed to a greater proportion of uncoated drug in the 30.4% loaded microspheres.

SUMMARY

The results of this investigation showed that the mean diameter of Disopyramide microspheres is affected by the processing conditions and the chemicals used. The dissolution $T_{50\%}$ increased linearly with the square of the mean diameter of the microspheres, and a decrease in the drug loading. In the mean time the addition of acetone to the external phase resulted in decrease in the dissolution $T_{50\%}$. Comparison of dissolution of the drug from the microspheres in SIF and SGF revealed no significant difference in the release of disopyramide. The dissolution data fitted the Higuchi model for dissolution from spherical matrices.

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