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The skin penetration cell: a design update

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Summary

Existing in vitro skin penetration cells based on the Franz cell were assessed for: (a) uniformity of stirring; and (b) receptor phase volume. Based on the results of these experiments two flow-through in vitro penetration cells were designed to meet the following specifications: (a) small receptor phase volumes; (b) instantaneous stirring; (c) variable skin surface areas; and (d) compatibility with current stirring apparatus.

Introduction

A variety of diffusion cells used for the in vitro study of percutaneous absorption are commercially available. However, many of these cells are subject to flaws in both design and production.

Vertically orientated diffusion cells, either static or flow-through, are usually based on the Franz cell (Fig. 1) (Franz, 1975). Typically these cells show: (i) slow or incomplete stirring of the receptor phase; and (ii) large receptor phase volumes, a problem more applicable to the 'flow-through' cell, requiring aliquot sampling and increasing both operator time and error. In this study we have compared several commercially available glass diffusion cells for both receptor phase volume and rapidity of stirring. We have used the results of these comparisons to aid in the design of two improved flow-through cells.

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Materials and Methods

Commercially available glass cells, both static and flow-through, were tested. Deionised water was placed in the receptor phase compartment along with a 3 mm × 10 mm stirring bar, the largest that each cell would accommodate, and a crystal of potassium permanganate. Parafilm was used to represent the skin sample. Each cell was stirred at 600 rpm for two minutes and then photographed. The degree of dispersal of mauve coloration from the permanganate crystal was used to qualitatively assess the degree of stirring. Complete and even colouration within 30 s was considered as instantaneous and acceptable stirring. The receptor phase volume of each cell was also measured.

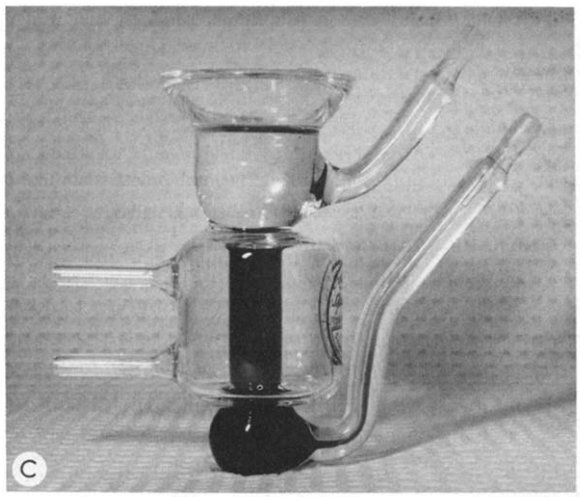
Results

Fig. 1A, B and C show three typical Franz-type diffusion cells. Each cell shows, to varying degrees, incomplete stirring of the upper portion of

the receptor phase immediately below the skin surface. The two major differences between these cells are: (a) the more gradual transition of the rising column of the receptor compartment to the bowl portion, and the narrower central column which prevents adequate stirring of the bowl portion.

Design flaws

Larger cell volumes may well be desirable in order to provide sink conditions in the receptor phase. However, in the flow-through cell such large volumes are distinctly undesirable. The main drawback appears to be in the ability to stir such volumes quickly and uniformly. In many of the cells tested even prolonged stirring (e.g. 30 min) did not produce adequate dispersal of the mauve colouration. It is essential that the diameter of the receptor phase compartment be as large as possible in order to stir a greater height of liquid at a fixed stirring speed. The narrow rising columns of the cells shown in Fig. 1 appear to inhibit stirring. Similarly, a narrow rising column which opens abruptly into a large "tulip-shaped" bowl will not produce adequate stirring. A wider vertical column, removal of the bowl shape and a more gradual increase in diameter will overcome such problems.



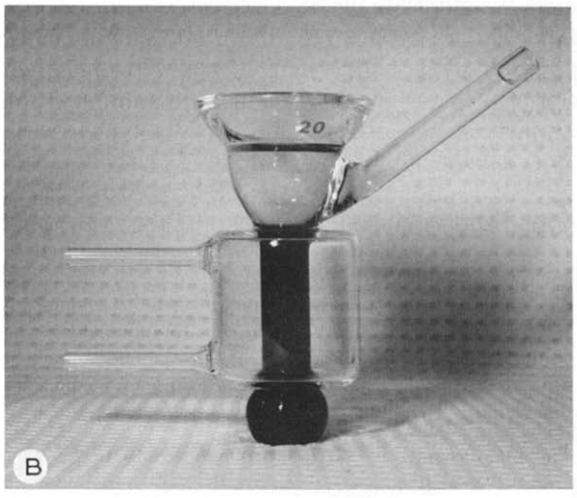


Fig. 1. Franz-type diffusion cells (A, B, C). Subtle differences in construction result in large variations in receptor phase stirring of the upper portion of the cells. Volumes = 11 ml; 9.7 ml; and 11.5 ml (left to right). The top of the cell has been removed for photography.

Of the cells tested, variation in the quality of stirring was found between cells of apparently the same design. Such variations should be considered when conducting replicates of an experiment.

The "GH" cell design

The new cells were designed to meet existing requirements in this laboratory and to overcome the problems of currently available cells. Each cell had to meet the following criteria:

(1) Flow-through design
(2) Instantaneous stirring of the receptor phase
(3) Receptor phase volume of 5.5 ml or less
(4) Accommodate a skin surface area of either 1 cm^2 or > 4.5 cm^2
(5) Compatibility with existing stirring apparatus

Due to the two skin types in use, i.e. full-thickness hairless mouse skin and full-thickness guinea pig skin, differing surface areas were desired; 1 cm^2 for mouse skin and 5 cm^2 for guinea pig skin. For the latter skin type diffusion cells of less than 3 cm^2 have been found, in this laboratory, to give poor uniformity of results. The external dimensions of the cells were determined by the dimensions of commercial diffusion cell stirrers. Receptor phase volume was determined as a minimum collection rate of one cell volume per hour using a flow rate of 5.5 ml/h. With this flow rate all of the receptor phase collected during a one hour interval can be prepared for scintillation counting without aliquot sampling.

The two cell designs are shown diagrammatically (Fig. 2A and B). Critical to both cells is the design of the receptor phase compartment. It is important to maintain a wide diameter in relation to height in order to achieve rapid and even stirring. In Fig. 3A we have ensured a small volume by drastically reducing the height of the column. In Fig. 3B the funnel-shaped internal design gives a progressive increase in receptor compartment diameter without affecting stirring.

Both cells use a similar approach to "top" design. The skin is sandwiched between two areas of ground glass; no "O"-ring was used. The tops overlap the edge of the receptor compartment so that as the top is placed on the cell the skin is automatically pulled down under slight tension and thus avoids the variable tension applied by the operator when assembling cells using an "O"-ring seal. No leakage of material has been encountered in any experimental situation. The tops are secured in place with a clamp. A spacer, approximately 6 mm thick, is used around the neck of the smaller cells to keep the clamp jaws parallel.

Two other important design features are: (1) both cells are built on the same body, only the receptor phase insert differs; and (2) the water jacket in both cells includes the whole of the receptor phase right up to the skin surface.

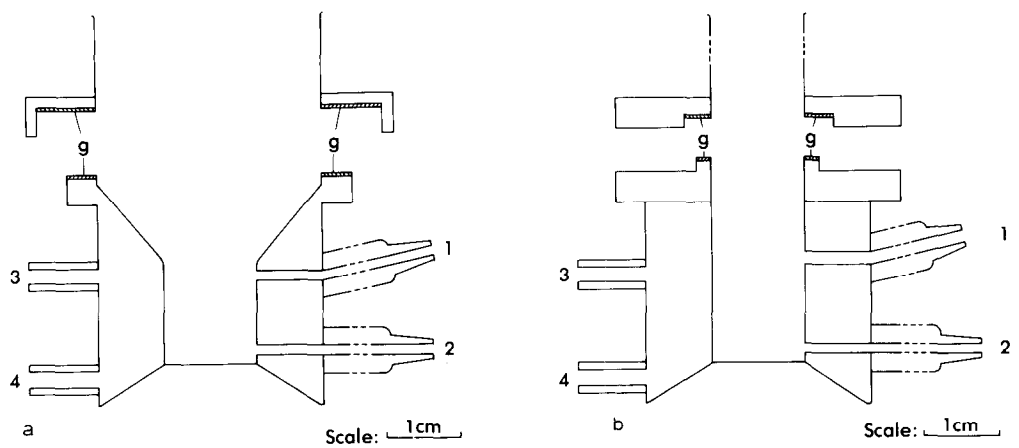
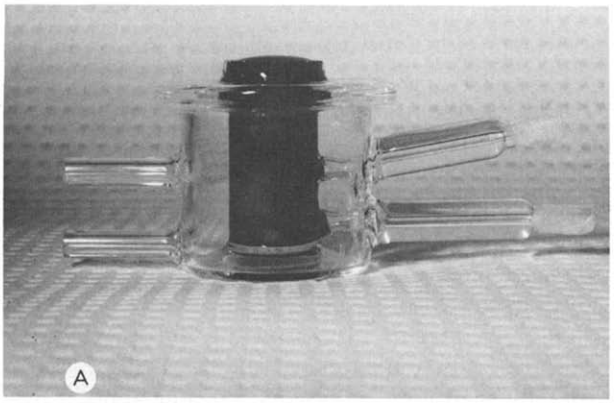


Fig. 2. Scale elevations of "GH" flow-through diffusion cells. Left (Fig. 2A) for guinea pig skin (volume = 5.3 ml), right (Fig. 2B , for hairless mouse skin (Volume = 3.0 ml). g = ground glass; 1 & 2 = receptor phase inlet and outlet; 3 & 4 = water jacket inlet and outlet.



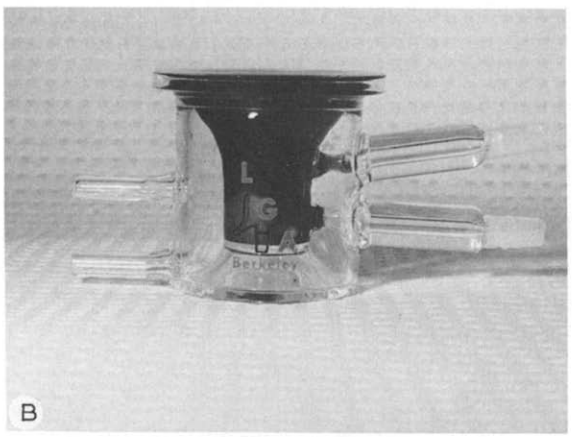


Fig. 3. A: a "GH" flow-through diffusion cell for use with hairless mouse skin. Complete and instantaneous (< 30 s) stirring of the receptor phase is seen. (The top of the cell has been removed for photography.) B: a "GH" flow-through diffusion cell for use with full thickness guinea pig skin. The gradual increase in the diameter of the receptor compartment achieved with the funnel design gives complete and instantaneous (< 30 s) stirring. (The top of the cell has been removed for photography).

Conclusions

Whilst we would be the first to admit that the two new diffusion cells illustrated in this paper are not the ultimate in penetration cell design, we feel that they give the following advantages:

(1) they are easy to produce with a minimum of variation;
(2) small receptor phase volumes minimise operator time and error;
(3) stirring of the receptor phase is instantaneous;
(4) the water jacket extends right up to the level of the skin;
(5) the cells are compatible with existing stirring equipment.

Appendix

The diffusion cells described in this paper have been extensively tested and data from such experiments are already published (Gummer and Maibach, 1986).

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