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IN VITRO RELEASE OF SELECTED NONSTEROIDAL ANTIINFLAMMATORY ANALGESICS [NSAIA] FROM RESERVOIR-TYPE TRANSDERMAL FORMULATIONS

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ABSTRACT

Indomethacin [I], Ketoprofen [II] and Sulindac [III] were evaluated for in vitro percutaneous uptake from various ointment bases. Three doses for each NSAIA were employed for evaluation. Each reservoir system was evaluated for drug release across composite skin (semipermeable membrane) using a modified FDC assembly over a 12 h period. The drug release profiles were examined for mechanism of drug release and developing recommendations for designing a dermal product for a NSAIA.

FOR ALL NSAIAs: This study demonstrated that I, II and III can penetrate the composite skin barrier with differing efficiencies. II penetrated with maximal ease while I with minimal ease. The drug release rate increased with increasing drug load. O/W and water soluble system compositions yielded superior drug release rates when compared to other reservoir systems. The drug release characteristics indicated adherence to diffusional pathways borne out of Q versus square-root-of-time relationship. The Qmax:Drug Load (Dose) ratio as a function of Dose was influenced by the compositional characteristics for any given system. Statistically significant differences ($p<0.01$) were observed when apparent permeability coefficients were compared between various compositions and within the dose levels for each composition tested.

INTRODUCTION

Drugs intended for localized action such as NSAIAs need to be administered at the desired site. Oral administration of NSAIAs exhibit limited efficacy due to inadequate/limited solubility in

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gastric medium. Administration of these agents via the dermal route can bypass gastric irritation and provide relatively consistent drug levels at the site for prolonged periods, provided their passage through skin is demonstrated.

OBJECTIVES

1. To comparatively evaluate the in vitro transcutaneous availability of I, II, and III each at three dose levels from the following reservoir type topical formulations:

Class I:	Oleagenous system - Eucerin^{R}, Vaseline
Class II:	Water soluble system - PEG ointment USP
Class III:	Oil-in-Water system - Acid Mantle Creme^{R}
Class IV:	Water-in-Oil system - Cold Cream

2. To determine the mechanism of drug release from these systems for each NSAIA.

EXPERIMENTAL

1. Analytical Methodology: A UV spectrophotometric method of analysis was employed for the determination of I (318nm), II (255nm), and III (285nm) in Sorenson's buffer.

2. Reservoir Type Dermal Systems: Ointments were prepared by intimately mixing known amount of I or II or III with a variety of ointment bases representative of their corresponding class. The following dose levels, mg, were employed: I - 50, 100, 150; II - 150, 225, 300; and III - 150, 250, 400.

3. Preparation, Experimental Setup and Determination of Drug Release Profiles for Evaluation of I, II, and III Release from Reservoir Systems: Any given system composition was prepared with finite physical dimensions which coincided with the donor compartment of the diffusion cell calibrated for its volume. The

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entire assembly was then laminated by an impermeable backing thus exposing only one surface (with finite area of 4.91 cm^2) through which drug release could occur (1). The drug release profiles were determined by employing the procedure outlined in Ref. 1.

4. Analysis of Drug Release Profiles: Drug release profiles over a 12 h period were expressed in terms of cumulative drug released (Q) as a function of time. Additionally, Q versus $t^{0.5}$ relation was explored. Furthermore, Q_{max}:drug-load for each system composition and apparent in vitro permeability coefficients for each system composition (re: Q vs $t^{0.5}$) were determined.

RESULTS AND DISCUSSION

1. Formulation Studies and Drug Release Profiles of Selected NSAIAs' Reservoir Systems: The topical reservoir systems prepared for I, II and III showed no signs of incompatibility between the base and the drug. The analysis of drug release data was conducted in coherence with the release of drug from ointment bases containing drugs in suspension (2-4). Figures 1-3 illustrate the drug release profiles for I, II and III at all loading levels.

Apparently, II penetrated the composite skin barrier (semipermeable membrane) with maximal ease while I with minimal ease. For I, II and III water soluble system (PEG Ointment USP) and O/W system (Acid Mantle Creme) exhibited more rapid drug release rates when compared with other system compositions. The drug release rate increased with increasing drug load (dose) for all system compositions as well as drugs tested. Statistically significant differences were observed when drug release rates were compared

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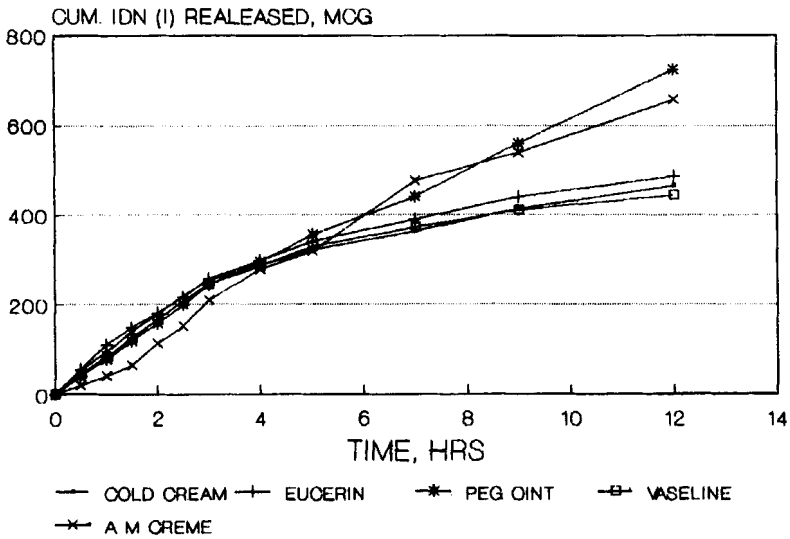

FIG. 1. Indomethacin (I) Release Profile from Different Topical Reservoir Formulations at Various Drug Loading Levels; a. 50 mg, b. 100 mg and c. 150 mg.

within formulations and between drugs products. The drug release data apparently indicated that the presence of both lipid and aqueous favoring components facilitate enhanced transcutaneous release over compositions that are strictly hydrophilic or lipophilic in character. The drug release rates exhibited by O/W compositions containing I, II or III attest this observation.

Good linearity (r=0.91 or better) between Q and $t^{0.5}$ for all drug loads and all system compositions as well as for all drugs tested was observed. Thus the data indicated adherence of drug release to diffusional pathways. All formulations tested exhibited minimal 'burst effect' indicative of minimal migration

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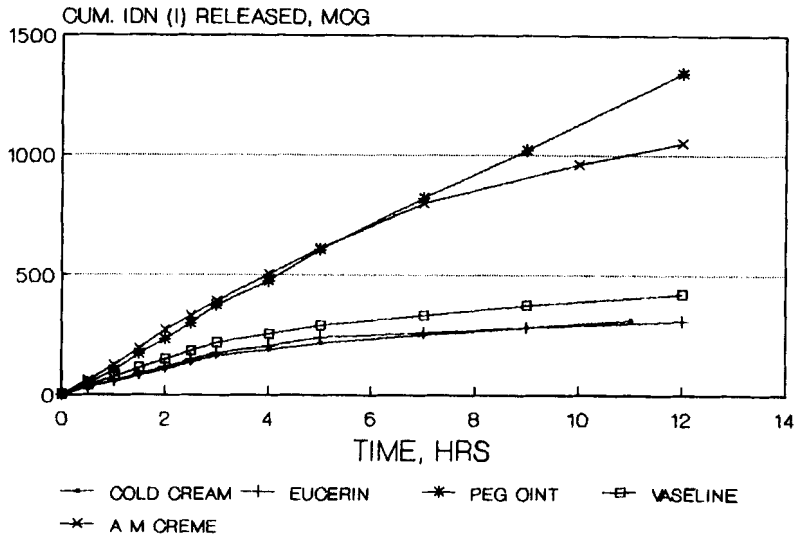

Fig. 1.b. 100 mg

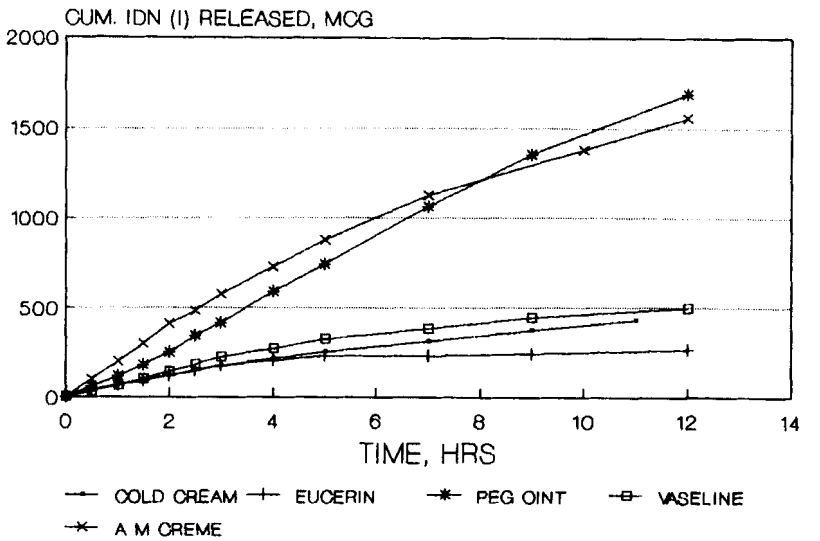

Fig. 1.c. 150 mg

FIG. 1 continued

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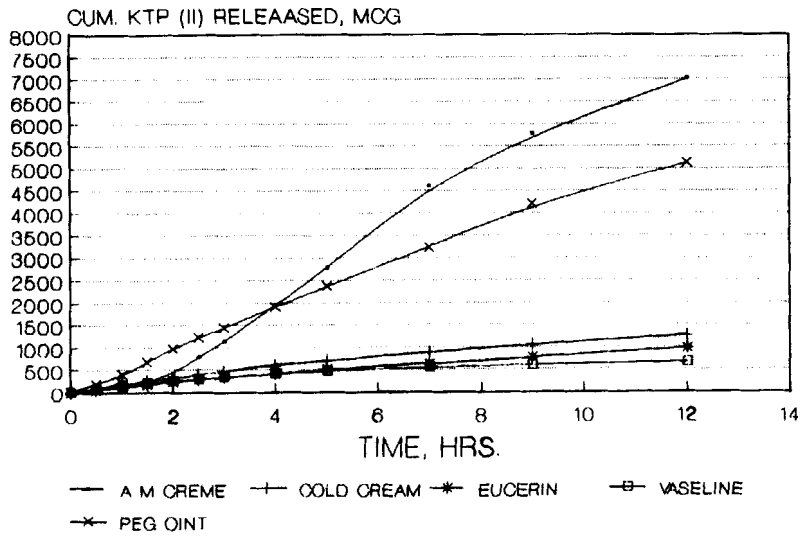

Fig. 2.a. 150 mg

FIG. 2. Ketoprofen (II) Release Profile from Different Topical Reservoir Formulations at Various Drug Loading Levels; a. 125 mg, b. 225 mg and c. 300 mg.

of drug particles towards the release surface prior to experimentation. Thus, it appears that these formulations may not be able to provide for an immediate effect/relief by releasing an adequate amount of drug at the desired site. Statistically significant differences were observed when apparent permeability coefficient values for drugs tested as well as for different formulations evaluated for any given drug were compared.

The changes in Q_{max}:drug-load ratio with respect to drug loading for all compositions can provide insight as to the characteristics of system compositions. Additionally, the

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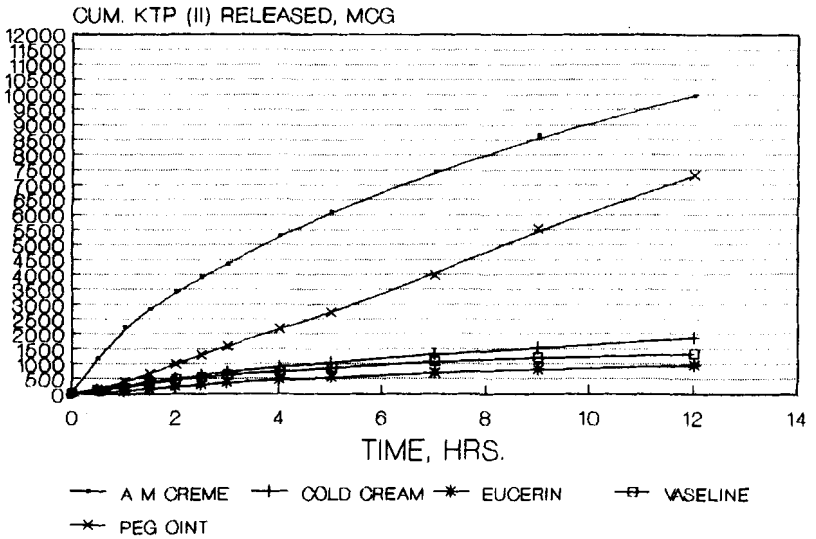

Fig. 2.b. 225 mg

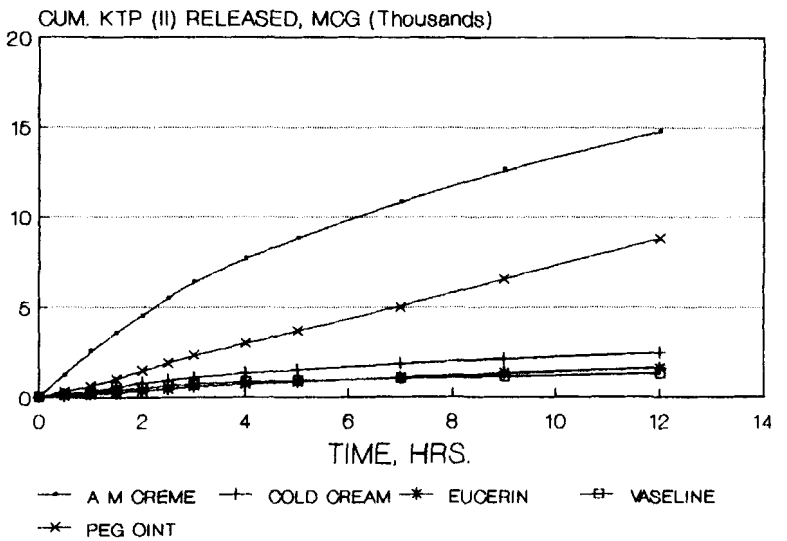

Fig. 2.c. 300 mg

FIG. 2 continued

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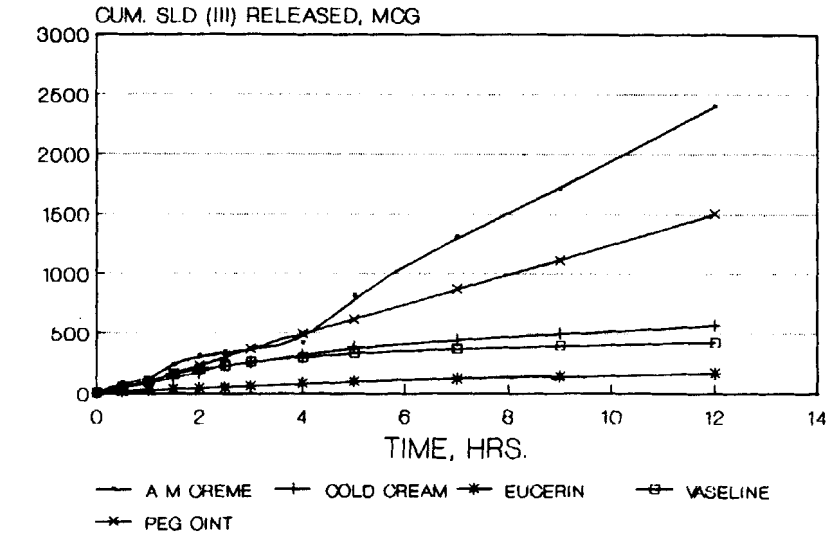

Fig. 3.a. 150 mg

FIG. 3. Sulindac (III) Release Profile from Different Topical Reservoir Formulations at Various Drug Loading Levels; a. 150 mg, b. 250 mg and c. 400 mg.

resultant changes in the system matrix with changes in drug load can be evidenced by changes in drug release rate thus effecting changes in ratio. Hence, changes in this ratio can assist in identifying system components which can promote dermal uptake thus providing rational means for justifying a system for formulation development. For I, II and III Q_{max}:drug-load was consistently higher for lower drug loading of the systems when compared with higher drug loading. While O/W (Acid Mantle Creme) and water soluble (PEG ointment) system compositions exhibited markedly higher ratio values comparable values for this parameter were observed for the other system compositions (Table 1). The data

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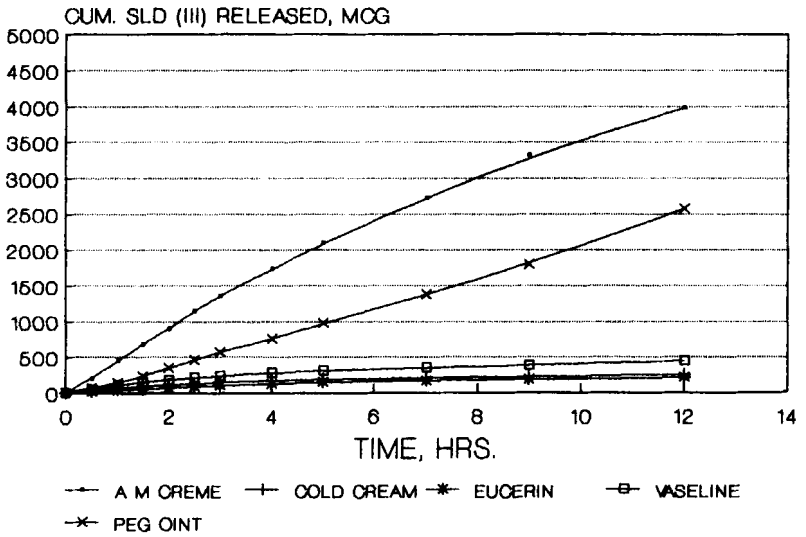

Fig. 3.b. 250 MG

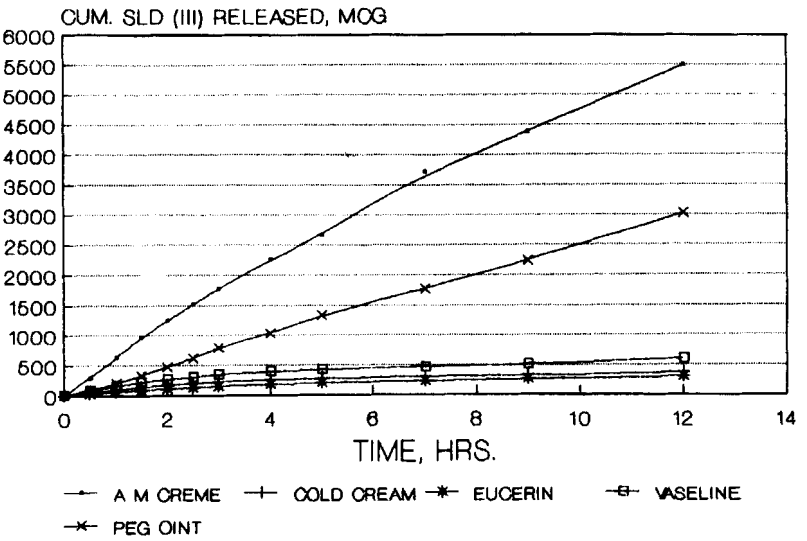

Fig. 3.c. 400 MG

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TABLE 1

Q_{max}:Drug-Load Ratios for I, II and III at Various Loading Levels in Various System Compositions

Drug	Dose, mg	Q_{max}:Drug-Load				
		A	B	C	D	E
I	50	0.013	0.009	0.010	0.009	0.015
	100	0.011	0.003	0.003	0.004	0.013
	150	0.010	0.003	0.002	0.003	0.011
II	150	0.047	0.008	0.007	0.004	0.034
	225	0.044	0.008	0.004	0.006	0.032
	300	0.049	0.008	0.005	0.004	0.029
III	150	0.016	0.004	0.001	0.003	0.010
	250	0.016	0.001	0.001	0.002	0.010
	400	0.014	0.001	0.001	0.002	0.010

A: Acid Mantle Creme; B: Cold Cream; C: Eucerin; D: Vaseline; E: PEG Ointment USP

indicated that, at potentially lower dermal doses O/W system composition might prove to be useful for yielding greater amounts of drug at the desired site. For potentially higher dermal doses of these drugs a combination of O/W and water soluble system composition could provide for reasonably rapid drug release rates.

CONCLUSIONS

1] This study demonstrates that I, II and III can penetrate through the in vitro skin barriers (semipermeable membrane).

2] The release of I, II and III from various system compositions is influenced by changes in the characteristics of the system components as well as the drug loading levels.

3] The release characteristics of I, II and III support adherence to diffusional mechanisms/pathways.

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4] It appears that, O/W and water soluble compositional characteristics could provide means for effective formulation development of dermal product(s) for these selected NSAIAs.

REFERENCES

1. U. Patel and U.V. Banakar, 7th Pharm. Technol. Conf./Expo. Proc., London, England (April 13, 1988) p 1-14.

2. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).

3. W.I. Higuchi, J. Pharm. Sci., 56, 315 (1967)

4. U.V. Banakar, Pharm. Manuf., 1(7), 36 (1984).

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