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EFFECT OF ANIONIC SURFACTANTS ON THE RELEASE OF CHLORPHENIRAMINE MALEATE FROM AN INERT, HETEROGENEOUS MATRIX

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ABSTRACT

The release from a matrix compressed from a physical mixture of chlorpheniramine maleate, chlorinated poly(propylene), lactose and an anionic surfactant (sodium lauryl sulfate and dioctyl sodium sulfosuccinate) has been investigated. The formation of a poorly water-soluble complex between the chlorpheniramine and the anionic surfactant slows the release to a minimum at low concentrations of surfactant; however, at higher concentrations of surfactant the release is faster due to solubilization in the micellar phase of the ion-pair. The interaction between the chlorpheniramine maleate and the anionic surfactant also influences the release of a second, noninteracting compound from the matrix.

INTRODUCTION

In a recent report (1) the release of highly water-soluble medicinal compounds (procaine hydrochloride, ephedrine hydrochloride) from an inert, heterogenous matrix was investigated. The amount of medicinal compound released per unit area was linearly related to the square root of time. The effects on release of the concentration of medicinal compound, particle size of medicinal compound, agitation of dissolution medium, and porosity and tortuosity of the matrix were presented. A subsequent publication (2) reported that the process by which the matrix was prepared effected the release.

Studies (3-6) have shown that the incorporation of a surfactant in a matrix may produce a faster release of a medicinal compound presumably because of the lowering of surface tension and the decrease of contact angle. Investigators (7,8) observed that the interaction between a charged medicinal compound and an oppositely charged surfactant may result in a slowing of release from a matrix.

With the incorporation of nonionic and cationic surfactants in a matrix of chlorinated poly(propylene) the release of procaine hydrochloride is linearly related to the square root of time, and as the concentration of the surfactant is increased, the release is faster (9). Wells and Parrott (9) found that with the incorporation in the matrix of an anionic surfactant (sodium lauryl sulfate) the release of procaine hydrochloride is linearly related to the square root of time; however, the release pattern

depends on the concentration of the anionic surfactant. As the concentration of the sodium lauryl sulfate is increased to 4%, the release is progressively slowed to a minimum as a poorly soluble 1:1 complex between the cationic procaine and the anionic surfactant is formed, and as the concentration of the anionic surfactant is further increased, the release is increased as the complex is micellarly solubilized.

Feely and Davis (10) reported that the rate of release of chlorpheniramine maleate from a hydroxypropyl methylcellulose matrix was reduced as more sodium lauryl sulfate was added to the matrix. This report is concerned with the effect of anionic surfactants within a matrix on the release of chlorpheniramine maleate from a nonswelling, insoluble matrix.

EXPERIMENTAL

Preparation of Compressed Matrixes. The preparation and measurement of the characteristics of the matrixes have been reported (9). Matrix formulations are given in Table 1. The combined weight of surfactant and lactose was kept constant so that an approximately constant porosity of the matrixes was maintained. Chlorpheniramine maleate (Spectrum Chemical Co., lot 91218C1) was classified by U.S. standard sieves into a 100/200-mesh size fraction. Lactose and the surfactants were a 80/100-mesh fraction. Chlorinated poly(propylene) passed a 200-mesh sieve. Aerosol OT-B (American Cyanamid Co. lot SPS-16447) passed a 100-mesh sieve.

TABLE 1

Matrix Formulations of Chlorpheniramine Maleate (CPM), Lactose, Chlorinated Poly(propylene) (CPP), Sodium Benzoate (SB) and Sodium Lauryl Sulfate (SLS) or Dioctyl Sodium Sulfosuccinate (DSS)

Matrix	Milligrams						Percent Surfactant
	CPM	CPP	Lactose	SLS	DSS	SB	
1	40	300	60	0			0
2	40	300	45	15			3.75
3	40	300	30	30			7.50
4	40	300	15	45			11.25
5	40	300	0	60			15.00
6	60	240	140		0	0	0
7	60	240	105		29.75	5.25	6.76
8	60	240	70		59.50	10.50	13.52
9	60	240	35		89.25	15.75	20.28
10	60	240	0		119.00	21.00	27.04
11		240	194.7			5.25	1.18*
12		240	189.5			10.50	2.38*
13		240	184.3			15.75	3.59*
14		240	179.0			21.00	4.77*

*percent sodium benzoate and no surfactant

Dissolution and Solubility. The dissolution of chlorpheniramine maleate (CPM) and sodium benzoate (SB) was conducted at 150 rpm using 600 mL of distilled water at 37°C by methodology described previously (9). The percent of CPM released during the study ranged from 27 to 57% from matrixes 1-5 and from 17 to 46% from matrixes 6-10. The percent of SB released ranged from 27 to 63% from matrixes 6-10 and from 44 to 65% from matrixes 11-14.

RESULTS AND DISCUSSION

Daly et al. (11) observed a reduction in the release rate of chlorpheniramine maleate (CPM) from Synchrom matrixes containing increasing amounts of sodium lauryl sulfate (SLS). The authors attributed this to the interaction of the surfactant with the swelling polymer to cause a more viscous diffusional path for the medicinal compound. They reported no increase in release rate at the higher concentrations of the surfactant.

Feely and Davis (12) studied the effect of SLS on the release of CPM from Methocel K100M matrixes. They observed a linear decrease in release rate with increased fractions of SLS. Using automated conductimetric titrations they demonstrated that the slower release was due to the formation of a poorly soluble complex between the CPM and SLS. They reported that the retarding ability of the surfactant appeared to be saturatable, and the release was constant when all the CPM had been complexed. As such a saturation effect was not observed with

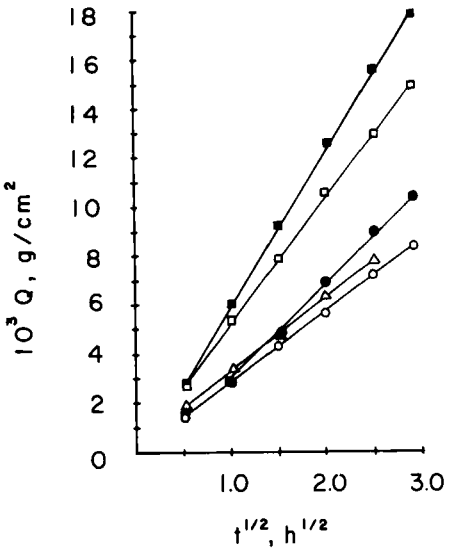

FIGURE 1

Effect of concentration of sodium lauryl sulfate on release of chlorpheniramine maleate from matrixes 1-5. Key: (●) 0%; (○) 3.75%; (△) 7.5%; (□) 11.25%; and (■) 15.0% SLS.

procaine hydrochloride and SLS in a chlorinated poly(propylene) matrix, it was of interest to study this difference (9).

Initially, CPM and SLS were incorporated into an inert, heterogeneous matrix rather than the hydrophilic matrix used by Feely and Davis. The matrix formulas are given in Table 1. The release of CPM from matrixes 1-5 containing from 0 to 15% SLS was measured. With all matrixes Q, the cumulative amount per unit area of CPM released at time t, was linearly proportional to the square root of time. The pattern of release with a minimum is similar to that of procaine hydrochloride from a similar matrix (9). As shown in Figure 1, Q, the amount of CPM released per

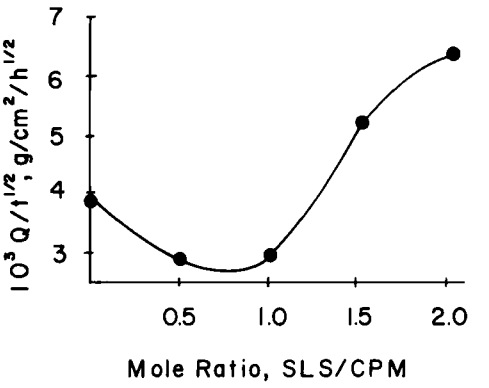

FIGURE 2

Effect of mole ratio of sodium lauryl sulfate to chlorpheniramine maleate on $Q/t^{\frac{1}{2}}$ from matrixes 1-5.

unit area at time t, was decreased as the concentration of SLS was increased to 7.5%; and as the concentration of SLS was further increased to 15%, the release was increased.

The release rates, $Q/t^{\frac{1}{2}}$, of CPM at various mole ratios of SLS to CPM are shown in Figure 2. At low concentrations of SLS complexation between the cationic CPM and anionic SLS forms a poorly soluble 1:1 complex within the pores of the matrix and slows release (9). The solubility product of CPM and SLS is $1.3 \times 10^{-7} M^2$ (10). The small value of the solubility product indicates that precipitation of the complex occurs readily in the microenvironment of the pores at the concentration used in this study. In addition the precipitation of the complex provides a more tortuous pathway and less porous matrix through which the dissolved CPM must diffuse. At mole ratios of SLS to CMP

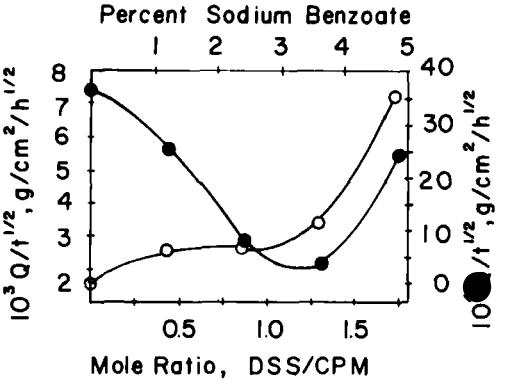

FIGURE 3

Effect of mole ratio of dioctyl sodium sulfosuccinate to chlorpheniramine maleate on $Q/t^{\frac{1}{2}}$ of sodium benzoate and chlorpheniramine maleate. Key: (○) sodium benzoate and (●) chlorpheniramine maleate.

exceeding 1, the release is faster due to solubilization of the ion-pair into the micellar phase.

It has been shown that for an inert, heterogeneous matrix as the porosity of the matrix is increased, there is a greater percent reduction of $Q/t^{\frac{1}{2}}$; and there is also a reduced ability to recover by solubilization the reduction in release rate at the highest percent surfactant because the concentration of free surfactant within the matrix is a function of pore volume (9).

Feely and Davis (12) did not observe an increase in release rate at higher concentrations of surfactant as the hydrophilic matrix swelled and eroded so that the porosity was greater than in the inert matrix under consideration. Thus, the free concentration of surfactant within the pores was less and reduced the ability to solubilize the complex. Also because of the more

porous hydrophilic matrixes, their mole ratios of CPM to SLS may not have been large enough to show an increased release.

As shown in Figure 3, the $Q/t^{\frac{1}{2}}$ rate of CPM is slowed to a minimum as the concentration of dioctyl sodium sulfosuccinate (DSS) is increased to a mole ratio of 1 due to complexation. When the mole ratio of DSS to CPM exceeds 1, the release of CPM is increased because the complex is solubilized into the micellar phase as an ion-pair. In the microenvironment of the pores the concentration of CPM in true solution is increased and with solubilization of the complex the porosity is increased and the tortuosity is decreased. Thus, the release is faster.

The $Q/t^{\frac{1}{2}}$ rate of an additional nonreactive compound, sodium benzoate (SB), is nonlinear as shown in Figure 3. According to the Higuchi equation

$$Q = \sqrt{D\varepsilon \frac{C_s}{\tau} t (2A - \varepsilon C_s)} \qquad \text{(Eq. 1)}$$

in which D is the diffusivity of the compound in the dissolution medium, ε is the porosity of the matrix, C_s is the solubility of the compound in the dissolution medium, τ is the tortuosity, and A is the concentration of the medicinal in the matrix, one would anticipate that the release would be proportional to the square root of A; however, the assumption in the derivation of the Higuchi equation that $A>C_s$ by a factor of 3 or 4 is not valid for highly water-soluble compounds. For highly water-soluble compounds A/C_s <4, and the concentration

of medicinal compound within the pores of the matrix does not reach saturation. The highest concentration of SB attainable is

$$C = A/\varepsilon \qquad \text{(Eq. 2)}$$

Substituting Eq. 2 for the solubility term in Eq. 1

$$Q = A\,[(Dt)/\tau]^{\frac{1}{2}} \qquad \text{(Eq. 3)}$$

which for highly water-soluble compounds describes Q as directly proportional to A.

There may be more than one medicinal compound in a solid dosage form. Although the second medicinal compound may not interact with the surfactant, its release could be influenced by the interaction of an ionized medicinal compound and an oppositely charged surfactant since that interaction changes the porosity and tortuosity of the matrix. To compare the effect of complexation of CPM and DSS on the release profile of an additional unreactive compound, matrixes 11 to 14 were prepared with the same concentration (A) of sodium benzoate as matrixes 7-10 but without surfactant or CPM. Porosity was maintained relatively constant by the additional lactose.

The $Q/t^{\frac{1}{2}}$ rates from matrixes containing only SB are compared in Figure 4 to those from matrixes containing CPM, DSS and SB. As predicted by Eq. 3 the release of SB from matrixes containing no CPM or no surfactant is proportional to its concentration.

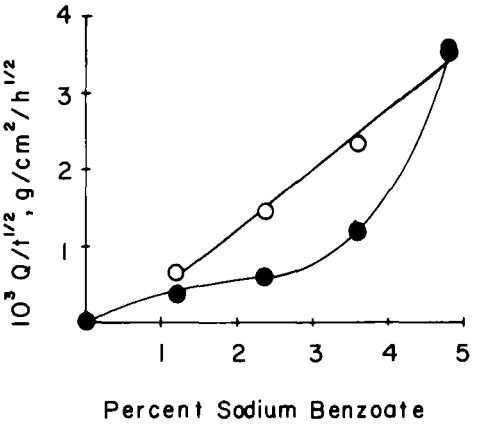

FIGURE 4

The $Q/t^{\frac{1}{2}}$ rate of sodium benzoate from matrixes containing (●) dioctyl sodium sulfosuccinate and chlorpheniramine maleate and from matrixes containing (○) no DSS and no CPM.

The $Q/t^{\frac{1}{2}}$ rates of SB from matrixes 8 and 9 containing CPM and DSS are slower due to complexation forming a poorly soluble complex of CPM and DSS, which upon precipitation within the pores, decreases the porosity and increases the tortuosity. In matrix 10 sufficient DSS is present to solubilize the complex, and the release of SB becomes indistinguishable from that of a matrix 14 containing no CPM and no DSS because solubilization of the complex increases the porosity and decreases the tortuosity.

CONCLUSION

The incorporation of an anionic surfactant in an inert, heterogenous matrix containing a cationic medicinal compound modifies the release of the medicinal compound. At low mole ratios of SLS or DSS to CPM the release of CPM is slowed as a

poorly soluble complex is formed; and then with a further increase in the mole ratio the release is faster as the complex is solubilized in the micellar phase as an ion-pair. The release from the matrix of a second medicinal compound, which does not interact with the surfactant, is modified by the complexation of CPM and the oppositely charged surfactant.

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