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COMMUNICATION

Release Kinetics of Tretinoin from Dermatological Formulations

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ABSTRACT

Tretinoin, or retinoic acid, can be used in the treatment of a variety of skin diseases, depending on its concentration. Formulations containing tretinoin 1% have been used in the therapy of malignant cutaneous diseases, namely, Kaposi's syndrome. In lower concentrations, it has been used in antiacne formulations and in the treatment of anti-aging effects on photodamaged skin. The aim of the present study was to determine the variation profile of in vitro release of tretinoin, in order to establish the drug's partition coefficient between its carrier and the stratum corneum. The samples studied were formulations of tretinoin 0,05% in carbopol 940 (a synthetic polymer), sodium carboxymethylcellulose (a semisynthetic polymer), and carob gum (a natural polymer) gels. The release profiles obtained from these formulations were compared to release profiles of tretinoin creams. The formulations studied exhibited both good chemical and physical stabilities when submitted to rheological determinations, pH measurements, and drug dosage, throughout a 6-month period. The obtained results show that identical polymer viscosities result in identical release profiles; however, the release kinetics of tretinoin varies strongly in the way in which the drug is incorporated in the formulation (whether it is a solution or a suspension).

INTRODUCTION

Tretinoin (all-*trans*-retinoic acid; vitamin A acid) has been applied for topical treatment of several diseases such as: therapy of premalignant and malignant cutaneous diseases, namely Kaposi's syndrome (1,2); clinical manifestations of photodamaged skin including pigmentation, fine and coarse wrinkling, and roughness; acne; and psoriasis (3-17). Tretinoin decreases and prevents lesions by increasing epithelial cell turnover and decreasing horny cell adherence (18,19). In this study, formulations of carbopol 940 (a synthetic polymer), sodium

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carboxymethylcellulose (a semisynthetic polymer), and carob gum (a natural polymer) gels containing tretinoin were prepared.

The purposes of this investigation are:

- the study of physical and chemical stability of tretinoin in hydrophilic gels.
- the determination of the in vitro drug release from the formulations at different times.
- the comparison of release profiles obtained with tretinoin delivery from a commercially available cream.

MATERIALS AND METHODS

Materials

Tretinoin (Roche); carbopol (Merck); sodium carboxymethylcellulose, high viscosity (BDH); carob gum LBG HG M175 (Indal); triethanolamine (Merck); and isopropyl myristate (Henkel).

Tretinoin Hydrogels Preparation

Dermatological hydrophilic gels were prepared as shown in Table 1. Carbopol 940 was dusted onto distilled water (without stirring) and left to settle for 24 hr. Then, triethanolamine was added, stirring slowly to avoid the inclusion of air. Tretinoin and preservatives were added to ethanol and then to the rest of the preparation. Sodium carboxymethylcellulose and carob gum were dispersed in hot water (100°C) containing nipagine and nipasol. Stirring was maintained until cooling and then tretinoin was added.

Stability Studies

Hydrogels were stored in glass containers, well stoppered, for 6 months at ambient temperature (23°C) and in the dark. They were checked after preparation and throughout a 6-month period. Physical evaluation of the samples' stability was carried out by visual inspection and rheological tests. Chemical stability was evaluated by pH measurements and spectrophotometric analysis.

Rheological Measurements

Hydrogels were examined at 22°C using a rotational viscometer (Rheomat 30). Measurements of different rates of shear for corresponding shear stress were made using Model No. 25.

pH

The pH was measured in each gel, using a pH meter (MicropH 2002, Crison, precision 0.01 pH units), which was calibrated before each use with buffered solutions at pH 4 and 7.

Tretinoin Assay

Each gel (0.25 g) was treated with absolute ethanol until completely dissolved, filtered, and assayed by spectrophotometric analysis at 346 nm (Shimadzu UV-160 spectrophotometer). The concentration was calculated on the basis of a calibration curve constructed from solutions of known amounts of tretinoin in absolute ethanol (20).

Table 1

Formulations of the Dermatological Gels

	Formulation			
	F1	F2	F3	F4
Tretinoin	0.05 g	0.05 g	0.05 g	0.05 g
Carbopol 940	0.75 g	0.75 g	—	—
Sodium carboxy methylcellulose	—	—	3.5 g	—
Carob gum	—	—	—	2.25 g
Ethanol 96%	1.5 ml	30 ml	—	—
Triethanolamine	0.3 ml	0.3 ml	—	—
Nipagine	0.18 g	0.18 g	0.18 g	0.18 g
Nipasol	0.02 g	0.02 g	0.02 g	0.02 g
Distilled water	ad 100 g	ad 100 g	ad 100 g	ad 100 g

In Vitro Tretinoin Release

Uniform samples of the gels and of the commercially available cream were applied to the external surface of a cylindric container (27.28 cm^2) and immersed into 350 ml of isopropyl myristate at 32°C under continuous mechanical stirring at a rate of 200 rpm. Five-milliliter aliquots of the dissolution medium were withdrawn at predetermined time intervals during 3 hr, filtered, and then assayed by spectrophotometric analysis at 350 nm (Shimadzu UV-160 spectrophotometer). Isopropyl myristate was used as dissolution medium because of its similarity with the lipids of the skin (21).

RESULTS

Hydrophilic gels presented good stability. Therefore, no macroscopical physical changes were observed during storage.

Initial rheological characteristics of the various tretinoin formulations were analogous as can be seen in Fig. 1; studies carried out for 6 months showed no significant differences in their rheological behavior.

The pH values did not change and there was no loss of tretinoin from gels (Table 2).

Relative to in vitro tretinoin release, Fig. 2 shows a low drug delivery from the dermatological formulations studied which is in agreement with previous results (21); however, the fastest drug release has been obtained with hydrogels F1, F3, F4, followed by hydrogel F2 and then by the commercially available cream F0.

CONCLUSIONS

Although in vivo experiments are required, the present work allows one to conclude:

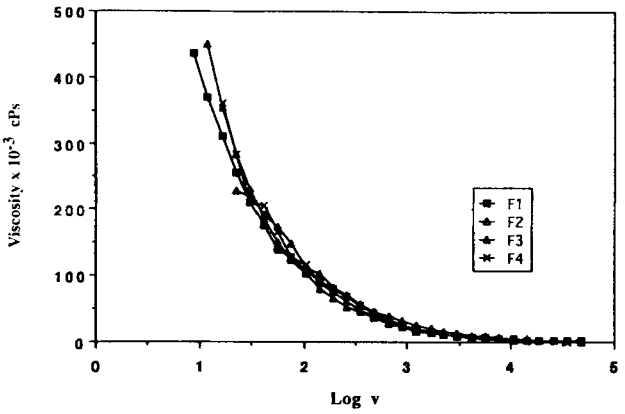

Figure 1. Rheograms of tretinoin gels (F1, F2: carbopol gel; F3: sodium carboxymethylcellulose gel; F4: carob gum gel).

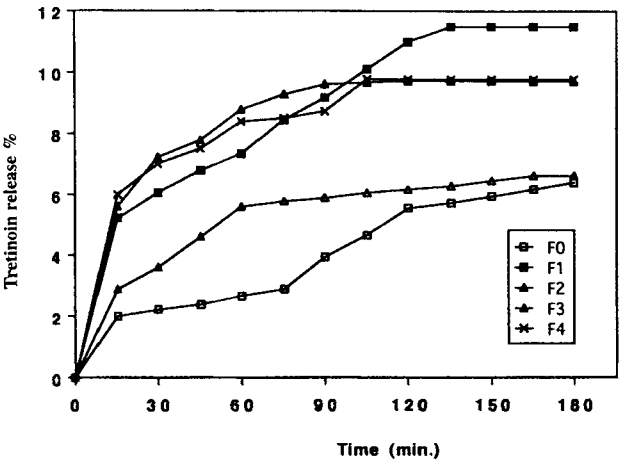

Figure 2. In vitro tretinoin kinetics from dermatological formulations (F0: commercially available cream; F1, F2: carbopol gel; F3: sodium carboxymethylcellulose gel; F4: carob gum gel).

Table 2

pH Values and Tretinoin Assay Results

Formulation	Initial pH	Final pH	Initial Tretinoin Concentration (mg/100 g)	Remaining Tretinoin % After 6 Months storage
F1	5.10	5.08	49.25	100.0
F2	5.15	5.07	49.76	94.2
F3	6.54	6.52	47.13	97.8
F4	5.60	5.40	48.72	95.2

In vitro tretinoin release kinetics is not significantly affected by the nature of the polymer. Thus, carbopol 940 (a synthetic polymer), sodium carboxymethylcellulose (a semisynthetic polymer), and carob gum (a natural polymer) gels with identical viscosity, display analogous release profiles.

The pharmaceutical dosage form (gel or cream) and the way tretinoin is incorporated into the topical formulation (solution or suspension) have a great importance on drug delivery.

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