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IN-VITRO RELEASE STUDIES OF CHLORPHENIRAMINE MALEATE FROM TOPICAL BASES USING CELLULOSE MEMBRANE AND HAIRLESS MOUSE SKIN

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ABSTRACT

In-vitro release of chlorpheniramine maleate from various dermatological bases including a polymeric gel base, the modified hydrophilic base and the modified hydrophilic petrolatum base, was studied. The additive ingredients known to enhance the drug release from the topical bases were also evaluated at different concentration levels. These included urea, ethanol and dimethylsulfoxide (DMSO). The rank order of drug release through the cellulose membrane was observed to be: the gel base > the modified hydrophilic base > the modified hydrophilic petrolatum base. In general, the presence of the additives adversely affected the drug release except for the (DMSO) and ethanol in certain cases.

The formulations with optimum in-vitro release profiles of the drug through the cellulose membrane, were selected for further studies of the drug release using hairless mouse skin as the diffusion barrier. Here again, the gel formulation gave the best in-vitro release of the drug, and the data correlated well with the results previously obtained from the cellulose membrane.

The in-vitro data were treated with various kinetic principles to determine the relevant parameters, such as the steady state flux, the diffusion coefficient and the permeability coefficient. Using these information, the formulations were evaluated for their suitability for delivering chlorpheniramine maleate via the diadermatic dosage form.

INTRODUCTION

Antihistamines are chemical agents that exert their effects in the body primarily by competitively blocking the actions of histamines at the receptor sites (1.2). There are several classes of antihistaminic drugs known including ethanolamines, ethylene-diamines, alkylamines and others. One of the potent alkylamines approved by the FDA is Chlorpheniramine Maleate (CM). (CM) appears to be well absorbed from the gastrointestinal tract, however, the drug undergoes substantial metabolism during absorption due to the first-pass effect. Only about 25-45% of the orally administered dose of the drug reaches the systemic circulation as the unchanged entity (2). The drug has an onset of action within about 20-60 minutes, and the duration of action approximately 4 hours. The peak plasma concentration of 32-48ng/ml is observed in 2 hours after the administration of a single dose of 12mg of drug by mouth (3,4).

At present, (CM) is marketed in tablet, capsule, syrup and injectable dosage forms. And, when used orally, the usual dosage regimen is 4-6 times daily. The present study was undertaken to investigate the in-vitro release of this drug from various dermatological bases using the cellulose membrane and the hairless mouse skin as the diffusion barriers. Also, to study the effects of several additive ingredients known to enhance the drug release from such formulations.

EXPERIMENTAL

Materials: Chlorpheniramine maleate[1], hydroxypropyl methyl cellulose (Methocel KM100)[2], propylene glycol[3], methyl and propyl parabens[3], sodium lauryl sulfate[3], cholesterol[4], stearyl alcohol[4], petrolatum, USP[5], white wax[5], monobasic potassium phosphate[6], methanol[6], ethanol[6], urea[4], dimethylsulfoxide[7], and the cellulose membrane[8].

TABLE I

FORMULATION (S)

Ingredient		% W/W (A)	% W/W (B)	% W/W (C)
Clorpheniramine maleate	=	2.00	2.00	2.00
Methocel K-100M	=	2.00	—	—
Propylene glycol	=	5.00	10.00	—
Methyl paraben	=	0.25	0.25	—
Propyl paraben	=	0.05	0.05	—
White petrolatum	=	--	25.00	75-90
Stearyl alcohol	=	—	5.00	3.00
Sodium lauryl sulfate	=	—	1.00	—
Cholesterol, USP	=	—	—	3.00
White wax	=	—	—	2.00
*Additive(s)	=	q.s.	q.s.	q.s.
Water purified q.s. to	=	100.00	100.00	100.00

(A) = Gel Base (B) = Water Washable Base (C) = Absorption Base

***ADDITIVE(S)**

DMSO and Ethanol = 5%, 10%, and 15% and Urea = 4%, 6%, and 10%

Equipment: Franz diffusion cells apparatus[9], thermostatic water bath and circulator[10], viscometer[11] and spectrophotometer[12].

Preparation of Samples

(a) All gel and ointment formulations were prepared according to the accepted manufacturing procedures. (Table I).

Assay Procedure For Chlorpheniramine Maleate

Plots of absorbance versus wavelength for solutions of CM in water and phosphate buffer were developed. The maximum absorbance values were observed at 261nm for both solutions. Beer's law was followed for 1-20 ug/ml concentrations. The stability of drug in buffer solution was determined. After 24 hours at 37°C no potency deviation was noticed.

Content Uniformity

All samples were analyzed for the CM contents. Only samples with drug contents of 100 ± 10% were used in these studies.

IN-VITRO RELEASE STUDIES

Using Cellulose Membrane: The studies were carried out utilizing the Franz diffusion cell apparatus, each having the diffusion area of 1.76 cm^2, according to previously described methods (5, 6).

Using Hairless Mouse Skin: A group of three 6-8 weeks old male mice were sacrificed, and the skin was removed from the abdominal portions and carefully cleansed and prepared for use in each of these experiments. Using the same buffer solution as the diffusion medium, studies were carried out on the preparations with the highest in-vitro diffusion.

RESULTS AND DISCUSSIONS

Drug Release Using The Cellulose Membrane: The general rank order of drug release was: gel base > the modified hydrophilic ointment base > the modified petrolatum base respectively. The inclusion of the additive ingredients had little or no effect in enhancing the drug release in most cases.

To analyze these data in terms of more meaningful parameters, the data were treated with simplified Higuchi's equation 1, (7). This is usually valid for the samples exhibiting drug release under 30%.

$$Q = 2C\ Dt^{1/2}/¶ \qquad \text{Eq.....1}$$

Where Q = the amount of drug release/unit area mg/cm^2, and C = the initial concentration of drug in the sample mg/cm^2, D = the diffusion coefficient, t = time after application and ¶ = is a constant.

When the percentage release data of drug from the samples were plotted versus the square root of time, the straight lines were obtained. This suggests that the data followed the criteria of Higuchi's equation, Figure 1.

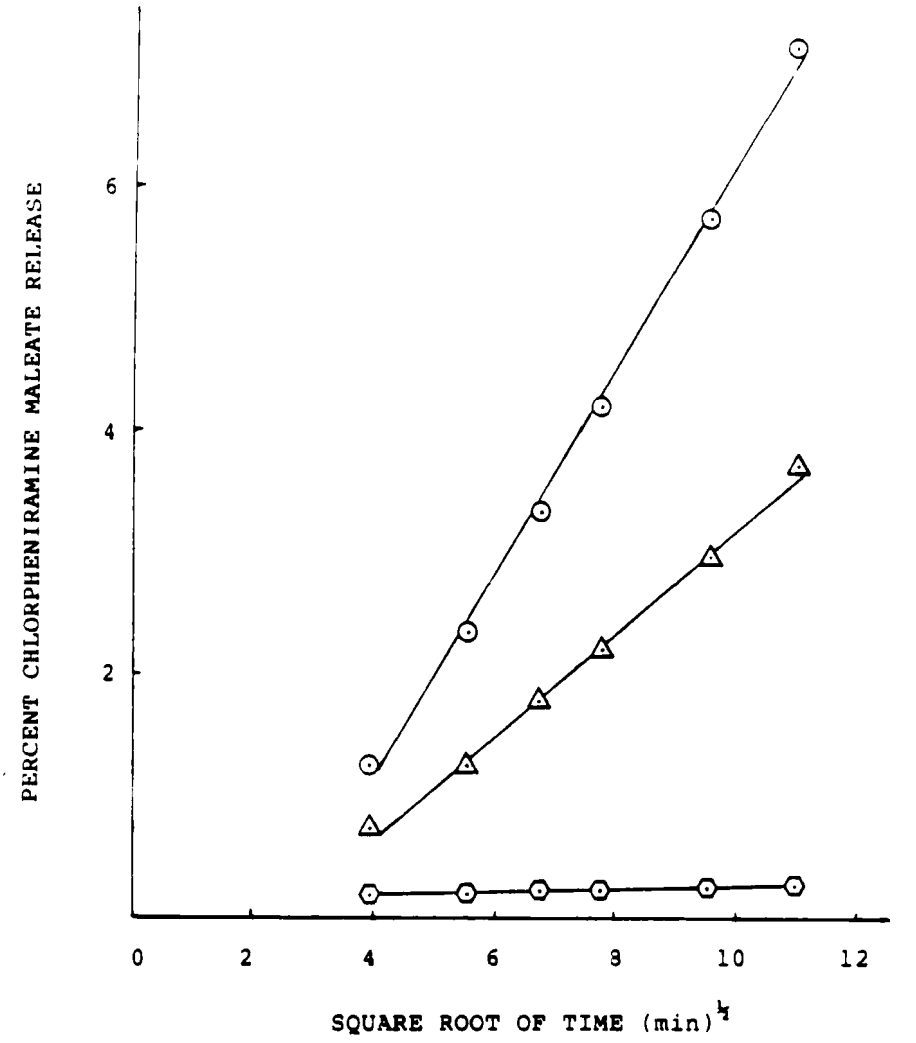

FIGURE 1

Percent Release of Chlorpheniramine Maleate From The Bases Versus Square Root Of Time. ⊙ - Gel Base △ - Modified Hydrophilic Ointment Bases, ⬡ - Modified Hydrophilic Petrolatum Base.

The steady state flux values for the drug from various bases were calculated using the equation 2, and are exhibited in Table II.

$$J_{ss} = DC.kp/h \qquad \text{Eq.....2}$$

Where J_{ss} = the steady state flux ($mg/cm^2/h$), D = diffusion coefficient, C = the initial concentration of drug (mg/cm^3), kp = partitition coefficient and h = thickness of the membrane (cm).

Also, the lag time values for the drug release were computed using equation 3.

$$t_{lag} = h^2/6D \qquad \text{Eq.....3}$$

Where h = thickness of the membrane, D = diffusion coefficient and t_{lag} = lag time. The results are also exhibited in Table II.

In addition, the values for the diffusion coefficient, the permeability and the partition coefficient were calculated, and are listed in Table III. From this, one observes that the highest diffusion coefficient value ($20 \times 10^{-8} cm^2/sec$) was obtained for the gel formulation compared to the lowest value of ($0.02 \times 10^{-8} cm^2/sec$) obtained from the hydrophilic petrolatum base. This could be attributed to the fact that the drug was more freely available from gel vehicle than from the complicated hydrophilic petrolatum base. Similarly, the highest permeability coefficient value (5.7×10^{-6}) was obtained for the gel based formulation, suggesting that the drug molecules are relatively easily removed from this system. However, an inverse relationship between the drug release and the calculated partition coefficient values was observed. The gel base with maximum drug release yielded the lowest partition coefficient value, whereas, the petrolatum base with minimum drug release gave the highest value for this attribute.

Since the release of drug from the experimental samples was low, the data can be interpreted either in zero or first order kinetic fashion. It was observed that the gel formulation ($K = 6.24 \times 10^{4} min^{-1}$) gave the highest release rate constant value, whereas, this remained the lowest in the case of the modified hydrophilic petrolatum base ($k = 0.23 \times 10^{4} min^{-1}$).

TABLE II

STEADY STATE FLUX AND LAG-TIME VALUES OF CHLORPHENIRAMINE FOR VARIOUS BASES USING THE CELLULOSE MEMBRANE.

Sample	* J_{ss} mg/cm² h (±SD)	Lag-Time Hour (±SD)
Formulation (A) Gel =	1.46 ± 0.07	0.09 ± 0.01
Formulation (B) Modified Hydrophilic Ointment =	0.75 ± 0.04	0.51 ± 0.03
Formulation (C) Modified Hydrophilic Petrolatum =	0.05 ± 0.00	0.83 ± 0.66

* J_{ss} = The Steady State Flux.

Note = Each reading is an average of three determinations.

TABLE III

VALUES OF THE DIFFUSION, PERMEABILITY AND PARTITION COEFFICIENTS FOR VARIOUS BASES USING THE CELLULOSE MEMBRANE

Sample	* (D) $D \times 10^8$	** (P) $P \times 10^6$	*** (K_p)
Formulation (A) Gel =	20.00	5.70	0.58
Formulation (B) Modified Hydrophilic Ointment =	3.52	2.90	1.68
Formulation (C) Modified Hydrophilic Petrolatum =	0.02	0.20	20.11

* (D) = the diffusion coefficient (cm²/sec.)
** (P) = the permeability coefficient (cm/sec.)
*** (Kp) = the partition coefficient

TABLE IV

IN-VITRO RELEASE DATA OF CHLORPHENIRAMINE MALEATE FROM THE SELECTED BASES AND ADDITIVES USING THE HAIRLESS MOUSE SKIN.

Sample		Drug Released/Minutes (% ± SD)					
		(15)	(30)	(45)	(60)	(90)	(120)
Formulation (A) Gel	=	0.28±0.06	0.48±0.13	0.64±0.14	0.81±0.26	1.13±0.43	1.36±0.46
Formulation (A) Gel + 6% Urea	=	0.32±0.03	0.46±0.06	0.60±0.06	0.75±0.10	1.02±0.16	1.29±0.23
Formulation (A) Gel + 5% DMSO	=	0.23±0.01	0.33±0.03	0.45±0.06	0.56±0.10	0.80±0.13	1.04±0.20
Formulation (C) Hydrophilic Petrolatum Base	=	0.29±0.00	0.42±0.01	0.47±0.03	0.55±0.02	0.68±0.03	0.82±0.06
Formulation (C) Hydrophilic Petrolatum Base + 15% Ethanol	=	0.22±0.03	0.32±0.03	0.38±0.03	0.45±0.03	0.58±0.04	0.72±0.04

Note: Each reading is an average of three determinations

TABLE V

VALUES OF THE STEADY STATE FLUX OF CHLORPHENIRAMINE MALEATE FROM THE SELECTED BASES USING THE HAIRLESS MOUSE SKIN.

Sample		Steady State Flux ± SD (mg/cm^2h)
Formulation (A) Gel Base	=	0.28 + 0.15
Formulation (A) Gel + 6% Urea	=	0.25 ± 0.05
Formulation (A) Gel + 5% DMSO	=	0.21 ± 0.06
Formulation (C) Hydrophilic Petrolatum Base	=	0.16 ± 0.02
Formulation (C) Hydrophilic Petrolatum Base + 15% Ethanol	=	0.14 ± 0.00

Note: Each reading is an average of three determinations.

TABLE VI

VALUES OF THE DIFFUSION AND PERMEABILITY COEFFICIENTS OF CHLORPHENIRAMINE MALEATE FROM THE SELECTED BASES USING THE HAIRLESS MOUSE SKIN

Sample		(D) $D \times 10^6$ cm^2/sec	(P) $P \times 10^4$ cm/sec
Formulation (A) Gel Base	=	0.65	1.10
Formulation (A) Gel + 6% Urea	=	0.58	1.01
Formulation (A) Gel + 5% DMSO	=	0.38	0.82
Formulation (C) Hydrophilic Petrolatum base + 15% Ethanol	=	0.24	0.65

(D) = Diffusion Coefficient (P) = Partition Coefficient

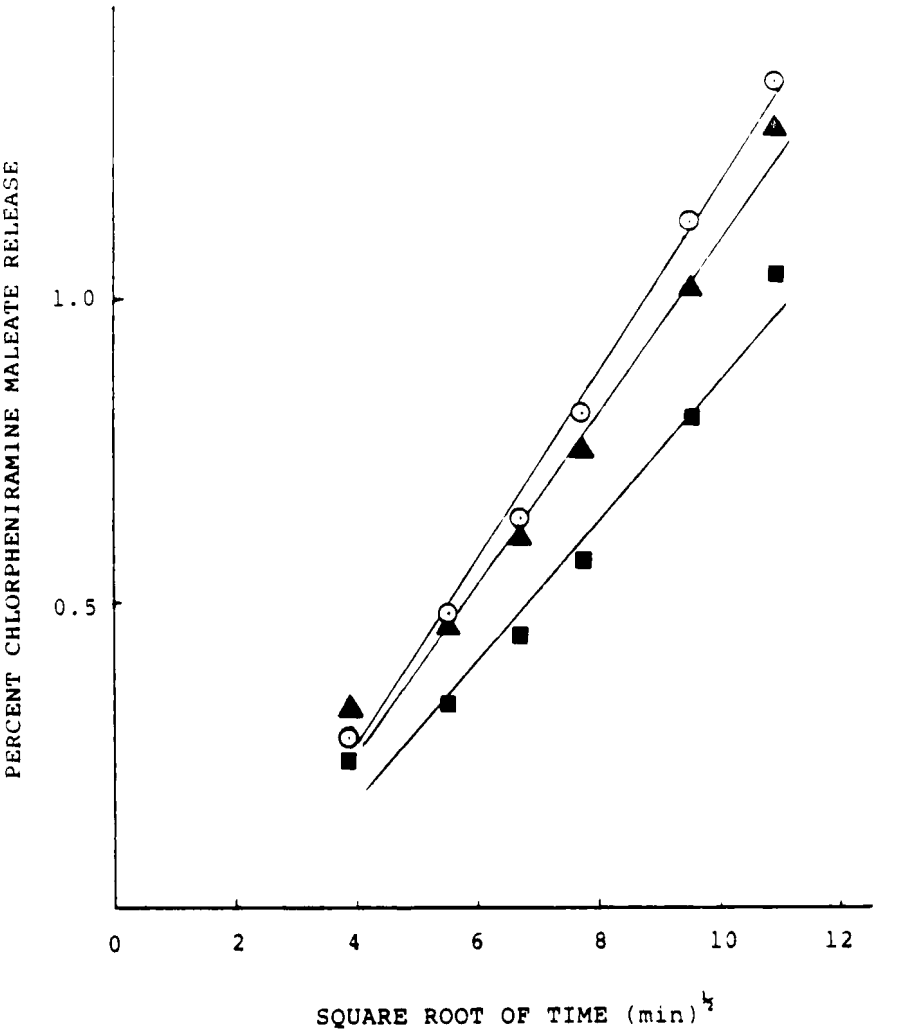

FIGURE 2

Percent Release of Chlorpheniramine Maleate From The Selected Gel Bases Using The Hairless Mouse Skin Versus Square Root Of Time. ⊙- Gel Base, ▲ - Gel + 6% Urea, ■ - Gel + 5% DMSO.

The modified hydrophilic ointment base ($k = 3.17 \times 10^{4} min^{-1}$) exhibited a significant increase ($p < 0.05$) of the drug release in the presence of urea at 6% ($k = 3.82 \times 10^{4} min^{-1}$) and 10% ($K = 3.76 \times 10^{4} min^{-1}$). This may be due to the increased solubility of the drug in the presence of this additive, causing an increase in the thermodynamic activity of the drug during permeation through the membrane.

Drug Release Using The Hairless Mouse Skin: The formulations with maximum drug release through the cellulose membrane were selected for further release studies using the hairless mouse skin as the diffusion barrier. The drug release data from the experiments are exhibited in Table IV. Here also, the gel formulation gave the maximum release of the drug and the inclusion of alcohol in the modified hydrophilic petrolatum base adversely affected the drug release.

Similar to the previous experiments, the data were used to calculate the values for the steady state flux parameter, and the results are shown in Table V. The maximum value was observed from the gel formulation (0.28 $mg/cm^2/h$), and this suggests that the drug release was fastest from the gel base compared to the other formulations. Also, from these data, the values for the diffusion and the permeability coefficients were calculated and are shown in Table VI. Here again, the gel formulation gave the highest values for the diffusion as well as the permeability coefficients. In addition, when the percentage drug release data were plotted versus square root of time, straight lines were obtained as exhibited in Figure 2. This suggests that the drug release again follows the Higuchi's model similar to the studies with the cellulose membrane.

In conclusion, the preliminary results of this study indicate that (CM) is a suitable drug entity to be incorporated in dermatological bases for possible development of diadermatic dosage form.

NOTES

1. Sigma Chemical Corp., St. Louis, MO.
2. Dow Chemical Co., Midland, MI.
3. Amend Drug Chemical Co., Irvington, NJ.

4. Ruger Chemical Co., Irvington, NJ.
5. Clay-Park Lab., Inc., Bronx, NY.
6. Fisher-Scientific Co., Fairlawn, NJ.
7. Eastman Kodak Co., Rochester, NY.
8. Spectrum Medical Industries Inc., Los Angeles, CA.
9. Crown Glass Corp., Corning, NY.
10. Yamato Scientific Co., Japan
11. Brookfield Engineering Lab. Inc., Stoughton, MA.
12. Shimadzu Seisakusho Ltd., Japan.

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