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MECHANISM OF MOLECULAR-SCALE DRUG ENTRAPMENT USING COLLOIDAL POLYMERIC LATICES

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ABSTRACT

The mechanism of a molecular-scale entrapment of cationic drug by negatively charged latices was investigated using the measurement of zeta potential as a physical/analytical tool. It was found that as the amount of the drug was increased the zeta potential of latex particles decreased. The simultaneous presence of a dicarboxylic acid with the drug increased the zeta potential. Entrapment products were prepared using diluted latices, a cationic drug (Chlorpromazine hydrochloride), and an entrapment facilitator (succinic acid). The dissolution of the drug from the products was found to be first order in all cases. The data showed that (a) the smaller the particle size the faster the release rate,

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(b) the order of combination (latex to drug or vice versa) did not affect the release rate, and (c) the use of entrapment facilitator (a dicarboxylic acid), did not change the release rate but increased the amount of drug entrapped. The agreement of the first order dissolution and the first order desorption, which is assumed in Stern's electric double layer model, indicated that the entrapment occurred via surface adsorption of the drug by latex particles.

INTRODUCTION

Latices of copolymers composed of acrylic and methacrylic acid, which are anionically charged either due to the partial ionization of their ionogenic carboxylic groups under suitable pH conditions or due to surface sorbed surfactants used in their preparation, have been shown to be capable of being flocculated by cationic drugs. This provides a means for their molecular-scale drug entrapment which can be used to control drug release (1). It has been found that highly uniform drug dispersions are obtainable using this entrapment process. Excellent reproducibility of drug content throughout the entrapment product has been demonstrated (2). Dicarboxylic acids, when used in their anionic forms, can function as drug entrapment facilitators and thereby increase the amount of cationic drug entrapped by the negatively charged colloidal polymeric latices (3,4). The formation of complexes between the polymer carboxylic groups, drug, and acid anions, as well as an inclusion type complex have been speculated as the possible mechanisms for the facilitated entrapment process (3). This paper provides a systematic investigation for the mechanism of this entrapment process.

EXPERIMENTAL

Materials

The polymeric latices used in this study were copolymers of methyl methacrylate and methacrylic acid (Rohm and Haas Company) as shown in

Table I. Chlorpromazine hydrochloride (Smith Kline & French Laboratories) was chosen as a model cationic drug. Succinic acid and malonic acid were the two dicarboxylic acids chosen as the entrapment facilitators. All other chemicals were reagent grades.

Determination of Zeta Potential

Preliminary studies showed that the zeta potential of the latex particles could only be obtained with the Zeta Meter (Zeta Meter Inc., New York) using an extrapolation method since the latex particles were too small to be visualized under the microscope of the Zeta Meter. This extrapolation method involved adding an appropriate polyelectrolyte (A 2.5 mg/ml aqueous solution of Al^{3+} was used in this study) in small, even increments to the sample, which was examined in the electrophoresis cell after each addition. The zeta potential of the first flocculated mass detected by the microscope was determined. This was continued with small additions of the electrolyte to obtain at least two additional zeta potential determinations. The zeta potentials were then plotted vs. electrolyte dosage. The curve connecting these points was extrapolated to the zeta potential axis. The intercept, which represented zero electrolyte addition, was taken as an approximation of the zeta potential of the sample. Linear regression was used to obtain the best estimate of the intercept.

TABLE I

Copolymeric Latices of Methyl Methacrylate and Methacrylic Acid

Designation	pH	Total Solid Content (%)	MMA/MAA Ratio*
A	2.8	38.0	80/20
B	3.1	40.5	70/30
C	2.8	39.3	60/40

*MMA = Methyl Methacrylate, MAA = Methacrylic Acid

Effect of Chlorpromazine HCL on Zeta Potential of Latex Particles

Diluted latices (60 ppm) were used for each zeta potential measurement and their pH was adjusted to 3.0 using a few drops of 6N HCl aqueous solution. Into a 100 ml beaker were added 50 ml of the 60 ppm latex dilution and various amounts of 0.5 mg/ml chlorpromazine HCl aqueous solution. The mixtures were stirred for 10 minutes and the zeta potential for the latex particles was determined using the extrapolation method. The pH of the chlorpromazine HCl aqueous solution was also adjusted to 3.0 before addition.

Effect of Dicarboxylic Acids on the Zeta Potential of Latex Particles

Samples were prepared (Table II) to study the effect of the presence of a dicarboxylic acid on the zeta potential of each latex. The amount of the dicarboxylic acid used is equimolar to the amount of chlorpromazine HCL necessary to bring the zeta potential of each latex to zero.

The scheme in Table III was designed to investigate the effect of the simultaneous presence of an equimolar amount of succinic acid and chlorpromazine HCl on the zeta potential of each latex.

TABLE II

Samples Prepared to Study the Effect of a Dicarboxylic Acid on the Zeta Potential of Latex Particles

Sample*	Succinic Acid (mg)	Malonic Acid (mg	Zeta Potential (mv)
A1	-	-	-17.0
A2	0.45	-	-12.4
A3	-	0.29	-14.8
B1	-	-	-16.8
B2	0.68	-	-10.7
B3	-	0.45	-10.4
C1	-	-	-37.1
C2	0.9	-	-24.9
C3	-	0.6	-19.5

* Fifty milliliters of 60 ppm latex was used in the preparation of each sample.

Table III

Preparation of Samples to Observe the Effect of the Simultaneous Presence of a Dicarboxylic Acid and Chlorpromazine HCl on the Zeta Potential of Latex Particles

Sample*	Succinic Acid (mg)	Malonic Acid (mg)	Chlorpromazine HCl (mg)	Zeta Potential (mv)
A4	-	-	1.0	0
A5	0.45	-	1.0	-11.6
A6	-	0.29	1.0	-11.5
B4	-	-	1.5	0
B5	0.68	-	1.5	- 9.5
B6	-	0.45	1.5	-12.6
C4	-	-	2.0	0
C5	0.9	-	2.0	-36.5
C6	-	0.6	2.0	-41.9

*Fifty milliliters of 60 ppm latex was used in the preparation of each sample.

Dissolution Rate Analysis of Entrapment Products

Three entrapment products were prepared using a 1% latex B (pH adjusted to 3.0).

Product P1: While well stirred, 50 ml of a 4% chlorpromazine HCl aqueous solution (pH adjusted to 3.0) was added in 5 ml increments to 400 ml of 1% latex B. Two minutes stirring was allowed between successive additions. Absolute alcohol was then added to the mixture in 5 ml increment until flocculation was observed. The floccule was filtered and was dried overnight at 37 $\pm$ 2°. The particle size of the dried floccule was reduced using a mortar and pestle, and was separated into three particle size ranges using 60, 80, and 100 mesh sieves.

Product P2: While well stirred, 400 ml of 1% latex B was added in 20 ml increments to 100 ml of 2% chlorpromazine HCl aqueous solution (pH adjusted to 3.0). Absolute alcohol was then added to the mixture in 5 ml

increment until the flocculation was observed. The dried floccule was separated into three fractions as before.

Product P3: This product was obtained in the same manner as P2 except that 0.9008 g of succinic acid (equilmolar to 2 g of chlorpromazine HCl) was added to chlorpromazine aqueous solution and the mixture was stirred for 20 minutes before 1% latex B was added. The dried floccule was separated into three fractions as before.

Dissolution Apparatus: The dissolution apparatus employed was a flow-through cell assembly with accumulative reservoir (5). The dissolution cell is adapted from a Millipore filter[1].

Drug Dissolution Rate Analysis: The dissolution fluid was USP simulated gastric fluid (without enzyme) which was regulated to flow through the dissolution cell at 3.5 ml/min. The dissolution test was conducted at 37 $\pm$ 2^{0}. Exactly 100 mg of the entrapment product was placed in the dissolution cell which was half-filled with 4 mm glass beads. Four milliliters of the dissolution fluid was withdrawn from the reservoir at designated time points, with time zero being taken as the time when the first drop of the dissolution fluid was returned to the reservoir. The concentration of chlorpromazine in the withdrawn sample was determined spectrophotometrically at 255 nm. The samples were returned to the reservoir after analysis. The products tested were P1 60/80 mesh fraction and <100 mesh fraction, P2 60/80 mesh fraction, and P3 60/80 mesh fraction. Each test was run in triplicate.

Determination of Total Amount of Drug Entrapped

Exactly 100 mg of entrapment product was dissolved in 100 ml of 75% ethanol. The concentration of chlorpromazine was determined spectrophotometrically at 258 nm after appropriate dilution.

1. Swinex - 25 Ultrafiltration Cell, Millipore Corp., Bedford, Mass.

RESULTS AND DISCUSSION

As shown in Figure 1, the zeta potential of the particles of each latex decreased as the amount of chlorpromazine hydrochloride increased. Chlorpromazine exists predominately in the cationic form at pH 3. This phenomenon can be explained by Stern's electric double layer model, where the cationic drug is specifically adsorbed onto the negatively charged latex particle surfaces, and thus net charges on the surfaces are reduced.

The results indicate that about 0.75, 1.5 and 2.0 mg of chlorpromazine hydrochloride are required to bring the zeta potential of latex A, B, and C to zero respectively. It should be noted that no flocculation was observed at these levels, since these latex particles are hydro-

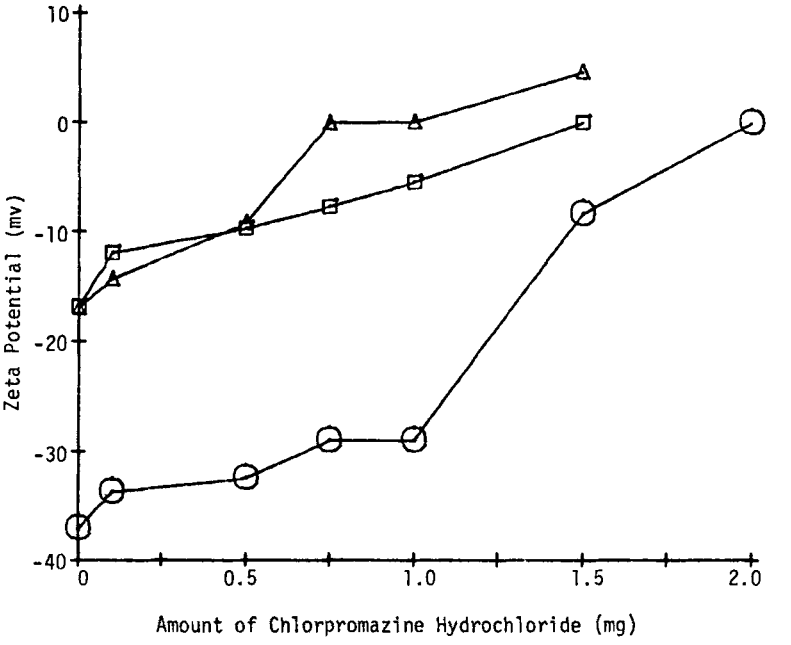

Figure 1

Zeta Potential of A, B, and C Latex Particles at Various Levels of Chlorpromazine Hydrochloride △ Latex A, □ Latex B, ○ Latex C

philic and thus are also protected by a hydration sheath in addition to the electric double layer. Latex A with the lowest MAA content required the lowest drug addition to bring the zeta potential to zero. The general coincidence between the MAA ratio and the amount of added drug required to bring the zeta potential of each latex to zero, is supporting evidence that the partial ionization of the ionogenic carboxylic groups is responsible for drug interaction, rather than any surface charge from sorbed anionic surfactant.

The results in Table 2 show that the presence of dicarboxylic acid alone decreases the zeta potential of the latex particles. This result can be explained on the basis of an acid-base interaction. Table IV gives the dissociation constants for the acids involved, where $(CH_3)_3CCOOH$ is used as a reference compound for the tertiary carboxylic groups in the polymer. Succinic and malonic acids are both stronger acids than the tertiary carboxylic groups in the polymer chain. The ionization of the teritiary carboxylic groups is thus partially suppressed when either succinic or malonic acid is present. This leads to decreased surface charges and thus a smaller zeta potential.

The results shown in Table III indicate that while the presence of a suitable amount of the cationic drug can reduce the zeta potential of latex particles to zero, the simultaneous presence of an equimolar

Table IV

Dissociation Constants of Acids

Acid	pk at 25°	
	pk_1	pk_2
Succinic acid	4.16	5.61
Malonic acid	2.89	5.69
$(CH_3)_3CCOOH$	5.05	----

amount of a dicarboxylic acid allows the maintenance of a negative zeta potential. Apparently, the interaction between the dicarboxylic acid and chlorpromazine decreases the tendency of both the acid-base interaction described in the previous section and the specific adsorption of the cationic drug by the latex particles.

Figure 2 shows a typical dissolution profile observed in this study. Since all dissolution profiles have shapes characteristic of a first order kinetic process, they were treated as such. The first order kinetics for this sytem can be described by Eq. 1:

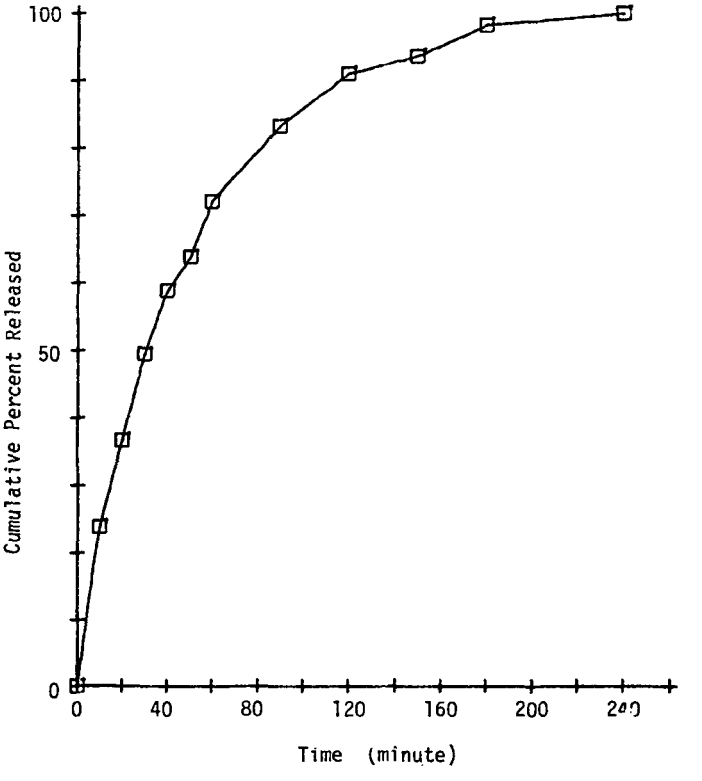

Figure 2

Dissolution Profile of Product P1 < 100 mesh fraction in Simulated Gastric Fluid

$$\log\left(1 - \frac{C_t}{C_\infty}\right) = -\frac{k}{2.303}\, t \qquad \text{(Eq. 1)}$$

where C_∞ is the amount of the available drug released at infinite time and C_t is the amount of available drug released at time t. Thus a plot of log $(1 - C_t/C_\infty)$ vs. t should give a straight line and k can be calculated from the slope of the straight line. A typical straight line obtained using the linear regression method is shown in Figure 3. Excellent correlations are observed (R^2 ranges from 0.97 to 0.99).

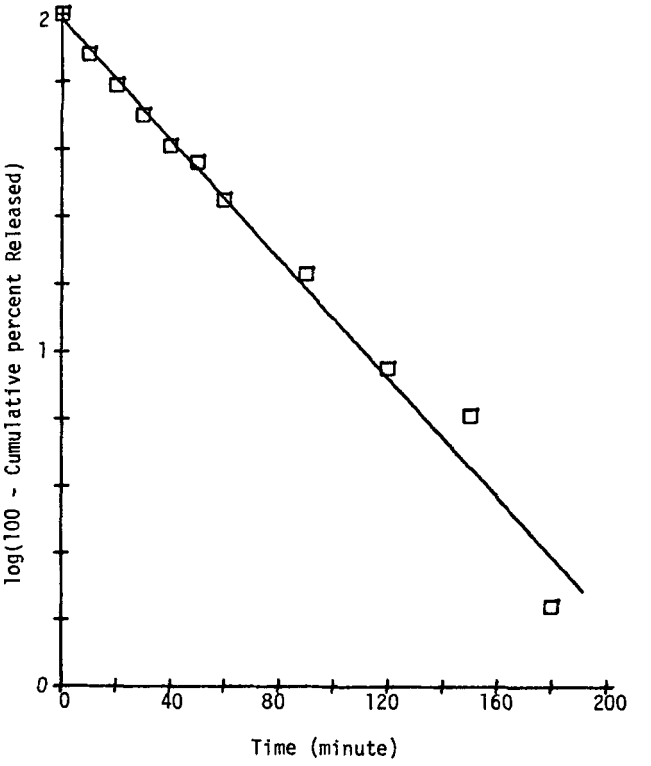

Figure 3

First-Order Kinetic Treatment of Dissolution Data for Product P1 < 100 mesh Fraction in Simulated Gastric Fluid

Statistical analyses were conducted to test the identity (same slope and intercept) of the following three pairs of regression lines at the 95% confidence level (6):

P1, 60/80 mesh and <100 mesh,

P1 and P2, both 60/80 mesh,

P2 and P3, both 60/80 mesh.

The results of the statistical treatment were:

(a) For P1, the regression lines were significantly different for the 60/80 mesh and the <100 mesh fractions. The slopes were also significantly different, with the slope of the <100 mesh fraction being larger. This essentially indicates that as the particle size of the entrapment product is decreased, the rate of the drug release is increased. Apparently this is due to the larger surface area of the smaller particles. The total amount of the drug entrapped, however, remained the same regardless of the particle size (Table V).

(b) There was no significant difference between the regression lines of the 60/80 mesh fractions of P1 and P2 products. Therefore P1 and P2 have the same dissolution behavior even though the order of the addition of the drug solution and the 1% latex was reversed. As also shown in Table V, the amount of drug released in the simulated gastric fluid from 100 mg of product and the total amount of drug entrapped in 100 mg of product are the same.

(c) There was a significant difference between the two regression lines for 60/80 mesh fractions of P2 and P3 products. The slopes, however, were not significantly different. This indicates that the succinic acid does have an effect on the properties of products P2 and P3. The fact that the two slopes, i.e., the dissolution rate constants, are not significantly different suggests that succinic acid does not affect the release rate of the drug from these two products. The difference of the two intercepts of the regression lines is thus inferred from these statistical treatments.

TABLE 5

Amount of Chlorpromazine Hydrochloride Released in Simulated Gastric Fluid at Infinite Time and the Total Amount of Chlorpromazine Hydrochloride Entrapped

Product	Particle Size(mesh)	Amount of Drug Released in Simulated Gastric Fluid at Infinite Time(mg)[a] Seperate Run	Average		Total Amount of Drug Entrapped(mg)[a] Seperate Run	Average		Percentage of Total Drug Released in Gastric Fluid at Equilbrium
P1	< 100	3.34	3.37	S[b]	4.91	4.85	NS[b]	69.5
		3.39			4.79			
P1	60/80	2.52			4.86	4.64		53.9
		2.21	2.50	NS	4.42		NS	
		2.77						
P2	60/80	2.77			5.82	5.62		55.3
		3.46	3.11	S	5.41		S	
		3.09						
P3	60/80	3.65			7.22	7.21		51.1
		3.75	3.68		7.20			
		3.63						

a. For 100 mg entrapment product
b. S = Significantly different at 95% confidence level,
NS = Not significantly different at 95% confidence level.

The intercept is related to the amount of the drug initially available for release in the simulated gastric fluid, i.e., C_∞, which is the amount of the drug released at infinite time. As shown in Table V, the amount of the drug released from P3 was significantly greater than the amount released from P2.

Table V also indicates that the total amount of drug entrapped in the product was significantly greater for the product containing succinic acid (P3) than for the product without it (P2). This is consistent with the higher adsorption capacity of the system when the cationic drug and the dicarboxylic acid are simultaneously present as is concluded form the zeta potential of latex particles.

CONCLUSION

Stern's electric double layer model, which is used to interpret the zeta potential results, assumes a Langmuir monomolecular layer adsorption of the drug on the particle surface, and the Langmuir theory projects the desorption kinetics of such a system to be first order. The agreement of the hypothesized first order desorption and the experimentally determined first order dissolution of the drug is therefore not surprising. As the drug is being released from the particles in the simulated gastric fluid, the low pH value (1.2) of the dissolution medium would result in a hydrophobic surface around each particle (due to the supression of the ionization of the surface carboxylic groups). It was observed that the particles remained dispersed throughout the dissolution tests. The drug released from the particles would thus be limited to that on the particle surface. Therefore the drug release in the simulated gastric fluid would be equivalent to the desorption of the drug from a particle surface. In this system, it is concluded that the adsorption of the drug ions onto the polymeric latex particles bearing an opposite charge, occurs by charge attraction, and can be followed by zeta potential measurements

of the colloidal particles. The mechanism by which the simultaneous presence of equimolar dicarboxylic ion and drug ion increases the absorption capacity of the latex particles has been explained based on acid-base interactions.

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