International Journal of Pharmaceutics, 41 (1988) 49–53
Elsevier

IJP 01368

A new in vitro model for quantitative study of cream permeability

Anna Orbe and Lars-Olof Sundelöf

Institute of Physical and Inorganic Chemistry, Faculty of Pharmacy, Uppsala University, Biomedical Center, Uppsala (Sweden)

(Received 12 June 1987)
(Accepted 29 June 1987)

Key words: Barrier cream; Permeability determination; Membrane; Diffusion cell; Dissolution rate

Summary

A new in vitro procedure has been developed for a quantitative study of the permeability of pharmaceutical creams and ointments. It is based on the use of a standard Nuclepore membrane as support for the cream. Such a membrane has the advantage that the pores are very well defined geometrically, which simplifies the interpretations of results, and a number of pore sizes are aviable. The membrane is clamped in a suitable cell as a separation wall between a donor and a receiving chamber, the content of which can be analyzed by any suitable method as a function of time. The handling technique is described in some detail, as is also the monitoring of "leakage" through unfilled pores by a radioassay method. Results are given for a few model systems.

Introduction

A quantitative and reliable study of the permeability of creams and ointments is essential in many applications in pharmacy and medicine. One such important application is in the development of barrier creams. A number of experimental methods have been described (Boman, et al., 1982; Guillemin et al., 1974; Romaguera et al., 1985; Wahlberg 1971 and 1972; Lodén, 1986; Lauwerys et al., 1978) in the literature, but few of those stand up to the requirements for more fundamental physicochemical investigations. Essential requirements are reproducibility in cream layer preparation, and the possibility to check homogeneity and lack of "holes". The method should also provide a high sensitivity analysis for a broad class of substances, both organic and inorganic. Preferably, the method should be as close to actual applications as possible.

In this paper a method will be described which seems to fulfil these requirements quite well. It is based on the use of a standard Nuclepore membrane as support for the cream. This means, for instance, that the cream can be physically worked into the membrane pores in much the same way as a cream is applied to human skin. Such a membrane has two advantages. In the first place it acts as a physical "skin", where the pores are very well defined geometrically-cylindrical holes with given diameter and depth. Secondly, the membrane can be obtained in a variety of pore dimensions. The membrane can be clamped in a suitable cell as a separation wall between a donor and a receiving chamber, the content of which can be analyzed by any suitable method, as a function of time.

The membrane support just described also has the advantage that it can serve to test the ease by which a cream or ointment can be spread in an acceptable manner on the "skin". It is easy to test

Correspondence: A. Orbe, Institute of Physical and Inorganic Chemistry, Faculty of Pharmacy, Uppsala University, Biomedical Center, Box 574, S-751 23 Uppsala, Sweden.

a membrane, on which a cream has been spread, for leakage due to incomplete spreading by monitoring some suitable test substance (in the case of water, for instance solutions of $^{22}Na^{+}$). This can be done in parallel with permeability measurements of other substances.

The method also provides an opportunity to follow the dissolution of the cream layer as well as the potentiality of filling the cylindrical pores more permanently with suitable preparations (gels, cross-linked polymers) for specialized investigations.

This paper describes some central experiments that show the potentiality of the technique. Vaseline and two commercial barrier creams, Kerodex 71 and Kerodex 77, have been used for illustration purposes.

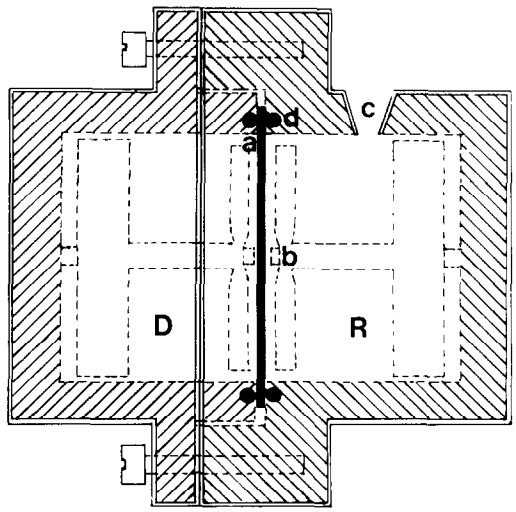

Fig. 1. Schematic drawing of the diffusion cell; D, donor chamber; R, receiving chamber; a, Nuclepore membrane; b, magnetic stirrer; c, sample port; d, "O"-rings.

Materials and Methods

Materials

Sodium-22 chloride (NEZ 081-12841S8, 1 mCi/ml) was obtained from New England Nuclear, Boston, MA, U.S.A. Sodium lauryl sulphate-35 (SJ43, 1 mCi) was obtained from Amersham International plc, U.K. *o*-Methoxyphenol was obtained from Fluka AG, Switzerland.

Vaseline was obtained as ACO White Vaseline, ACO Läkemedel AB, Sweden. Two commercially available barrier creams were used, namely Kerodex 71, stated to protect against water phases (Bicapa, Stockholm, Sweden) and Kerodex 77, stated to protect against epoxy glue and devised to be used as a general waterproof barrier cream (ArSiMa, Copenhagen, Denmark).

Polycarbonate membranes produced by Nuclepore Corporation, California, USA, with pore diameters 50 nm (110603) and 100 nm (110605) were used. Their physical size was 25 mm in diameter and ca. 0.006 mm thick.

Experimental design

In this study cells identical to those used in other membrane studies (King 1984) were utilized. The cells consist of two halves that are clamped together with the membrane in between (see Fig. 1). Both halves are provided with electrically driven stirring rotors and one of the halves has an opening for extraction of samples for analysis. The donor and receiving chambers have volumes of ca. 4 ml each. If necessary, the cells can be kept in a climate room for constant temperature.

At given intervals the concentration of the receiving chambers can be assayed, the liquid withdrawn being replaced by known amounts of solution/solvent. The experiment is performed as a transport across the membrane from one homogenous solution to another. The sample volume has been kept at 0.100 ml (always weighed). The cream-covered side of the membrane always faced the receiving side. In all experiments presented here room temperature was used (ca. 21° C).

In the dissolution experiments the prepared membrane was weighed and mounted into the cell. It was then left in contact with the solvent and for a set of times the membrane was taken out, dried at room temperature and weighed. To find out the loss due to mounting/dismounting separate experiments were performed allowing a correction to the directly observed dissolution data (see Fig. 3).

Analytical methods

The sodium-22 chloride was determined in an

Autogamma scintillation spectrometer Packard 5166. The sodium lauryl sulphate-35 was determined in an Isocap/300 scintillation counter, Nuclear Chicago Division.

Results and Discussion

In order to evaluate the technique, essentially 3 different types of experiments were performed. The first type concentrated on the physical preparation of the cream layer to obtain a reproducible and reliable manual technique. In the second type the rate of dissolution or disappearance of the cream layer was studied to determine a possible equilibrium situation, which characterizes the cream/membrane layer. The third type, finally, consisted of actual permeability measurements designed to determine both the tightness of the cream layer and the rate of permeation of relevant substances.

The preparation of the cream layer was always done manually with the supporting membrane placed on a horizontal support. The cream had to be worked into the pores very gently for some time, to give an even and reproducible filling. The various creams behaved somewhat differently under this preparation. In order to give good results Kerodex 71, for instance, had to be worked into the membrane very thoroughly and during this process some phase inversion might occur. The reproducibility of the preparation was tested in several different ways. In the first place the weight of cream layer could be determined by weighing and it was found to vary somewhat from spreading to spreading. However, after contact with solution containing 1% (w/w) of sodium lauryl sulphate, it was found that after a short time an equilibrium situation was reached giving a cream layer of constant and quite reproducible weight (Fig. 2). It is seen that during the first 20 min or so, the weight of the cream layer decreases rapidly to attain an almost constant value thereafter. This means that if permeation rates are determined after this initial period of 20 min, they conform to the situation in the cream layer of constant weight. From Fig. 2 it is also seen that the weight of cream layer varies somewhat from cream to cream.

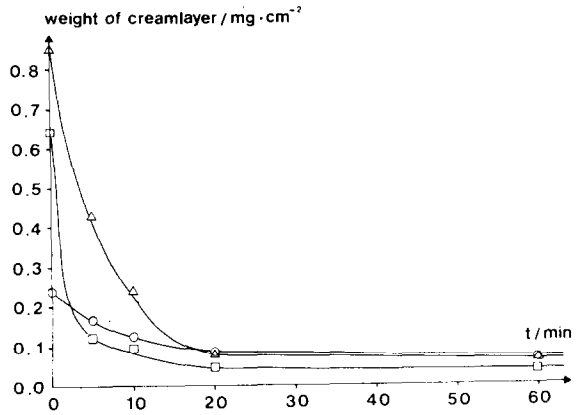

Fig. 2. Dissolution rates of cream in presence of 1% sodium laurylsulphate in both chambers. The loss of cream due to mounting/dismounting (see text) is included. ○, Kerodex 71; □, Kerodex 77; △, vaseline. Nuclepore membrane with 50-nm pores were used.

In part this is due to individual preparations, in part it reflects differences between the creams in density, ease of spreading and solubility. The initial part of the decaying curves show some individualities. This could partly be due to statistical errors, but could also to some degree show differences in the properties of the creams.

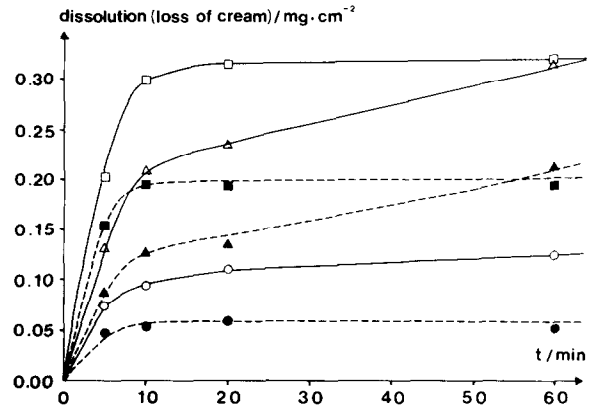

Fig. 3. Dissolution rates uncorrected (solid curves, unfilled symbols) and corrected (dashed curves, filled symbols) for loss of cream due to mounting/dismounting (see text). ○, ●, Kerodex 71; □, ■, Kerodex 77; △, ▲, vaseline; all applied to a Nuclepore membrane with 50-nm pores. The donor chamber contained initially 0.01 M *o*-methoxiphenol and the receiving chamber water.

In order to obtain the dissolution rate, it was necessary to dismantle the cell and take out the membrane for weighing. This also meant some loss of cream. To get an idea of magnitude of this effect separate experiments (results in Fig. 3) were performed, where the membrane was mounted and then immediately taken out again, weighed, put back into the cell, taken out and weighed, and so on. In this way a correction for loss of cream could be made, giving the dashed curves in Fig. 3. From this figure it is seen that vaseline behaves somewhat differently from the other two creams.

After an initial rapid dissolution phase a second slower dissolution period sets in. Finally, even the dissolution of vaseline levels out, but at later times than shown in Fig. 3. This level then stays constant over more than 12 h.

In order to increase the reproducibility of tests, it seems advisable to wash the membrane after spreading of the cream. The washing could be made with a solution containing sodium lauryl sulphate, for instance. The membrane/cream system becomes quite well defined after this procedure.

To test the tightness of the cream-covered membranes, the rate of permeation of sodium ions was measured. This was conveniently done by means of sodium-22 in the donor phase solution, following the concentration build-up in the receiving phase by scintillation measurements. The results of these measurements can be seen as filled symbols in Fig. 4. Although the figure only shows results for times in the order of 100 min, no permeation of sodium ions was detected during several hours (up to 48 h for Kerodex 71, 94 h for Kerodex 77 and 12 h for vaseline). For comparison, results for a similar membrane without cream are shown (filled asterisks). The difference between these two cases shows immediately the sensitivity of this method for the detection of an incomplete cream layer. As already mentioned this constitutes a valuable means for testing different ways of spreading a cream on a surface, e.g. in connection with tests of the "appeal" of a new product and how this goes with efficiency.

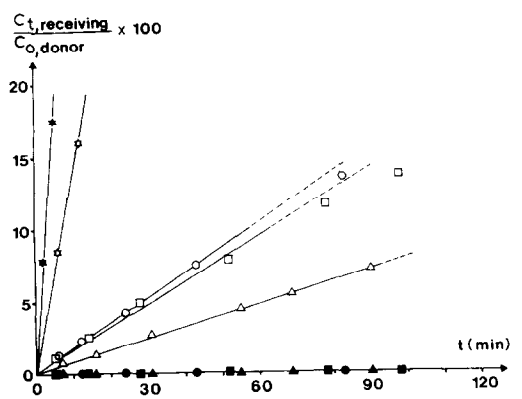

Fig. 4. Permeation of $^{22}Na^+$ (filled symbols; initial concentration in the donor chamber. $C_0 = 10^{-6}$ M) and *o*-methoxiphenol (unfilled symbols; $C_0 = 0.01$ M). ●, ○ Kerodex 71, 0.45 mg/cm^2; ■, □, Kerodex 77, 0.57 mg/cm^2; ▲, △, vaseline 0.47 mg/cm^2; and ★, ☆, membrane without cream. Nuclepore membranes with 100 nm pores were used.

The method was finally tested for selectivity as to individual properties of creams. To this end *o*-methoxiphenol was used as a permeant due to its solubility in both water and oil phases. The results from such permeation studies are also shown in Fig. 4. It is seen that *o*-methoxiphenol permeates through all 3 test creams and that there seem to be differences, vaseline being tighter than the other two. Repeated experiments show, however, some scatter that makes more precise distinctions between e.g. Kerodex 71 and Kerodex 77 difficult. These results could perhaps become more consistent by careful pretreatment (washing) of the cream-covered membranes. On the other hand there is always a very clear distinction between the permeation of different compounds. Certain surfactants like sodium lauryl sulphate do not permeate at all during the first 24 h. For an unprepared membrane, finally, the open asterisks indicate a very high permeation rate.

Acknowledgement

We wish to express our gratitude to ACO Läkemedel AB for financial support and in particular to Dr. Conny Bogentoft and Dr. Paul Persson for many stimulating discussions. The assistance of Mr. Bertil Abrahamsson with some of the experiments is gratefully acknowledged.

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