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COMMUNICATION

Transdermal Delivery of Isosorbide 5-Mononitrate from a New Membrane Reservoir and Matrix-Type Patches

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ABSTRACT

Isosorbide 5-mononitrate (5-ISMN) has a direct relaxing effect on vascular smooth muscle. In the present study we developed matrix and reservoir-type transdermal patches of 5-ISMN. We investigated the usefulness of a new film-forming material isolated from the roots of Salacia macrosperma *to serve as rate-controlling membrane for the reservoir-type patches. Matrix-type patches were formulated using polyvinyl chloride. Permeation studies through rat skin were conducted on both types of patches using Teflon cells. The mean ± SD flux values from the matrix- and reservoir-type patches were 99.55 ± 22.89 and 31.82 ± 8.31μg/cm² · hr, respectively.*

INTRODUCTION

The benefits of intravenous drug infusion can be closely duplicated, without its hazards, by using skin as the port of drug administration to provide continuous transdermal drug infusion into the systemic circulation (1). To provide continuous drug levels, several transdermal therapeutic systems have been developed for topical application onto the intact skin surface to control the delivery of drug and its subsequent permeation through the tissue. It is exemplified by the development and marketing of scopalamine, nitroglycerin, estradiol, and clonidine (2).

Isosorbide dinitrate (ISDN) has long been in clinical use. It is administered orally, sublingually, intravenously, and transdermally in the treatment and prophylaxis of angina pectoris, vasospastic angina, and congestive heart failure (3–5). A large proportion of ISDN is

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metabolized into two active metabolites, isosorbide 5-mononitrate (5-ISMN) and isosorbide 2-mononitrate (2-ISMN) (6–8).

5-ISMN, which has a direct relaxing effect on vascular smooth muscle, dilates coronary vessels, and improves oxygen supply to the myocardium, is now available as a separate entity in the market for oral and sublingual administration (9). The purpose of the preparation of a transdermal patch of 5-ISMN is to administer one of the major active ISDN metabolites directly in to the systemic circulation to provide extended activity which is independent of the metabolic fate of drug. In the present study we developed transdermal patches (both matrix and reservoir type) of 5-ISMN and carried out the in vitro diffusion studies.

MATERIALS AND METHODS

5-ISMN (kind gift by Dr. Karanth Pharma Chemical Labs Pvt., Ltd., Hyderabad, India); polyvinyl alcohol [S.D. Fine Chemicals (P) Ltd., Bombay, India]; methanol and cetonitrile of HPLC grade purchased from Ranbaxy Labs., New Delhi, India; and a film-forming material (FFM), kindly gifted by the Plant Biotechnology division of Pharmacy College, Kakatiya University, Warangal, India, which was extracted from roots of *Salacia macrosperma* (family hipposrataceae) were used. The extract is a light yellow, elastic solid mass with a melting range of 57–65°C. The molecular weight of FFM was estimated to be 1627 and the other experimental results (UV, IR spectra, and elemental analysis) suggested that the compound is a polymer of isoprene with the following structure: $(H_2C\text{–}C(CH_3)=CH\text{–}CH_2)_n$.

It was nontoxic, nonabsorbable, hydrophobic, and able to form a uniform and continuous film (10). All the other chemicals used in the study were of analytical reagent grade.

Preparation of Matrix-Type Patch

Polyvinyl alcohol (PVA) was used to fabricate the matrix device. Five hundred milligrams each of PVA and 5-ISMN was dissolved in methanol. Polymer solution (150 µl, which contains about 40 mg of drug) was casted on a thin sheet of aluminum foil, which acted as a backing membrane. After an overnight drying at room temperature, the patch was stored in an airtight container.

Preparation of Free Polymeric Membranes

Solution of FFM (0.75%) was prepared in benzene and poured in a glass ring (5.6 cm in diameter) kept on the surface of mercury. After evaporation of benzene at room temperature, the dried films were stored in a desiccator.

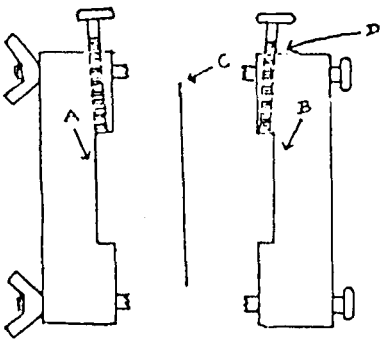
Skin Preparation and Permeation

An albino rat was decapitated prior to the removal of skin. The skin samples were harvested from the back side of rats and stored at −20°C. Frozen skin samples were thawed and the epidermal layers (comprising the stratum corneum and viable epidermis) were separated by immersing the skin in hot water (approx. 60°C) for 2 min. The epidermal layer was used for diffusion studies.

A specially designed (Fig. 1) diffusion cell made of Teflon was used in these investigations for the skin permeation studies. The diffusion cell comprises two compartments, the receiver and donor compartments, each with 1.2 ml capacity. The skin section and matrix device or polymeric membrane were mounted carefully between the two half cells of the diffusion cell and fastened with screws. For the matrix device, the receiver compartment was filled with distilled water, but for the reservoir device, water was filled in the receiver compartment and the donor compartment contained the solution of 5-ISMN (40 mg) in a mixture of propylene glycol and water, 700 and 500 µl, respectively. The temperature of diffusion cells was maintained at 37°C by immersion in water bath. The cells were continuously agitated. At predetermined intervals the entire contents of receiver compartment was emptied and replaced with fresh receptor fluid. Samples were stored at −20°C until analysis by HPLC.

Liquid Chromatographic Analysis

The test aliquots were analyzed for 5-ISMN content by the HPLC method (11). The high-performance liquid chromatograph equipped with a SPD-M6A photodiode array UV–VIS detector, LC-10AS pump, and a Rheodyne injector from Shimadzu, Japan, were used for the drug analysis. A 30 cm × 3.9 mm i.d. Bondapack C18 column (Waters, Milford, MA) with 5 µm spherical particles was used. Samples (1.2 ml) and dapsone (5 µg), which was used as internal standard, were vortexed with 6 ml of dichloromethane (DCM) for 2



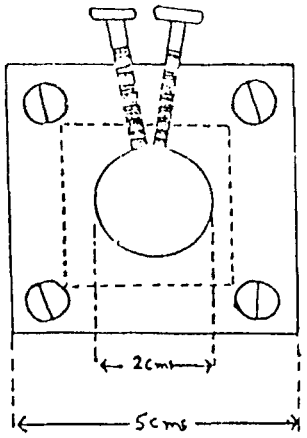


Figure 1. Diffusion cell.

min. After centrifugation for 10 min at 3000 rpm, the organic layer had to be separated and dried in vacuum. The residue was reconstituted in methanol (200 µl) and injected (20 µl) into the column. The analysis was carried out at wavelength 220 nm. A mixture of methanol, acetonitrile, and water (10:10:80) was used as eluent at a flow rate of 1 ml/min. The concentrations of samples were calculated from a standard graph prepared from peak area ratios versus concentrations of 5-ISMN.

RESULTS AND DISCUSSION

The mean cumulative percentage permeated versus time profiles of 5-ISMN from reservoir- and matrix-type formulations are shown in Figs. 2 and 3. It is clear from the figures that the permeation of 5-ISMN was nearly linear and there was an initial lag period after which the drug release was nearly linear until completion of the study, i.e., 48 hr. Regression analysis of the permeation curves was carried out and slope of the straight line obtained after plotting the mean cumulative amount permeated per square centimeter (µg/cm^2) versus time was taken as the experimental skin flux for 5-ISMN. After 48 hr, the mean ± SD cumulative percentage of dose permeated from the matrix formulation was 19.83 ± 4.55, which was significantly higher than that released from reservoir-type patch, which was 6.34 ± 1.66.

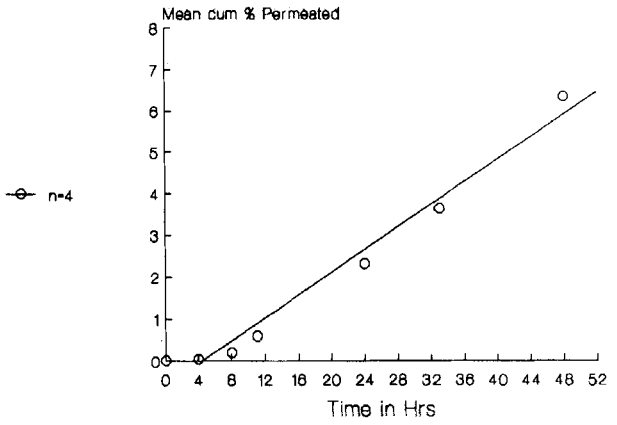


Figure 2. Skin permeation profile of 5-ISMN from reservoir-type formulation.

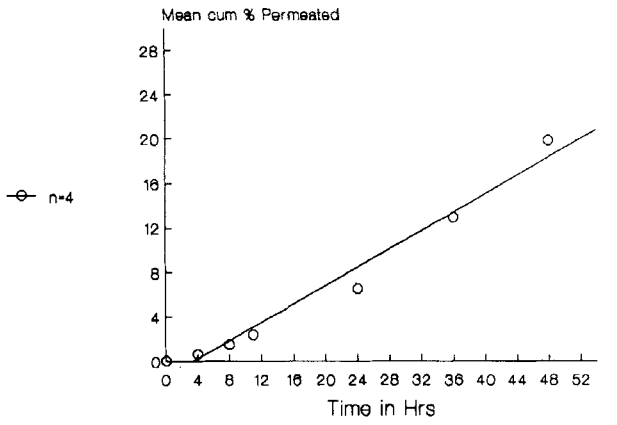


Figure 3. Skin permeation profile of 5-ISMN from matrix-type formulation.

The cumulative mean ± SD experimental flux values of 5-ISMN from the matrix and reservoir formulations were 99.55 ± 22.89 and 31.82 ± 8.31 μg/cm²/hr, respectively. From these results it may be stated that the reservoir-type patch showed slower release because of the hydrophobicity of the rate-controlling polymeric membrane. The matrix-type patch is able to give flux values about three times higher than those of the reservoir type.

The experimental flux values for nitroglycerine by using human cadaver skin from different marketed formulations were found to be in the range of only 19.2–20.3 μg/cm²/hr (12). The theoretically computed value for GTN was 13 mg/cm²/hr (13), which is several times more than the experimental flux values. For ISDN the reported theoretical flux was 4.8 mg/cm²/hr (13), but the estimated value for the marketed patches is not known.

In the present study, even though the formulations of 5-ISMN were prepared without any permeation enhancers, the mean experimental flux value was found to be much better, when compared to GTN. Still higher flux values, however, can possibly be achieved through formulation alterations. From this study, it may be unequivocally stated that although the 5-ISMN is less lipophilic than ISDN, it permeates through the skin well with comparable flux values to justify its administration by transdermal route.

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