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RELEASE AND PERMEATION STUDIES OF PROPRANOLOL HYDROCHLORIDE FROM HYDROPHILIC POLYMERIC MATRICES

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ABSTRACT

In-vitro release of propranolol hydrochloride, from various hydrophilic polymeric bases was studied. These included: methocel®, avicel® CL-611/ methylcellulose, polyvinyl alcohol/gelatin based systems. Several additives, such as, ethyl alcohol, dimethylsulfoxide (DMSO) and polyethylene glycol-400 were included in the formulations for possible enhancement of the drug release. The release studies were carried out using the cellulose membrane and the hairless mouse skin as the diffusion barriers. The general rank order for the drug release through these membranes was observed to be: the methocel® matrix > the avicel® CL-611 matrix > the polyvinyl alcohol/gelatin matrix > and the emulsion base. The additives in the formulations had little or no effect in enhancing the drug release. However, when the hairless mouse skin was soaked in (DMSO) for one hour prior to its use in the diffusion studies, the drug release was found to increase by 40% from the methocel® matrix formulation.

The drug release data were treated with various kinetic principles to assess the relevant parameters, such as the diffusion, partition and permeability coefficients. Using these information, the formulations were screened for their suitability to deliver propranolol hydrochloride via the diadermatic dosage form.

INTRODUCTION

Propranolol, an effective beta-adrenergic blocking agent was first introduced on the market as Inderal® by Ayerst Laboratories, Inc., (1,2). In addition to its effectiveness and use in the management of hypertension (3-8), it has been found to be useful in treating the hyperthyroid conditions. And, lately it has been indicated in the prophylaxis of common migraine headache. On oral administration, it is completely absorbed, however, the systemic availability is low with considerable variation in plasma levels (9,10). The hepatic extraction of propranolol is about 80 to 90%, and the main route of drug elimination is via the hepatic metabolism (11). One of its major metabolites is 4-hydroxypropranolol, and the half-life has been reported to be 3-4 hours (12-14). Since the drug is rapidly metabolized after oral administration, it therefore, necessitates the multiple dosage regimen and strict patient compliance.

In light of these, and considering the latest trends in the art of product formulations, the present study was undertaken to evaluate the in-vitro release and permeation of propranolol hydrochloride from various hydrophilic polymeric matrices using the cellulose and the hairless mouse skin as the diffusion barriers. Also, to evaluate the influence of some of the additive ingredients in enhancing the drug release from these bases.

EXPERIMENTAL

Materials: Propranolol hydrochloride (I)[1], methocel® K100M[2], methylparaben[3], propyl paraben[3], gelatin A-260[3], glycerin[3], propylene glycol[4], methylcellulose[4], avicel® CL-611[5], polyvinyl alcohol[6], hydrophilic ointment base, USP[7], ethanol USP[8], polyethylene glycol-400[9] and dimethyl sulfoxide[10] (DMSO)[10].

Equipment: The following equipment was used: Franz diffusion cell apparatus[11], constant temperature water bath[12], and a spectrophotometer[13].

Preparation of Samples

(a) - Matrices Formulations: For gel formulations (Table-I), the polymer was first slowly dispersed in a portion of previously heated water about 80°C, and then

TABLE I

FORMULATION(S)

Ingredient		%w/w			
		*(A)	(B)	(C)	(D)
Propranol Hydrochloride	=	1.00	1.00	1.00	1.00
Methocel® K100M	=	2.00	----	----	----
Avicel® CL 611	=	----	8.00	----	----
Methycellulose 400cps.	=	----	2.00	----	----
Polyvinyl Alcohol (20%)	=	----	----	50.00	----
Gelatin A-260	=	----	----	10.00	----
Hydrophilic Ointment, USP.	=	----	----	----	80.00
Glycerin	=	----	15.00	----	----
Propylene Glycol	=	10.00	----	10.00	----
Methyl Paraben	=	0.20	0.20	0.20	0.20
Propyl Paraben	=	0.05	0.05	0.05	0.05
Additive(s)	=	q.s.	q.s.	q.s.	q.s.
Purified Water q.s.	=	100.00	100.00	100.00	100.00

*(A) was also made at 1.5%, 2.0% and 3.0% drug concentrations

another portion of water at ambient temperature was added and mixed. Drug and other ingredients were predissolved in water and incorporated into the batch at approximately 50°C and mixed until cooled.

(b) - **Emulsion Formulations**: For emulsion formulations (Table-I), the drug and parabens were premixed in hot water at about 50°C and then incorporated in the previously melted emulsion base at 50°C. The samples were adequately mixed for 10 minutes and then cooled to room temperature.

Assay Procedure For Propranolol Hydrochloride: Plots of absorbance versus wavelength for solutions of drug in water were developed. The maximum values of absorbance were observed at 290nm. Beer's law was followed for 1-20-μg/ml concentrations. The stability of the drug in the diffusion medium was determined at 37°C for 24 hours and no loss of potency was noted.

Content Uniformity: All formulations prepared were analyzed and only samples with 100 ± 10% content of (I) were used in the diffusion studies.

In-Vitro Diffusion Studies: In-vitro diffusion studies were carried out by using the Franz diffusion cells according to a published procedure (15).

Preparation of Hairless Mouse Skin: A set of three hairless mice about 6-8 weeks old were sacrificed for each experiment by snapping the spinal cord at the neck. The circular section of the abdominal area of the skin was excised and the adhering fat and debris were carefully removed from the skin samples. These were soaked in normal saline solution until their use.

RESULTS AND DISCUSSION

Using The Cellulose Membrane: From the in-vitro release data of (I) form various formulations evaluated over a 24 hours period, the decreasing rank order of the drug release was observed to be: methocel® matrix > avicel® CL-611/ methyl-cellulose matrix > PVA/gelatin matrix > and the emulsion base. Methocel® matrix (Formulation A) exhibited the maximum drug release (11.75 mg/24hr), and this was observed to be minimum (6.53 mg/24hr) from the PVA/gelatin matrix (Formulation C). This could be attributed to the possible cross-linkages formed between the two polymers and thus restricting the movement of the drug molecules in the gel system. The release of (I) from the emulsion base (Formulation D) was the lowest (2.42 mg/24hr) among all the samples evaluated. This suggests that for a water-soluble drug like (I), the polymeric gel-based formulations are clearly the better vehicles for developing the dermatological dosage forms. However, the inclusion of additives in these bases had little or no effect in enhancing the drug release.

To analyze the release data in terms of more meaningful parameters, the data were first treated with the simplified Higuchi's equation (16), and plotted against the square root of time (t 1/2). From this, excellent linear relationships were observed and the drug release from these samples followed this model.

In addition, the effects of variation of polymer and drug concentrations in (Formulation A) were studied respectively. The polymer concentration was varied from 2.0% to 1.5% and 3.0%, and it was observed that this aspect of the formulation did not change the drug release patterns. On the other hand, the drug release was found to be directly proportional to the concentration of (I) in the formulation.

TABLE II

EFFECTS OF (DMSO) ON DRUG RELEASE-PERMEABILITY FROM METHOCEL MATRIX (FORMULATION A) USING HAIRLESS MOUSE SKIN.

	Drug Release (mg ± SD)		
Time (Hrs)	A	A(a)	A(b)
1	0.21 ± 0.17	-----	0.28 ± 0.03
2	0.26 ± 0.18	0.19 ± 0.01	0.31 ± 0.01
4	0.34 ± 0.04	0.26 ± 0.02	0.39 ± 0.03
8	0.53 ± 0.06	0.37 ± 0.03	0.57 ± 0.04
12	0.72 ± 0.08	0.47 ± 0.03	0.73 ± 0.03
24	0.81 ± 0.05	0.79 ± 0.09	1.13 ± 0.08

A = Methocel® Matrix (Formulation A).
A (a) = Methocel® Matrix + 5% DMSO
A (b) = Methocel® Matrix (Skin Soaked In DMSO For 1 Hour).
Note: Each Reading Is An Average of Three (3) Determinations.

And, this may be due to the enhanced thermodynamic activity of the drug molecules in the matrix system because of the higher drug level in the sample.

Using The Hairless Mouse Skin: Methocel® matrix (Formulation A), was further investigated for the drug release-permeation profile using the hairless mouse skin as the barrier. Here, the release of drug was observed to be significantly reduced to 0.81 mg/24 hours compared to 11.75 mg/24 hours through the cellulose membrane. This formulation was further modified by including (DMSO) in an effort to enhance the drug release through this biological membrane. The data obtained in these experiments reveal some interesting observations, i.e., when the hairless mouse skin itself was soaked in (DMSO) for one hour prior to its use in the diffusion studies, the release of drug was enhanced by 40%, as exhibited in Table II. And, the values of the release rate constant K (k=mg/hr) for formulations A, A(a) and A(b) were determined and found to be 0.046 (r=0.999), 0.027 (r=0.998) and 0.042 (r=0.999) respectively. To compare these data statistically, F-test and confidence interval 95% methods were employed, and the results are shown in Table III. According to these, the drug release is significantly different when the hairless mouse skin was soaked in (DMSO) for one hour than from Formulation A or A(a) containing 5% (DMSO).

TABLE III

COMPARATIVE DATA OF DRUG RELEASE-PERMEATION FROM METHOCEL® MATRIX (FORMULATION A) USING HAIRLESS MOUSE SKIN.

Sample	Drug Release-Permeation (mg ± SD)	(%)	Statistical Significance
A = Methocel® Matrix (Formulation A)	0.81 ± 0.05	(2.02)	---
A(a) = Methocel® Matrix + 5% DMSO	0.79 ± 0.09	(1.98)	N.S.
A(b) = Methocel® Matrix (Skin Soaked in DMSO For 1 Hour)	1.13 ± 0.08	(2.83)	S.S

Note: Each Reading Represents An Average of (3) Determinations.
N.S. Not Statistically Significant
S.S. Statistically Significant

TABLE IV

THE VALUES OF DIFFUSION, PERMEABILITY AND PARTITION COEFFICIENTS FOR DRUG RELEASE DATA FROM VARIOUS FORMULATIONS USING HAIRLESS MOUSE SKIN.

Sample	Diffusion Coefficient ($D \times 10^{-7}$ cm^2/sec)	Permeability Coefficient ($P \times 10^{-7}$ cm^2/sec)	Partition Coefficient ($P_e \times 10^{-1}$ cm^2/sec)
Methocel® Matrix Formulation-A.	3.00	1.90	0.38
Avicel® CL 611 Formulation-B	0.94	1.20	0.76
PVA/gelatin Formulation-C	0.73	1.10	0.85
Emulsion Base Formulation-D	0.11	0.40	2.30

In addition, the values for the diffusion coefficient (D), the permeability coefficient (P) the partition coefficient (P_e) were calculated and listed in Table IV. From this one observes that the sample with maximum drug release, i.e., (Formulation A) has the highest diffusion coefficient value of (3.0×10^{-7} cm^2/sec.) compared to the emulsion base (Formulation D) with this value of only (0.11×10^{-7} cm^2/sec.). Also, the highest permeability coefficient value of (1.90×10^{-7} cm^2/sec.) was obtained for (Formulation A) compared to the (Formulation D) with a value of (0.4×10^{-7} cm^2/sec.). On the other hand, the value for the partition coefficient for the (Formulation A) was obtained to be the lowest of all the formulation, i.e., 0.38×10^{-1} cm^2/sec.) compared to the value of (2.30×10^{-1} cm^2/sec.) for the emulsion base (Formulation D), which gave the minimum drug release under the experimental conditions. These data support the principles that for the higher drug release through the barriers, the formulations should possess relatively higher permeability and diffusion coefficient values.

FOOTNOTES

1. Ayerst Laboratories, Inc., Rouses Point, NY.
2. Dow Chemical Corporation, Inc., MI.
3. Amend Drug and Chemical Co., NJ.
4. Ruger Chemical Company, Inc. NJ.
5. FMC Corporation, Inc., PA.
6. Aldrich Chemical Co., Inc., WI.
7. Pharmaderm Inc., New York, NY.
8. U.S. Industrial Chemicals Co., NY.
9. J.T. Baker Chemical Co., NJ.
10. Fisher Scientific Company, Inc., NJ.
11. Crown and Glass Company, Inc., NJ.
12. Yamato Scientific Co., Ltd., Japan.
13. Shimadzu Baush & Lomb, Fisher Scientific Co., NJ.

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