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WATER BASED SILICONE ELASTOMER CONTROLLED RELEASE TABLET FILM COATING III - DRUG RELEASE MECHANISMS

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ABSTRACT

The release of potassium chloride from polyethylene glycol-silicone elastomer coated tablets was achieved by the diffusion through water-filled pores formed in the hydrated coating and the osmotic pumping generated by the saturated salt solution. The relative contribution of these two mechanisms to the overall drug release rate was shown to be a function of the polyethylene glycol loading in the coating. As the polyethylene glycol loading level increased, the transpore diffusion became the predominant release mechanism. The capability of the polyethylene glycol-silicone elastomer coatings to provide controlled

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release for therapeutic agents of different water solubilities and dose levels was also demonstrated. Both the rate and extent of release of the active ingredients could be altered by the type of diluent used in the tablet matrix.

INTRODUCTION

For the silicone elastomer system investigated in this study, the hydrophilicity of the polymer is greatly enhanced by the colloidal silica filler as demonstrated by the substantial water uptake of the free film in water[1]. It has also been shown that silicone elastomer free films consisting of 10% PEG swelled extensively in water. However, potassium chloride tablets coated with silicone elastomer containing 10% PEG showed no sign of drug release[2]. This result indicates that the permeation of potassium chloride through a swollen continuous silicone elastomer network is essentially negligible. The SEM photomicrographs for PEG-silicone elastomer tablet coatings and the corresponding freeze dried hydrated samples showed the presence of pores which were formed during the coating process and also produced by the leaching of PEG in water[2]. *In vitro* drug release test results further confirm the significant role of pore formation in the release of potassium chloride from the coated tablets, hence the transpore diffusion could be the major drug release mechanism. It has also been demonstrated that PEG-silicone elastomer coated potassium chloride tablets swelled and changed their shape from a flat disk to an oblate spheroid in deionized water during the course of drug release. This phenomenon may be the manifestation of an internal pressure buildup which may also contribute to the drug

transport from the coated tablets. Experiments were designed to investigate the nature of the driving force for the expansion of the coated tablet, to determine the correlation between the swelling phenomenon and the controlled drug release profiles and to quantitate the magnitude of force generated by the swelling of the coated tablets. The capability of the PEG containing silicone elastomer coating system to provide controlled release for other therapeutic agents with different physicochemical properties and dose levels was demonstrated using formulated tablets of chlorpheniramine maleate, pseudoephedrine hydrochloride and dextromethorphan hydrobromide. The influence of tablet diluents used on the drug release profiles for PEG-silicone elastomer coated tablets containing these agents was also investigated.

EXPERIMENTAL

Materials:

The coating components used were from the same source as reported previously[1,2]. The three therapeutic agents are USP grade products. Chlorpheniramine maleate and pseudoephedrine hydrochloride were obtained from Ruger Chemical Company. Dextromethorphan hydrobromide was supplied by Hoffman-La Roche.

Methods:

Measurement of the Internal Pressure Build-Up for Swelling Coated Tablets in Water:

The swelling of the PEG-silicone elastomer coated potassium chloride tablets in water was postulated to be the result of an appreciable internal pressure build-up. A method was developed to measure the force generated by the expansion of a coated tablet in water. A tablet sample holder was designed and used to confine

the lateral expansion of the coated tablet during the test. The top part of the holder consisted of two circular plexiglass disks, 9 cm in diameter, each with a centered die hole of 1.2 cm in diameter. The two disks were glued together with a piece of circular 20 mesh stainless steel screen placed between the two die holes. The top part was mounted onto a plexiglass supporting ring which was 9 cm in diameter and 7 cm in height. The tablet sample holder was placed in a 1,000 ml beaker. The beaker was filled with deionized water to the 900 ml mark. A coated tablet was then placed inside the center hole. The beaker with the holder was seated on a magnetic stirrer which was placed on the lower platen of the Instron Tensile Tester[a]. An aluminum rod, 17.5 cm in length and 1.27 cm in diameter, was connected to a 2.0 Kg compression load cell. The strip chart recorder was switched on and the aluminum rod was lowered into the die using the manual drive. When the rod was in contact with the tablet sample, deflection of the recorder pen was noted. The rod was then raised slowly until the recorder pen returned to the base line. The stirring of the water inside the beaker was achieved by a stir bar inside the supporting ring. The gap between the rod and the die wall as well as the screen underneath the sample allowed uniform circulation of the aqueous medium around the sample, so that a sink condition was maintained. As pressure was developed inside the dissolving tablet core, the coated tablet expanded vertically exerting force onto the rod. The magnitude of the force was recorded by the strip chart recorder. The experiment was conducted at room temperature. During the test, the strip chart recorder was switched off and the maximum expansion force was recorded by the deflection of the recorder pen at one fixed chart position.

Quantitation of the Extent of Swelling for Coated Tablets in Water:

It has been demonstrated that PEG-silicone elastomer coated potassium chloride tablets swelled and changed their shape from a flat disk to an oblate spheroid in deionized water during the drug release evaluation studies. The extent of swelling changed during the course of drug release. The extent of tablet swelling was quantitated by measuring the volume changes of the coated tablets using a volumetric apparatus which consisted of a 10 cc glass syringe barrel with a 0.2 cc calibrated scale and a 0.5 ml graduate pipette with a 0.01 ml subdivision. Both parts were fixed onto a buret clamp and held vertically on a buret stand. The tip of both parts was connected by a Tygon tubing (4.0 mm in internal diameter) and half-filled with deionized water. The position of the pipette was adjusted so that the water meniscus in the syringe barrel exactly read 6.0 cc. The position of the water level in the pipette was recorded. When a swollen tablet sample was immersed in the syringe barrel, an equal volume of water was displaced by the tablet sample. As a result, the water level in both parts rose. The pipette was then lowered until the water meniscus in the syringe barrel lined up with the 6.0 cc mark. The volume of the swollen tablet sample was calculated as the difference between the water levels in the pipette before and after the immersion of the sample and expressed in cm^3. During the *in vitro* drug release testing, the volume of the coated tablet was monitored. At each sampling time, the tablet sample was removed gently (to avoid any damage to the hydrated coating) from the dissolution medium.

Adhering surface water droplets were removed using a piece of filter paper. The volume of the tablet sample was measured immediately. After the measurement, the sample was returned to the dissolution medium and the release testing continued. The correlation between the tablet swelling and the drug release profile was subsequently established.

Preparation and Coating of Tablets Containing Different Therapeutic Agents:

The components of these tablets are given in Table 1. Chlorpheniramine maleate tablets were prepared by a wet-granulation procedure. The direct compression method was employed in the preparation of pseudoephedrine hydrochloride and dextromethorphan hydrobromide tablets. An adequate amount of granules or powder was weighed out individually and compressed into 7/16 inch standard cup shaped tablets using the Stokes Model RB2 rotary press[j] run in the manual mode. Tablet coating was conducted using the six-inch Glatt air suspension column[k]. The operation variables for coating were the same as those used for the coating of potassium chloride tablets[2]. The Standard USP Dissolution Method I, the basket method, was used to determine the drug release profiles for all coated tablets. The rotating basket speed was set at 100 rpm. Two dissolution media, the USP Simulated Gastric Fluid (without enzyme) and the USP Simulated Intestinal Fluid (without enzyme) were used. Both dissolution media were degassed by applying a vacuum for 10 minutes before use. Drug release from the coated tablets was monitored for 12 hours. The test was conducted in the simulated gastric fluid for the first 2 hours and in the simulated intestinal fluid for the remaining 10 hours. The amounts of drug released were determined by measuring the UV absorbance of the

Table 1. The Composition of Tablets Containing the Three Different Therapeutic Agents

Table Code	Components	Weight in Tablet (mg)
CL	Chlorpheniramine Maleate	12.0
	Lactose[b]	388.0
	Polyvinylpyrrolidone[c]	10.0
	Magnesium Stearate[d]	4.0
CA	Chlorpheniramine Maleate	12.0
	Calcium Phosphate, Dibasic[e]	385.0
	Starch, Potato[f]	95.0
	Polyvinylpyrrolidone	15.0
	Magnesium Stearate	5.0
SL	Pseudoephedrine Hydrochloride	120.0
	Directly Compressible Lactose[g]	280.0
	Magnesium Stearate	4.0
SC	Pseudoephedrine Hydrochloride	120.0
	Unmilled Dicalcium Phosphate[h]	285.0
	Avicel PH 101[i]	95.0
	Magnesium Stearate	5.0
DL	Dextromethorphan Hydrobromide	60.0
	Directly Compressible Lactose	340.0
	Magnesium Stearate	4.0
DC	Dextromethorphan Hydrobromide	60.0
	Unmilled Dicalcium Phosphate	330.0
	Avicel PH101	110.0
	Magnesium Stearate	5.0

Table 2. Maximum Swelling Force Recorded for Potassium Chloride Tablets Coated with Silicone Elastomer Containing PEG 8000 at Three Different Loading Levels.

Loading Level of PEG 8000	Maximum Swelling Force (g)
20	125.8* (11.58)
30	52.5 (9.35)
40	25.8 (5.85)

* Mean and standard deviation for six samples.

dissolution fluid sample withdrawn at fixed time intervals. A wavelength of 264 nm was used for the chlorpheniramine maleate; 256.5 nm for pseudoephedrine hydrochloride; and 278 nm for dextromethorphan hydrobromide.

RESULTS AND DISCUSSION

Maximum Force Recorded for the Swelling Coated Potassium Chloride Tablets:

Table 2 gives the maximum swelling forces for potassium chloride tablets coated with PEG-silicone elastomers containing PEG 8000 at three different levels. Unmilled dicalcium phosphate tablets coated with these formulations were also tested. The maximum swelling force recorded from these insoluble coated tablets were less than 10.0 g regardless of the PEG loading level in the coatings. This result indicates

that the internal pressure buildup in the potassium chloride containing coated tablets is primarily due to the osmotic effect of potassium chloride in solution. Since the thermodynamic activity of water is higher in the surrounding sink than it is in the saturated solution of potassium chloride, a unidirectional flow of water takes place through the hydrated silicone elastomer membrane and into the coated tablet. If the hydrated film coating is pore free, the pressure in the coated tablet rises and eventually reaches the osmotic pressure generated by the saturated potassium chloride solution. However, with pores existing in the hydrated film coating, the pressure buildup within the dissolving tablet would be relieved by the flow of potassium chloride solution through the pore out of the tablet. Drug release achieved by the mechanism is referred to as osmotic pumping effect[3]. Additionally, the magnitude of the swelling forces recorded for different coating formulations further supports the speculation that systems with low PEG loading levels in the formulations demonstrated higher internal pressure buildup because of the low porosity of the hydrated coating.

Extent of Swelling of Coated Tablets in Water:

The precision and accuracy of the apparatus designed for the measurement of the volume of a coated tablet in water were evaluated using ten plexiglass spheres with a diameter of 9.5 mm. The volume of each sphere was calculated using the measured diameter. The computed volume was compared with the volume measured using this apparatus. The difference between the calculated and the measured volume was found to be less than 5.0% and no statistical significance (at $\alpha = 0.05$) was shown between these two values for ten spheres tested using a paired t-test. Also, the difference between five measurements made for each sample was less

than 7.5%. Therefore, this apparatus provides an accurate and reproducible method for the volume determination of swollen tablets. Figures 1 to 3 show the changes in volume for the potassium chloride tablets coated with PEG-silicone elastomers containing three different levels of PEG 8000 during the 6-hour or 12-hour dissolution test in water. The changes in the release rate of potassium chloride from these coated tablets are also presented in Figures 1 to 3. During the course of drug release, extensive swelling of the coated tablets yielded approximately 40% increase in volume. Tablets of unmilled dicalcium phosphate were prepared and coated along with the potassium chloride tablets. No swelling of the coated insoluble tablets was observed when they were in contact with water. Therefore, it is concluded that the internal pressure which is responsible for the swelling of the coated tablet is generated by potassium chloride in solution. The contribution of the osmotic pumping effect to the release of potassium chloride from the coated tablet is not only evidenced by the swelling phenomenon, but also supported by the correlation between the swelling time profile and the release rate-time profile (Figures 1-3). It is apparent that the drug release rate of the system reaches the steady state when the system attains the maximum swelling. The decline of the drug release rate and the decrease in the swollen volume of the system also occur concurrently.

The Contribution of the Transpore Diffusion and the Osmotic Pumping to the Overall Release of Potassium Chloride:

Experimental evidence from previous experiments indicate that transpore diffusion and osmotic pumping are the two major mass transport mechanisms for the

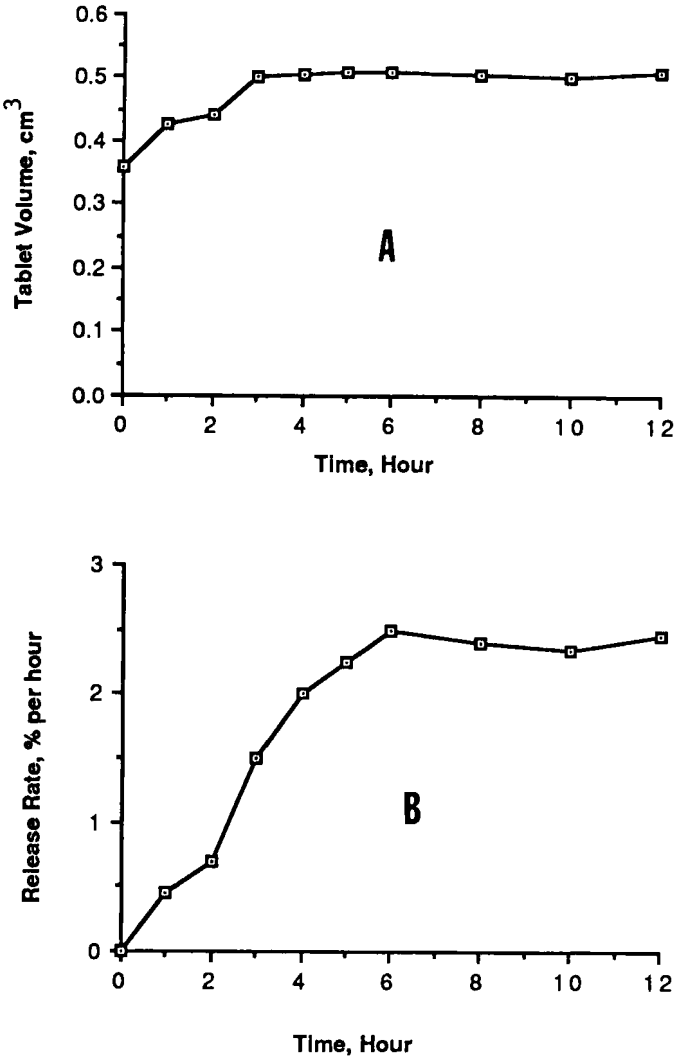

Figure 1

The Correlation Between the Swelling Profile and Release Rate Profile for Potassium Chloride Tablet Coated with Silicone Elastomer Containing 20% PEG 8000. Key: (A) Swelling Profile and (B) Release Rate Profile.

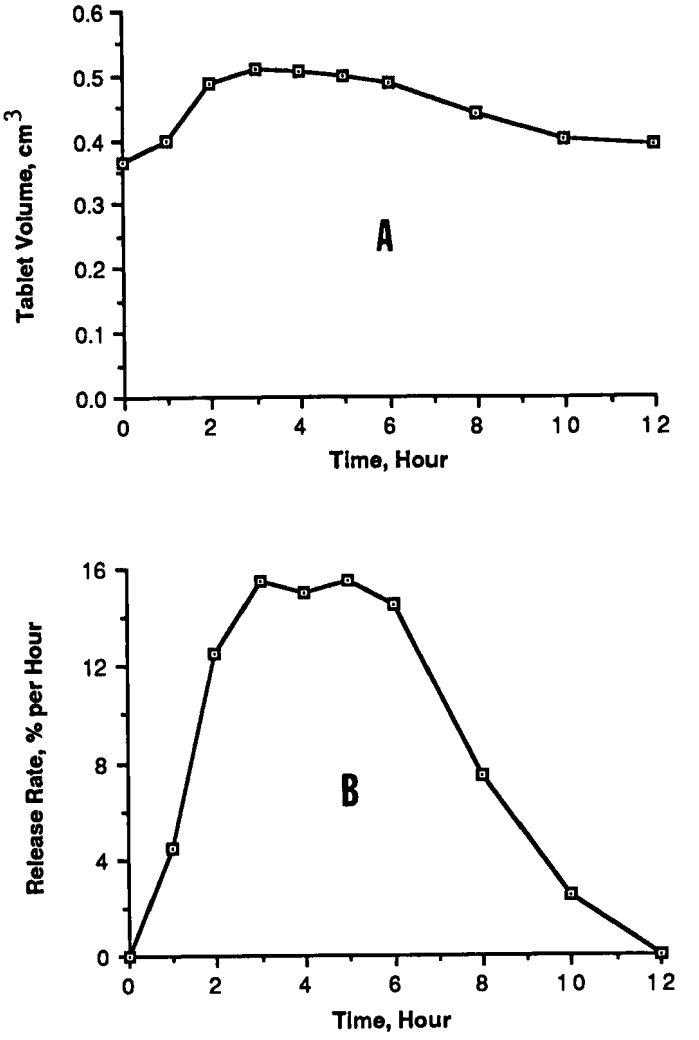

Figure 2

The Correlation Between the Swelling Profile and Release Rate Profile for Potassium Chloride Tablet Coated with Silicone Elastomer Containing 30% PEG 8000. Key: (A) Swelling Profile and (B) Release Rate Profile.

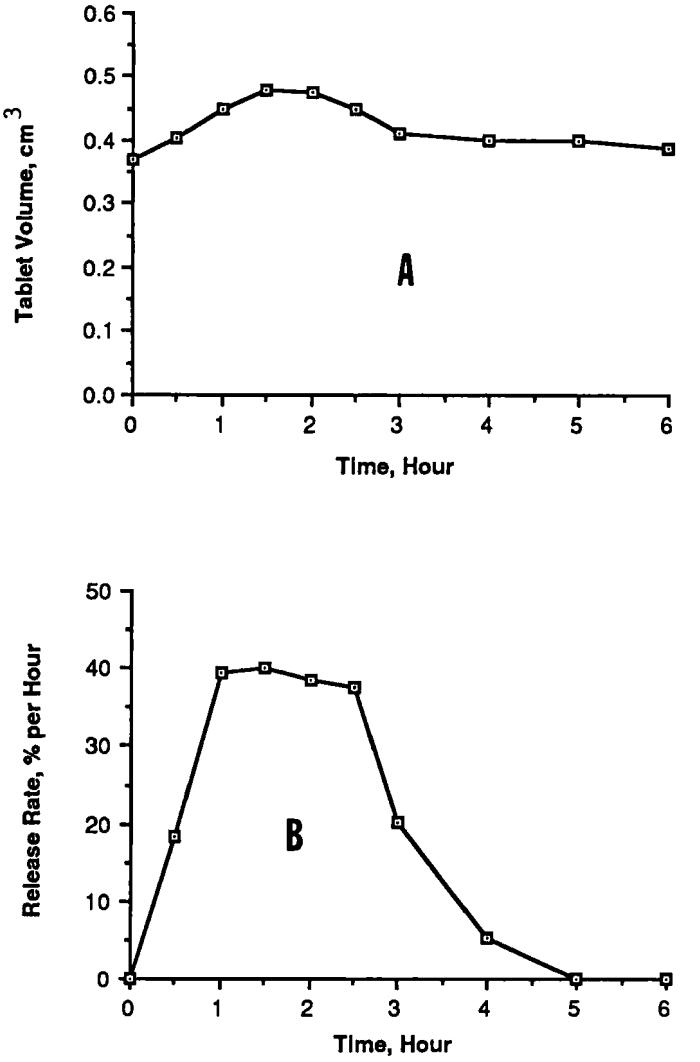

Figure 3

The Correlation Between the Swelling Profile and Release Rate Profile for Potassium Chloride Tablet Coated with Silicone Elastomer Containing 40% PEG 8000. Key: (A) Swelling Profile and (B) Release Rate Profile.

delivery of potassium chloride from the PEG-silicone elastomer coated tablets. Zenter et al., proposed a method to determine the relative contribution of the transpore diffusion and osmotic pumping to the release of potassium chloride from tablets coated with sorbitol containing cellulose acetate coating[4]. This method is somewhat tedious. A simplified method was developed in this study. The release rate of potassium chloride achieved by the transpore diffusion at the steady state can be described by Equation 1[5]:

$$R_d = \frac{A}{l} K_d DS \qquad \text{(Eq. 1)}$$

where R_d is the zero-order transpore diffusional rate of potassium chloride (g/hr). A is the surface area of the swollen tablet system (cm^2), l is the thickness of the hydrated film coating (cm), K_d is a constant representing the porosity and tortuosity of the hydrated coating, D is the diffusion coefficient of potassium chloride (cm^2/hr) and S is the aqueous solubility of potassium chloride (g/cm^3).

The zero-order release rate of potassium chloride response to the osmotic pumping effect is given by Equation 2[6]:

$$R_o = \frac{A}{l} K_o S \Delta\Pi \qquad \text{(Eq. 2)}$$

where R_o is the zero-order pumping rate of potassium chloride (g/hr), K_o is the water permeability of the hydrated film coating (cm^2/atm X hr), $\Delta\Pi$ is the osmotic pressure differential across the film coating and A, S and l are defined as Equation 1. Since deionized water was used as the dissolution medium, the osmotic pressure differential is equal to the osmotic pressure of a saturated potassium chloride solution (Π). By combining Equations 1 and 2, the following equation

results which describe the total drug release rate at steady state:

$$R_t = \frac{A}{l} S (K_d D + K_o \Pi) \qquad \text{(Eq. 3)}$$

The ratio between these two drug transport processes can be shown as follows:

$$\frac{R_o}{R_d} = \frac{K_o}{K_d} \frac{\Pi}{D} \qquad \text{(Eq. 4)}$$

In Equation 4, the (K_o/K_d) term is related to the properties of the hydrated silicone elastomer film coating and the (Π/D) term is determined by the saturated potassium chloride solution. In order to determine the (K_o/K_d) term for a specific PEG-silicone elastomer film coating, a method involving the use of another salt was developed. Sodium chloride was chosen because of its similar chemical nature to potassium chloride. Tablets of sodium chloride were prepared and coated along with the potassium chloride tablets. The zero-order release rate of the salt from both coated tablets was determined in deionized water at 25°C. For one specific coating formulation and with the same coating weight (60 mg), it is assumed that A, l, K_d and K_o are constants for both coated tablets. The following relationship can be established:

$$R_k = \frac{A}{l} S_k (K_o \Pi_k + K_d D_k) \qquad \text{(Eq. 5)}$$

$$R_n = \frac{A}{l} S_n (K_o \Pi_n + K_d D_n) \qquad \text{(Eq. 6)}$$

where the subscript k refers to potassium chloride and the subscript n indicates sodium chloride. Dividing Equation 5 by Equation 6, the resulting equation is:

$$\frac{R_k}{R_n} \quad \frac{S_k\ (K_o\ \Pi_k + K_d D_n)}{S_n\ (K_o\ \Pi_n + K_d D_n)} \qquad \text{(Eq. 7)}$$

After rearrangement, Equation 7 is stated as Equation 8.

$$\frac{K_o}{K_d} \quad \frac{R_n S_k D_k - R_k S_n D_n}{R_k S_n \Pi_n - R_n S_k \Pi_k} \qquad \text{(Eq. 8)}$$

Therefore, the (K_o/K_d) term for a specific coating formulation can be determined by solving Equation 8. The constants and parameters on the right-hand side of Equation 8 can either be calculated theoretically or measured experimentally. The osmotic pressures were calculated from Equation 9[7].

$$\Pi = \frac{RT}{\bar{V}_a} W_a \frac{Mv}{1000} \phi \qquad \text{(Eq. 9)}$$

Where R is the gas constant (82.057 cm^3 atm/mol K), T is the absolute temperature (^oK), W_a is the molecular weight of water (g/mol), M is the molality of the salt in the solution, v is the number of moles of ions formed from 1 mole of salt, ϕ is the molal osmotic coefficient and $\bar{V}_a$ is the partial molal volume of water in the solution. Some of these parameters are given in Table 3. The partial molal volume of water in the saturated solution of these two salts was determined using the Gibbs-Duhem equation method[9]. The $\bar{V}_a$ value for sodium chloride solution was determined to be 17.868 cm^3/mole and a $\bar{V}_a$ value of 17.412 cm^3/mole was obtained for the potassium chloride solution. The calculated osmotic pressure for sodium chloride solution was 398.86 atm and an osmotic pressure of 247.04 atm was computed for the potassium chloride solution. Table 4 gives the mean release rate (25°C) for sodium chloride and potassium chloride from tablets

Table 3. Some Physicochemical Properties of Potassium Chloride and Sodium Chloride Saturated Solution at 25°C.

	Sodium Chloride	Potassium Chloride
Formula Weight	58.5	74.5
Solubility (a)		
g/cm^3	0.317	0.312
Molality	6.145	4.810
Diffusion Coefficient (b)		
(cm^2/hr)	0.0572	0.0791
Molal Osmotic (b)	1.271	0.988

(a) From Reference 8.

(b) From Reference 7.

Table 4. Release Rate for Sodium Chloride and Potassium Chloride from Coated Tablets at 25°C and the Calculated (K_o K_d) Ratio for Silicone Elastomer Coatings Containing Three Different Levels of Polyethylene Glycol 8000.

PEG Loading Level (%)	Release Rate (mg/hr.) Sodium Chloride	Potassium Chloride	(K_o/K_d)
20.0	11.7* (0.70)	11.7 (0.55)	1.331×10^{-3}
30.0	60.1 (2.87)	66.7 (2.21)	7.203×10^{-5}
40.0	138.7 (4.62)	177.2 (5.85)	1.792×10^{-5}

* Mean and standard deviation for six samples.

Table 5. Relative contribution of Transpore Diffusion and Osmotic Pumping to the Overall Drug Release Rate of Sodium Chloride and Potassium Chloride from Coated Tablets.

	Drug Release Rate (mg/hr.)			
	Sodium Chloride		Potassium Chloride	
PEG 8000 Level (%)	Transpore Diffusion	Osmotic Pumping	Transpore Diffusion	Osmotic Pumping
20.0	6.07 (51.9%)*	5.63 (48.1%)	8.26 (70.6%)	3.44 (29.4%)
30.0	40.03 (66.6%)	20.07 (33.4%)	54.43 (81.6%)	12.27 (18.4%)
40.0	123.3 (88.9%)	15.40 (11.1%)	167.81 (94.7%)	9.39 (5.3%)

* Percent of the overall drug release rate.

coated with PEG-silicone elastomer formulations containing PEG 8000 at three different load levels. The (K_o/K_d) ratios calculated using Equation 8 are also presented in Table 4. By applying Equation 4, the ratio as well as the percent contribution of these two transport processes to the overall drug release of the two salts from coated tablets were calculated and are given in Table 5. Owing to the relatively higher diffusivity and lower osmotic pressure associated with potassium chloride, the transpore diffusion consistently played a more significant role in the release of this salt than in the case of sodium chloride. When comparing different formulations, it

was shown that as the PEG loading level increased from 20% to 30%, a nearly four-fold increase in the osmotic pumping release rate was achieved. At a 40% PEG loading level, the osmotic release rate dropped slightly. It is also noted that the PEG loading in the coating exhibited a more pronounced influence on the transpore diffusion release rate. An increase in PEG loading level from 20% to 30% resulted in an approximately seven-fold increase in the diffusional release rate and a three-fold increase was seen when the PEG loading level was increased to 40%. Since the transpore release rate is controlled by the degree of pore formation in the hydrated coating, the transpore diffusion process is expected to be more predominant in high PEG loaded coatings. The relationship between the osmotic pumping effect and the PEG loading in the coating appears to be somewhat complicated. For a low PEG loaded coating, due to the limited void fractions created in the hydrated film coating, the osmotic water inflow may readily exceed the bulk outflow of solution through the limited number of open pores. This situation may consequently lead to an appreciable hydrostatic pressure buildup. The development of this opposing pressure could cause a considerable reduction in the rate of osmotic water inflow as well as the osmotic pumping release rate. The existence of this hydrostatic pressure buildup has been evidenced by the significant internal expanding force recorded from the swelling coated tablets. As the PEG loading level in the coating increased from 20% to 30%, the hydrated film coating became more porous and less resistant to the solution outflow, resulting in a more significant osmotic effect. A further examination of the percent contribution of these two proposed release mechanisms would indicate that the transpore diffusion played a

more significant role than the osmotic pumping, particularly for high PEG loaded coatings. Despite the insignificant direct contribution of the osmotic pumping to the overall drug release, the osmotic pressure induced expansion of the coated tablet may possibly result in further pore formation and/or pore enlargement in the hydrated film coatings. This secondary osmotic pressure effect may enhance the drug release from tablets coated with high PEG loaded formulation because of the inherently tenuous nature of the hydrated coatings.

The Controlled Release of Three Different Therapeutic Agents from Coated Tablets:

The effect of tablet diluents and PEG loading level of the silicone elastomer coating on the release of chlorpheniramine maleate from coated tablets is shown in Figure 4. Due to the low dose level of this drug, the amount of active ingredient is only about 2% to 3% of the tablet weight, hence, the type of tablet diluent use may dictate the release behavior of the coated tablets. The pronounced difference between the extent and rate of drug release as seen in Figure 4 provides an excellent illustration of the diluent effect. Since the development of a significant osmotic pressure by the water insoluble tablet matrix is negligible, the release of the active ingredient is predominantly achieved by the transpore diffusion. On the other hand, for the lactose tablet matrix, an osmotic pressure is readily generated by the dissolving tablet core. The existence of this osmotic pressure effect was further evidenced by the noticeable swelling of the lactose containing coated tablets in water. Thus, the osmotic pumping as well as the transpore diffusion appear to be operative concurrently for the release of chlorpheniramine maleate from the water

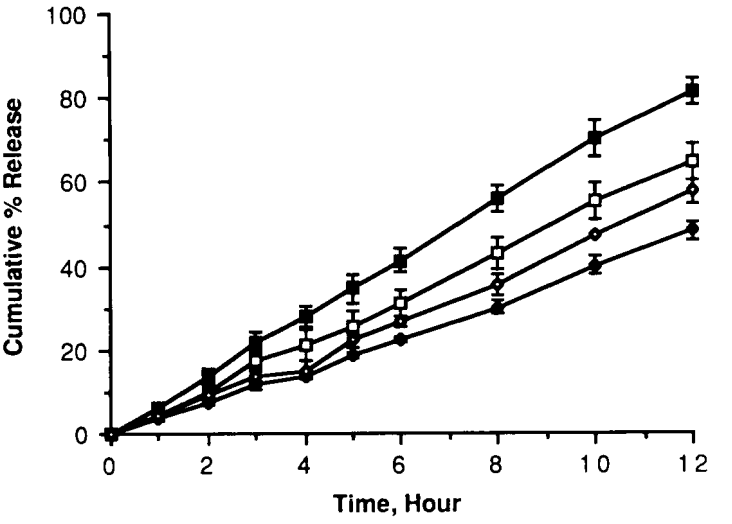

FIGURE 4

The Effect of Tablet Diluent Used and PEG Loading Level in Silicone Elastomer Coating on the Release Profiles of Chlorpheniramine Maleate from Coated Tablets. Key: Tablet Diluent; (■), (◇) Lactose and (□) (◆) Dicalcium Phosphate: PEG Level: (◇), (◆) 30% and (□), (■) 35%.

soluble tablet matrix. Furthermore, it is also possible to propose that the difference in the extent and rate of drug release from these two tablet matrices is a measure of the net osmotic pumping effect.

Figure 5 shows the effect of tablet diluent and coating formulation on the release of pseudoephedrine hydrochloride from coated tablets. The release of the active ingredient appears to be independent of the type of tablet diluent used. The high water solubility of pseudoephedrine hydrochloride (2.0 g/ml at 25°C) and its relatively high dose level in the tablet matrix may reduce the influence of the tablet diluent. Considering the tablets containing unmilled dicalcium

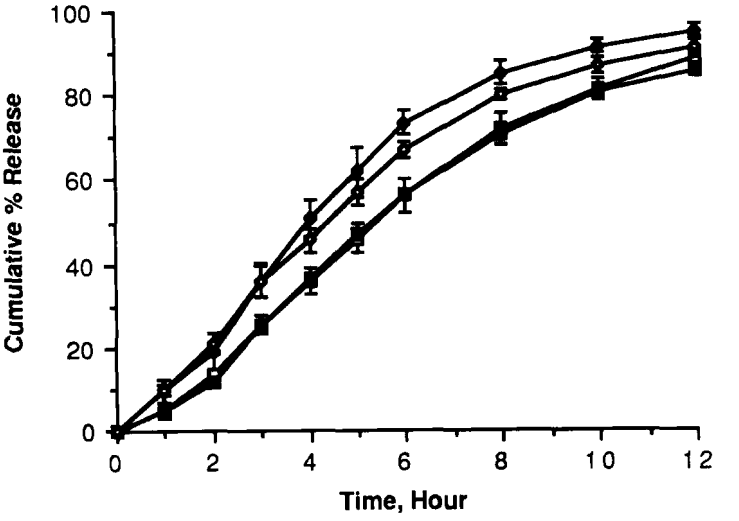

FIGURE 5

The Effect of Tablet Diluent Used and PEG Loading Level in Silicone Elastomer Coating on the Release Profiles of Pseudoephedrine Hydrochloride from Coated Tablets. Key: Tablet Diluent; (□), (◆) Lactose and (■) (◇) Unmilled Dicalcium Phosphate-Avicel; PEG Level: (□), (■) 30% and (◇), (◆) 35%.

phosphate and Avicel, the amount of pseudoephedrine hydrochloride present constitutes 25% of the tablet core. Any osmotic pressure buildup would be contributed by the presence of this water soluble active ingredient. On the other hand, in the lactose containing tablet, the penetrating dissolution medium probably would affect the dissolution of lactose and pseudoephedrine hydrochloride. The competition for free water between these two water soluble components may lead to a decrease in the solubility of both ingredients. The dissolving lactose may enhance the osmotic pressure buildup; but, at the same time, the saturated concentration of pseudoephedrine hydrochloride in the dissolving tablet matrix would be

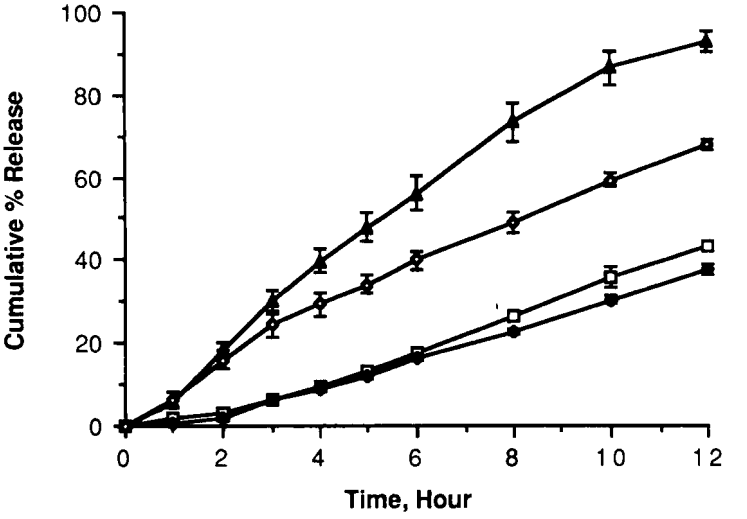

FIGURE 6

The Effect of Tablet Diluent Used and PEG Loading Level in Silicone Elastomer Coating on the Release Profiles of Dextromethorphan Hydrobromide from Coated Tablets. Key: Tablet Diluent; (▲), (□) Lactose and (◆) (◇) Unmilled Dicalcium Phosphate-Avicel; PEG Level: (□), (◆) 30% and (◇), (▲) 40%.

reduced. The counterbalance of these two effects may be considered as the plausible explanation for the insignificant diluent effect associated with the pseudoephedrine hydrochloride tablets.

Figure 6 illustrates the release profiles of dextromethorphan hydrobromide from coated tablets formulated with a water soluble diluent and a water insoluble diluent mixture, respectively. The effect of tablet diluent and coating formulations is shown to be significant. Because of the low water solubility of dextromethorphan hydrobromide (0.015 mg/ml at 25°C), the generation of an appreciable osmotic pressure in the unmilled dicalcium phosphate-Avicel containing coated tablet is unlikely. Therefore, the release of

the active ingredient from this system through the hydrated film coating is primarily achieved by the transpore diffusion mechanism. The greater extent of drug release obtained from the lactose containing tablet is apparently due to the osmotic pumping effect created by the dissolved lactose.

CONCLUSION

The experimental evidence for the generation of an osmotic pressure in the coated tablet and the existence of macro- and micro-pores in the hydrated silicone elastomer coating indicated that the release of drug was achieved by a transpore diffusion as well as an osmotic pumping effect. A method involving the use of sodium chloride and potassium chloride was developed to determine the relative contribution of these two proposed mechanisms to overall drug release. For low PEG loaded coatings, the release of the salts was achieved by the two mechanisms. At high PEG loading levels, the transpore diffusion became the dominant mechanism. The application of the PEG containing silicone elastomer coating system to attain controlled release for a variety of therapeutic agents from tablet dosage form was demonstrated. In addition to the coating formulation, the composition of the tablet matrix was shown to play a critical role in determining the release rate of the active ingredient. The aqueous solubility of the drug and tablet diluent as well as the dose level of the drug were shown to be the controlling factors.

NOTES

(a) Instron Tensile Tester; Model 1130, Instron Company, Canton, Massachusetts.

(b) Lactose, Hydrous, USP, Foremost McKesson, Inc., San Francisco, California.

(c) Polyvinylpyrrolidone (K-25), GAF Corporation, New York, New York.

(d) Magnesium Stearate, USP, Ruger Chemical Company, Irvington, New Jersey.

(e) Calcium Phosphate, Dibasic, Anhydrous, J.T. Baker Chemical Company, Phillipsburg, New Jersey.

(f) Starch, Potato, Sigma Chemical Company, St. Louis, Missouri.

(g) DT Lactose, Sheffield Products, Norwich, New Jersey.

(h) Di-Tab, Staffer Chemical, Westport, Connecticut.

(i) Avicel PH 101, FMC Corporation, Philadelphia, Pennsylvania.

(j) Stokes Rotary Press, Model R1B2, T.J. Stokes Machine Company, Philadelphia, Pennsylvania.

(k) Unit-Glatt Laboratory Six-Inch Coating Column, Glatt 7859, Holtinger/Brinzer (Germany).

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