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COMMUNICATION

In Vitro Release and Diffusion Studies of Promethazine Hydrochloride from Polymeric Dermatological Bases Using Cellulose Membrane and Hairless Mouse Skin

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ABSTRACT

The study was designed to investigate the feasibility of developing a transdermal drug dosage form of promethazine hydrochloride (PMH). The in vitro release and diffusion characteristics of PMH from various dermatological polymeric bases were studied using cellulose membrane and hairless mouse skin as the diffusion barriers. These included polyethylene glycol (PEG), hydroxypropyl methylcellulose (HPMC), cross-linked microcrystalline cellulose, and carboxyl methyl cellulose sodium (Avicel® CL-611), and a modified hydrophilic ointment USP. In addition, the effects of several additive ingredients known to enhance the drug release from topical formulations were evaluated. The general rank order for the drug release from these formulations using cellulose membrane was observed to be PEG > HMPC > Avicel CL-611 > hydrophilic ointment base. The inclusion of the additives had little or no effect on the drug diffusion from these bases, except for the hydrophilic ointment formulation containing 15% ethanol, which provided a significant increase in the drug release. However, when these formulations were studied for drug diffusion through the hairless mouse skin, the Avicel CL-611 base containing 15% ethanol exhibited the optimum drug release. The data also revealed that this formulation gave the highest steady-state flux, diffusion, and permeability coefficient values and correlated well with the amount of drug release.

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INTRODUCTION

Antihistamines are a diverse group of drugs that possess the ability to inhibit various histamine actions in the body. They bear certain structural resemblance to histamine and act principally through a simple reversible competitive antagonism of histamine at the receptor sites (1). Consequently, antihistamines are helpful therapeutically in preventing or reversing the histamine actions by competing with histamine H_1 receptor sites on the affected cells (2). Some of these antihistamines also exhibit antiemetic, anti–motion sickness, and antivertigo effects. Though their precise mechanism of action is not known, it may be related to their central anticholinergic actions. These drugs may diminish vestibular stimulation and depress labyrinthic functions. Their action on the medullary chemoreceptive trigger zone may also be involved in the antiemetic effect and may produce sedation by depressing the central nervous system (3,4). Promethazine hydrochloride (PMH) is one of the most potent and widely prescribed antihistaminic drugs for the prevention and treatment of nausea, vomiting, motion sickness, etc. Presently, it is available in tablets, syrup, injectable, and suppository dosage forms. However, its use during nausea and vomiting becomes limited to the suppository or injectable dosage forms, which presents an inconvenience to both physicians and patients. Therefore, this study was conducted to assess the possibilities of delivering PMH through the skin, which will provide an effective and convenient means to deliver this clinically important drug via the topical drug dosage form.

EXPERIMENTAL

Materials

The following chemicals were used as received: PMH and sodium lauryl sulfate from Sigma Chemical Company, Missouri; polyethylene glycol 400 (PEG400), PEG3350, and propylene glycol from Ruger Chemical Company, New Jersey; hydroxypropyl methylcellulose (HPMC) (Methocel k-100) from Dow Chemical Company, Michigan; Avicel® CL-611 from FMC Corporation, Pennsylvania; methyl and propyl parabens from Amend Drug and Chemical Company, New Jersey; cetyl alcohol from Amend Drug and Chemical Company, New Jersey; white petrolatum from Clay-Park Laboratories, New York; alcohol, USP, from Quantum Chemical Corporation, New Jersey; urea from Fisher Scientific Company, New Jersey; oleyl alcohol from Croda, New Jersey; cellulose membrane (molecular weight cutoff 1000) from Spectrum Company, California. All other chemicals used were reagent grade.

Equipment

The equipment used was a Franz-Chein diffusion cell apparatus from Crown Glass Company, New Jersey; thermostatic water bath from Yamato Scientific Company, Japan; and a spectrophotometer (Beckman DU-640) from Beckman Instruments, Incorporated, California.

Preparation of Samples

Polyethylene Glycol Base

All ingredients were accurately weighed in the percentage ratio shown in Table 1. The PEGs were heated to 65°C ± 5°C on a water bath. They were cooled to 50°C ± 5°C, and the drug was incorporated and mixed, then cooled and stored in a tightly closed glass container.

Hydroxypropyl Methylcellulose Base

All ingredients were accurately weighed in the percentage ratio shown in Table 1. The HPMC was dispersed in a portion of previously heated water to 80°C ± 5°C. Then, cold water was added and mixed. Later, the drug and preservative ingredients, previously dissolved in a small portion of water, were added and stirred. Any additive ingredient was also incorporated in the formulation at this time. The samples were further cooled to 30°C while stirring and were stored in a tightly closed glass container.

Avicel Base

All ingredients were accurately weighed in the percentage ratio shown in Table 1. Avicel CL-611 was slowly dispersed in previously heated water to 80°C ± 5°C. The dispersion was cooled to 45°C ± 5°C. The drug and preservatives, previously dissolved in a small amount of water, were then added and mixed. Any additive ingredient required was also incorporated at this stage of the preparation. The samples were cooled to 30°C and stored in a tightly closed glass container.

Modified Hydrophilic Ointment, USP, Base

All ingredients were accurately weighed in the percentage ratio shown in Table 1. The aqueous phase and oil phase ingredients were separately heated to 80°C ±

Table 1

Formulation(s)

Ingredient	% w/w (A) Peg Base	(B) HMPC Base	(C) Avicel Base	(D) Ointment Base
Promethazine HCL (PMH)	1.00	1.00	1.00	1.00
Polyethylene glycol–400	84.50	—	—	—
Polyethylene glycol -3350	15.00	—	—	—
Hydroxypropyl Methylcellulose	—	2.00	—	—
Avicel CL-611	—	—	4.00	—
Petrolatum, USP	—	—	—	25.00
Cetyl Alcohol	—	—	—	10.00
Sod. lauryl Sulfate	—	—	—	1.00
Propylene glycol	—	—	—	12.00
Methyl paraben	—	0.20	0.20	0.20
Propyl paraben	—	0.05	0.05	0.05
Additive(s)	0–15	0–15	0–15	0–15
Purified water g.s.	—	100.00	100.00	100.00

Additive(s)	(I) (%)	(II) (%)	(III) (%)
Alcohol, USP	5	10	15
Propylene glycol	5	10	15
Urea	1	2	3

5°C. The heated water phase was added to the heated oil phase and mixed for 15 min. The emulsion was cooled to 45°C ± 5°C while mixing. The drug, previously dissolved in a small portion of water, was then added and mixed. Any additive ingredient included in the formulation was also incorporated at this point. The samples were then cooled to 30°C and stored in a tightly closed glass container.

Analytical Methods

Content Uniformity

All samples prepared were analyzed for PMH contents. Only samples with drug contents of 100% ± 10% were used in the drug release studies.

Diffusion Studies

The amounts of PMH released from the various formulations were determined spectrophotometrically at a wavelength of 249 nm.

In Vitro Diffusion Studies

In vitro diffusion studies were carried out using Franz diffusion cells according to a published procedure (5).

Preparation of Hairless Mouse Skin

A set of three hairless mice about 6 to 8 weeks old was sacrificed for each experiment by snapping each mouse's spinal cord at the neck. A circular section of the abdominal area of the skin was excised. The adhering fat and debris were carefully removed from the skin samples. These were then soaked in normal saline solution until used in the diffusion studies.

RESULTS AND DISCUSSION

Using the Cellulose Membrane

From the in vitro data of PMH from various formulations evaluated over a 2-hr period, the decreasing rank order of the drug release was observed to be PEG >

Table 2

Steady-State Flux and Lag Time of Promethazine Hydrochloride from Selected Bases Using Cellulose Membrane

Base	Steady-State Flux[a] ± SD [Jss] (mg/cm^2/hr)	LAG-TIME[a] ± SD [t-lag] (hr)
PEG (formulation A)	1.505 ± 0.20	0.004 ± 0.00
HPMC (formulation B)	0.993 ± 0.06	0.009 ± 0.00
Avicel/CL-611 (formulation C)	0.321 ± 0.03	0.095 ± 0.02
Ointment, USP (formulation D)	0.059 ± 0.00	2.747 ± 0.21

[a] Average of three determinations.

HPMC > Avicel CL-611 > modified hydrophilic ointment, USP base. Formulation A exhibited the maximum percentage drug release (35.5/2 hr); the percentage drug release was observed to be minimum (1.4/2 hr) from the hydrophilic ointment, USP (formulation D). This could be attributed to the possible entrapment of the drug in the complexed emulsion system of the base. To analyze the release data in terms of the more meaningful parameters, the data were treated with the simplified Higuchi equation (6) and plotted against the square root of time. This treatment gave straight lines that indicated that the release of the PMH from these bases followed this model.

The comparison of the steady-state flux and lag-time values of PMH release from these bases as given in Table 2 indicate that the PEG base (formulation A) had the maximum steady-state flux value (1505 mg/cm^2 hr) compared to the hydrophilic ointment base (formulation D), which gave the value of 0.059 mg/cm^2 hr) only. However, the lag-time value was minimum (0.004 hr) for formulation A compared to 2.74 hr for formulation D, suggesting that the drug was more readily available for diffusion from formulation A than from formulation D. In addition, the values for the diffusion, permeability, and partition coefficients were determined and are shown in Table 3. According to these, the highest diffusion coefficient value (446.5×10^{-8} cm^2/sec) was obtained from formulation A, and the lowest value (0.68×10^{-8} cm^2/sec) was obtained from formulation D. Also, the value for the permeability coefficient was observed to be the highest (27.91×10^{-6} cm^2/sec) for formulation A compared to all other formulations evaluated. However, the value for the partition coefficient for formulation A was the lowest (0.13×10^{-1} cm^2/sec) compared to the value of 3.24×10^{-1} cm^2/sec) for the hydrophilic ointment base (formulation D), which gave the minimum in vitro drug release using the cellulose membrane. These data support that, for greater drug release through this barrier, the formulations should possess relatively higher permeability and diffusion coefficient values.

Table 3

Diffusion, Permeability, and Partition Coefficients Calculated from the In Vitro Data for Selected Semisolid Bases Using Cellulose Membrane

Base	Diffusion Coefficient [D] (cm^2/sec) D × 10^8/cm^2/sec	Permeability Coefficient [P] (cm^2/sec) P × 10^6/cm^2/sec	Partition Coefficient [*Kp*]
PEG (formulation A)	446.5	27.91	0.13
HPMC (formulation B)	191.5	18.38	0.19
Avicel/CL-611 (formulation C)	20.0	5.94	0.60
Ointment, UCP (formulation D)	0.68	1.09	3.24

Table 4

Steady-State Flux and Lag Time of Promethazine Hydrochloride from Selected Bases Through Hairless Mouse Skin

Base	Steady-State Flux[a] ± SD [Jss] (mg/cm^2/hr)	LAG-TIME[a] ± SD [t-lag] (hr)
PEG	0.005 ± 0.002	48.87 ± 38.06
HPMC + 5% alcohol	0.005 ± 0.002	7.19 ± 4.54
HPMC + 1% urea	0.120 ± 0.003	5.59 ± 1.93
Avicel + 15% alcohol	0.170 ± 0.003	2.94 ± 0.97
Modified USP + 15% alcohol	0.007 ± 0.004	23.93 ± 16.16

[a] Average of three determinations.

In addition, the inclusion of additive ingredients in most formulations showed little or no significant effect in enhancing the drug release from these bases except in the case of hydrophilic ointment base (formulation D) with 15% ethanol. Here, a threefold increase in the release of PMH was observed compared to that for the basic formulation without alcohol. This could be attributed to the softening effect of ethanol and the change in the thermodynamic activity of the drug in the formulation.

Using the Hairless Mouse Skin

The formulations exhibiting the greater drug release through the cellulose membrane were further studied using the hairless mouse skin as the diffusion barrier. Here, the drug release was observed to be significantly reduced from all formulations evaluated. Avicel CL-611 (formulation C) with 15% ethanol gave the maximum drug release through this barrier, and it was observed to be minimum from PEG base (formulation A). The values for the steady-state flux and lag time are shown in Table 4. From this, one observes that the steady-state flux value (0.17 mg/cm^2 hr) was the highest, and the lag time was the lowest (2.94 hr) for formulation C containing 15% ethanol, which exhibited the maximum diffusion through this barrier. Also, the values for the diffusion, permeability, and partition coefficients were calculated (Table 5). Here again, the data indicate that formulation C, with 15% ethanol, gave the highest values for the diffusion coefficient (0.673×10^{-8} cm^2/sec) and the permeability coefficient (0.313×10^{-6} cm/sec), respectively. This supports the principles that, for the increased drug release through the biological membrane, the formulations did possess relatively higher diffusion and permeability coefficient values. To optimize drug diffusion from formulation C with 15% ethanol, the effects of oleyl alcohol at 2%, 4%, and

Table 5

Diffusion, Permeability, and Partition Coefficients Calculated from the In Vitro Data from Selected Bases Through Hairless Mouse Skin

Base	Diffusion Coefficient [D] (cm^2/sec) D × 10^8/cm^2/sec	Permeability Coefficient [P] (cm^2/sec) P × 10^6/cm^2/sec	Partition Coefficient [*Kp*]
PEG	0.053	0.083	35.83
HPMC + 5% alcohol	0.277	0.197	1.536
HPMC + 1% urea	0.363	0.230	1.324
Avicel + 15% alcohol	0.673	0.313	0.960
Modified USP + 15% alcohol	0.157	0.140	2.590

6% were further studied. The in vitro release data suggest that the inclusion of oleyl alcohol had no significant effect in further changing the thermodynamics and the drug release from the above formulation.

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