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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 topical bases was studied using cellulose membrane and hairless mouse skin as the diffusion barriers. These included a polymer gel base, a modified hydrophilic ointment base and a modified petrolatum base. The effects of the additive ingredients, such as, urea, ethanol and dimethylsulfoxide (DMSO) on the drug release were also investigated. The rank order of drug release through the cellulose membrane was observed to be: the gel base > the modified hydrophilic ointment base > the modified hydrophilic petrolatum base. In general, the presence of additives adversely affected the drug release except for the (DMSO) and ethanol in certain cases.

The samples with maximum drug release through the cellulose membrane were further studied for the drug release using hairless mouse skin as the diffusion barrier. Here again, the gel base gave the best in-vitro release of the drug, and the data correlated well with the results obtained through the cellulose membrane. These 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 etc. Using these information, the samples were evaluated for delivering drug via diadermatic dosage form.

INTRODUCTION

Histamine, a biogenic amine, is a chemical mediator that is widely distributed in mamalian tissue mast cells and the circulating basophils. If liberated from these cells, the free form of histamine plays an early transient role in the inflammation process (1). The reactions mediated by histamine are attributed to the receptor activity, which involves two distinct receptors: H_1 and H_2 receptors. This has the most significant effects on the cardiovascular system, exocrine glands and smooth muscles.

Antihistamines are chemical agents that exert their effects by competitively blocking the actions of histamine at the receptor sites (2,3). And, one of the alkylamines approved by the FDA is chlorpheniramine maleate . It is well absorbed from the gastrointestinal tract, however, due to the first pass effect only 25-45% of the orally administered dose reaches the blood circulation (3). And, the onset of action is observed within 20-60 minutes. The peak plasma concentration of 32-48 ng/mL is usually reached in 2 hours after a single dose of 12 mg of drug by mouth (4,5). At present, the drug is marketed in tablet, capsule, syrup and injectable dosage forms, and the normal oral dosage regimen is about 4-6 times a day.

The present study was undertaken to investigate the in-vitro release of chlorpheniramine maleate from topical bases using cellulose membrane and hairless mouse skin as the diffusion barriers. Also, to evaluate the effects of the additive ingredients on the drug release from these formulations.

EXPERIMENTAL

Materials: Chlorpheniramine maleate[1], hydroxypropylmethyl cellulose (Methocel KM 100)[2], propylene glycol[3], methyl and propyl parabens[3], sodium lauryl sulfate[3], cholesterol[4], stearyl alcohol[4], white wax[5], petrolatum, USP[5], monobasic potassium phosphate[6], methanol[6], ethanol[6], urea[6], dimethylsulfoxide[7], cellulose membrane[8].

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

TABLE I

FORMULATION(S)

Ingredient		% W/W (A)	(B)	(C)
Chlorpheniramine 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 = 5%, 10% and 15%
Ethanol= 5%, 10% and 15%
Urea = 4%, 6% and 10%

Prepartion of Samples

(a)- Gel Formulation: All ingredients of formulation (A) in Table I, were accuratley weighed for the batch size. HPMC was slowly dispersed in a portion of water at 80°± 2°C., and the remaining water was added cold and mixed to form gel. Drug and other ingredients were predissolved in propylene glycol and incorporated into the batch.

(b)- Ointment Formulations: All ingredients of each ointment formulation were accurately weighed for the batch size as listed in Table I. The oil phase and the water phase ingredients were separately heated to 80°± 2°C. The water phase was then slowly added to the oil phase while stirring and mixed for 15-20 minutes at this temperature. The batch was cooled to 45°± 2°C and the drug predissolved in a small amount of water was incorporated in to the batch and mixed.

Content Uniformity

All samples were analyzed spectrophotometrically for the drug content (λ max = 261 nm). Only samples with drug content of 100 ± 10% were used in the diffusion studies.

IN-VITRO RELEASE STUDIES

Using Cellulose Membrane: The drug release studies were carried out using the Franz diffusion cells and procedure described (6). A pH 6, phosphate buffer solution was used as the diffusion medium and the drug release was studied at 15, 30, 45, 60, 90 and 120 minutes time intervals. The samples were analyzed by the U.V. method (λ max = 261nm).

Using Hairless Mouse Skin: The samples with optimum drug release through the cellulose membrane were used in this portion of the study. A group of 9-8 weeks old male mice were sacrificed, and the skin was removed from the abdominal portions and carefully cleansed and prepared for use in the diffusion studies. Using the same buffer solution and time intervals, the drug release studies were carried out as discussed previously.

RESULTS AND DISCUSSION

Drug Release Using Cellulose Membrane: The percentage drug release from the formulations evaluated are listed in Table II. The general rank order of the drug release was: the gel base > the modified hydrophilic petrolatum base > the modified hydrophilic ointment base respectively. The inclusion of additives had little or no effect in enhancing the drug release in most cases.

To analyze these data in terms of meaningful parameters, the data were first treated with simplified Higuchi's eq., (7)

TABLE - II

IN-VITRO RELEASE OF CHLORPHENIRAMINE MALEATE FROM VARIOUS BASES

Sample	Percent Drug Release/Minutes (15)	(30)	(45)	(60)	(90)	(120)
1. Gel Base	1.27	2.36	3.34	4.22	5.78	7.21
With Urea						
2%	--	--	--	--	--	6.52
6%	--	--	--	--	--	6.88
10%	--	--	--	--	--	5.48
With (DMSO)						
5%	--	--	--	--	--	6.45
10%	--	--	--	--	--	5.43
15%	--	--	--	--	--	5.43
With Ethanol, USP.						
5%	--	--	--	--	--	5.93
10%	--	--	--	--	--	4.83
15%	--	--	--	--	--	4.61
2. Mod. Hydrophilic Base	0.75	1.26	1.75	2.18	2.95	3.74
With Urea						
2%	--	--	--	--	--	4.12
6%	--	--	--	--	--	4.48
10%	--	--	--	--	--	4.41
With (DMSO)						
5%	--	--	--	--	--	3.41
10%	--	--	--	--	--	3.61
15%	--	--	--	--	--	3.54
With Ethanol, USP.						
5%	--	--	--	--	--	4.37
10%	--	--	--	--	--	3.73
15%	--	--	--	--	--	3.50
3. Mod. Hydrophilic Petrolatum Base	0.20	0.23	0.24	0.26	0.27	0.28
With Urea						
2%	--	--	--	--	--	0.28
6%	--	--	--	--	--	0.25
10%	--	--	--	--	--	0.29
With (DMSO)						
5%	--	--	--	--	--	0.62
10%	--	--	--	--	--	0.81
15%	--	--	--	--	--	4.21
With Ethanol, USP.						
5%	--	--	--	--	--	0.86
10%	--	--	--	--	--	1.39
15%	--	--	--	--	--	4.65

Note: Each Reading is The Average of Three Determinations. The Standard Deviation was less than 0.75 for all samples.

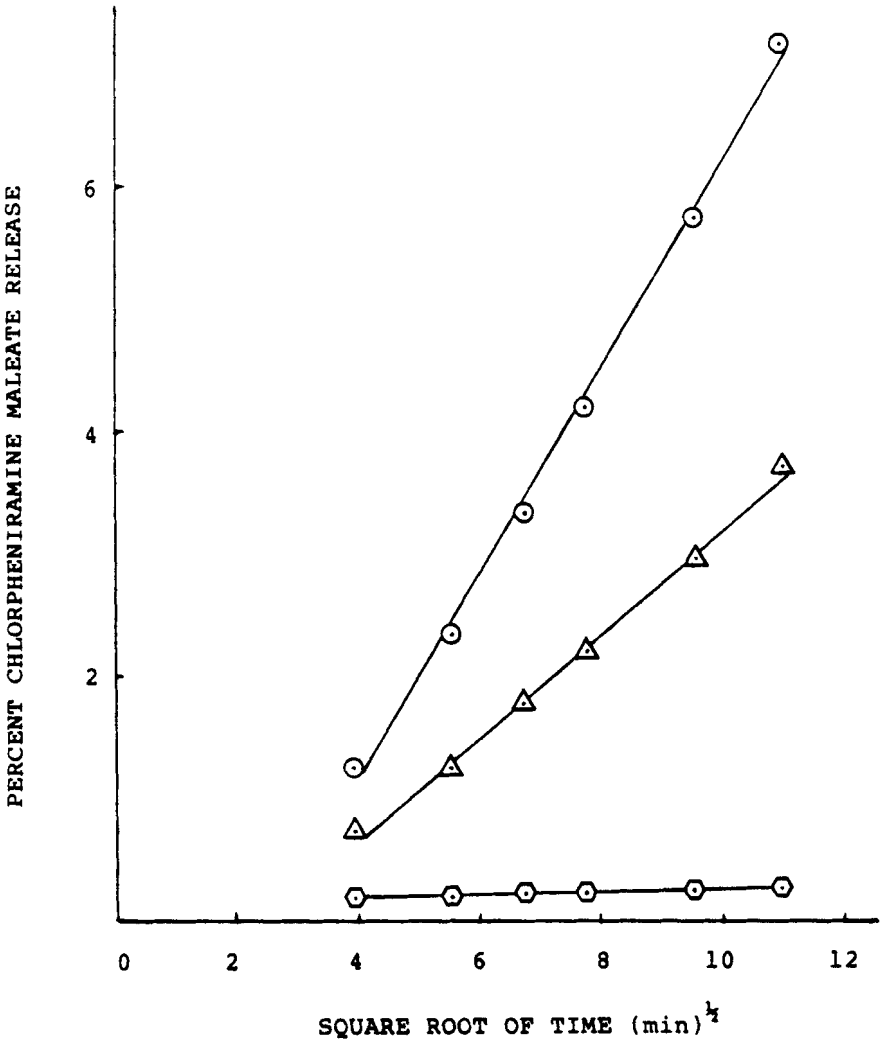

Figure 1

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

and graphs were constructed as exhibited in figure 1. According to this, the data follows the criteria of Higuchi's equation. Other parameters, such as, the steady state flux (J_{ss}) and the lag-time (t_{lag}) were calculated using equations 1 and 2 respectively, and the results are exhibited in Table III.

$$J_{ss} = DC.K_p/h \qquad \text{Equation ..... 1}$$

TABLE III

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

Sample		* J_{ss} mg/cm^2 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 IV

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

Sample		* (D) D x 10^8	** (P) P x 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 (cm^2/sec.)
** (P) = the permeability coefficient (cm/sec.)
*** (Kp) = the partition coefficient

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

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

Where t_{lag} = lag-time, h = thickness of the membrane, D = diffusion coefficient.

In addition, the values for the diffusion coefficient (D), the permeability coefficient (P) and the partition coefficient (K_p) were calculated. The results are exhibited in Table IV. From this, one observes that the highest (D) value ($20x10^{-8}cm^2$/sec) was obtained for the gel base compared to the lowest value of $0.02x10^{-8}cm^2$/sec) for the hydrophilic petrolatum base. This could be attributed to the fact that the drug was more freely available from the gel vehicle compared to the hydrophilic petrolatum formulation. Similarly, the highest (P) value ($5.7x10^{-6}$) was obtained for the gel base formulation suggesting that the drug molecules were relatively easily removed from the system. However, an inverse relationship between the drug release and the calculated (K_p) values was observed. The samples with maximum drug release yielded the lowest (K_p) value, whereas, the formulation with minimum drug release gave the highest value for this attribute.

Since the release of drug from all samples studied was low, the data could be treated with either zero or first order kinetics. Using the first order, the values for the release rate constant (K), y-intercept, and the regression coefficient (r) were calculated and are listed in Table V. From this, it is observed the gel formulation gave the highest (K) value compared to all other formulations evaluated. On the other hand, the modified hydrophilic ointment base exhibited a significant increase i.e. ($p < 0.05$) of the drug release in the presence of urea at 6% and 10% levels, as shown in Table II. This may be due to the increased solubility of the drug in presence of this additive, and causing an increase in the thermodynamic activity of the drug during the permeation process.

Drug Release Using Hairless Mouse Skin: The drug release data from the selected samples using the hairless mouse skin are ex-

TABLE V

DIFFUSION DATA EXPRESSED AS THE PARAMETERS OF OF FIRST ORDER KINETICS

Sample	Additive	(K x $10^4 min^{-1}$)*	(Y-Intercept)*	(r-Value)*
Formulation (A) Gel Base				
Control	None	6.24	1.995	0.994
Urea	2%	5.62	1.995	0.995
	6%	5.95	1.995	0.996
	10%	4.70	1.995	0.998
DMSO	5%	5.57	1.995	0.994
	10%	4.64	1.995	0.996
	15%	4.64	1.996	0.996
ETHANOL	5%	5.09	1.995	0.995
	10%	4.13	1.998	0.998
	15%	3.93	1.996	0.995
Formulation (B) Modified Hydrophilic Ointment Base				
Control	None	3.17	1.997	0.992
Urea	2%	3.51	1.997	0.995
	6%	3.82	1.997	0.991
	10%	3.76	1.997	0.991
DMSO	5%	2.88	1.997	0.998
	10%	3.07	1.996	0.998
	15%	2.99	1.998	0.989
ETHANOL	5%	3.72	1.997	0.996
	10%	3.17	1.996	0.997
	15%	2.98	1.998	0.994
Formulation (C) Modified Hydrophilic Petrolatum Base				
Control	None	0.23	1.999	0.984
Urea	2%	0.23	1.999	0.997
	6%	0.21	1.999	0.997
	10%	0.25	1.999	0.820
DMSO	5%	0.52	1.998	0.995
	10%	0.67	1.998	0.994
	15%	3.59	1.994	0.998
ETHANOL	5%	0.73	1.996	0.953
	10%	1.17	1.996	0.957
	15%	3.97	1.990	0.964

*K = First order rate constant, Y-Intercept = logarithm of the initial concentration of drug in the base and r-Value= standard regression coefficient.

TABLE VI

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 VII

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 VIII

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

Sample		(D) $Dx10^8$ cm^2/sec	(P) $Px10^6$ 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	=	0.24	0.65
Formulation (C) Hydrophilic Petrolatum base + 15% Ethanol	=	0.18	0.57

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

TABLE IX

DIFFUSION DATA EXPRESSED AS THE PARAMETERS OF THE FIRST ORDER KINETICS FOR THE SELECTED BASES USING THE HAIRLESS MOUSE SKIN.

Sample	Parameter(s)		
	$K \times 10^{4} min^{-1}$	Y-intercept	r-value
Formulation (A) Gel Base =	1.14	1.999	0.993
Formulation (A) Gel + 6% Urea =	1.08	1.999	0.986
Formulation (A) Gel + 5% Urea =	0.87	1.999	0.980
Formulation (C) Modified Hydrophilic Petrolatum =	0.69	1.999	0.989
Formulation (C) Hydrophilic Petrolatum base + 15% ethanol =	0.60	1.999	0.989

Note: Each reading is an average of three determinations.

TABLE X

COMPARISON OF THE RELEASE DATA OF CHLORPHENIRAMINE FROM THE CELLULOSE MEMBRANE AND THE HAIRLESS MOUSE SKIN.

Sample	Drug Released/2Hrs (%±SD).	
	Cellulose Membrane	Hairless Mouse skin
Formulation (A) Gel Base =	7.21 ± 0.16	1.36 ± 0.46
Formulation (A) Gel + Urea 6% =	6.88 ± 0.06	1.29 ± 0.23
Formulation (A) Gel + DMSO 5% =	6.45 ± 0.66	1.04 ± 0.20
Formulation (C) Modified Hydrophilic Petrolatum =	0.28 ± 0.03	0.82 ± 0.06
Formulation (C) Modified Hydrophilic petrolatum +15% ethanol =	4.65 ± 1.15	0.72 ± 0.04

hibited in Table VI. Here also, the gel formulation gave the maximum drug release. Similar to the previous experiments, these data were used to determine (J_{ss}) and the results are shown in Table VII. The highest value for this attribute (0.28mg/cm^2/h), was obtained also from the gel sample, which suggest that the drug release is fastest from this sample compared to the others investigated. In addition, the values for (D) and (P) were calculated and are listed in Table VIII. From this, it is again observed that the gel formulation gave the highest (D) and (P) values. Also, the data were treated with Higuchi's equation, and it followed its citeria.

Since the drug release through the hairless mouse skin remained low, the data once again considered to follow either zero or first order kinetics. Consequently, the values for first order rate constant (K), Y-intercept and the regression coefficient (r) were calculated, and exhibited in Table IX.

Table X exhibits the comparitive in-vitro release data of chlorpheniramine maleate using the cellulose membrane and the hairless mouse skin as the diffusion barriers. From this, the release of drug is observed to be higher through the cellulose membrane compared to the hairless mouse skin. The poor drug release through the hairless mouse skin could be attributed to the fact that the complexity of the composition of the skin offered more resistance to the penetrating drug molecules during the diffusion process. Interestingly, the modified hydrophilic petrolatum base formulation proved to be superior vehicle and gave the highest drug release through the hairless mouse skin as shown in Table X. Also, the (J_{ss}) value for this sample was observed to be higher with the hairless mouse skin than with the cellulose membrane.

In conclusion, the preliminary results of these studies indicate that chlorpheniramine maleate is a suitable drug entity for use in dermatological bases for possible development of the diadermatic dosage form.

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