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COMMUNICATION

PREFORMULATION STUDIES ON RIFAMPICIN OINTMENTS PART II. COMPARATIVE EVALUATION OF THE VARIOUS RELEASE TECHNIQUES

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ABSTRACT

A complex diffusion cell was proposed to determine the amount of drug released from topical formulations. The released drug is automatically removed from the diffusion layer by a prestaltic pump to a secondary reservior where it is diluted and could be spectrophotometrically assayed and then returned to the reservoir. A comparison study between the proposed technique and other techniques was conducted using Rifampicin as a model drug.

INTRODUCTION

Numerous in-vitro and in-vivo models have been reported to study the release of drugs from ointments and creams (1-5).

In the first part of this series (6), it was concluded that solid dispersions of rifampicin with either PVP or PEG as well as the presence of surfactants enhanced the drug release from ointments.

The goal of the present work was to determine the effeciancy of a proposed diffusion cell as a technique for the quantitation of drug release from ointment formulations and to give a correlation between the obtained results and those obtained from other techniques including modified intact skin.

Formulations which showed the best release results, in the first part (6) , were chosen as models for the comparison between the diffusion cell and other techniques.

EXPERIMENTAL

Ointment bases used in the tested formulations were a- Simple ointment BP 1973, b- Beeswax-Triolein 1:3, c- Dehymuls-K, d- Amphocerin-E. Bases a,c,d contained Rifampicin-PVP 40000 (1:5) solid dispersion 25%, while b contained Rifampicin-PEG 4000 in the same ratios. Formulations a,b,d contained Tween 80 1%, while c contained sodium lauryl sulphate in the same ratio. The procedure followed for solid dispersion and ointment preparations were as previously reported (6).

Evaluation Techniques:

A - Proposed Diffusion Cell Technique:.

The apparatus is composed of a double jacketed perspex cube. The release compartment capacity is 125 ml. The temperature of the jacket is regulated by an ultrathermostat. The cell is connected to a double jacketed secondary reservoir via a prestaltic pump (Figure 1 and 2). 125 mg ointment were homogenously spread on the dialysis membrane. The membrane is then fitted in the cell in such a way that its lower surface is just touching the release medium. The cell is allowed to operate, the prestaltic pump removes the released drug from the

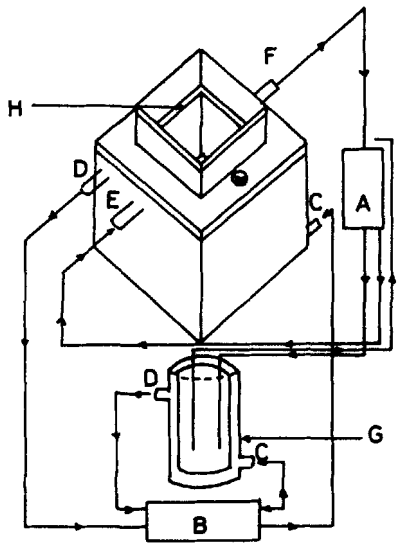

FIGURE 1
Diffusion cell apparatus (Diagramatic Sketch)
A. Prastaltic pump.
B. Ultrathermostat.
C. Heating water inlet.
D. Heating water outlet.
E. Release medium inlet.
F. Release medium outlet.
G. Secondary reservoir.
H. Diffusion membrane.

diffusion layer to the secondary reservoir. In this reservoir the medium is diluted with 25 ml Mcllavine's buffer (pH 7.4) and returned to the cell. Samples were removed from the secondary reservoir and the amount of Rifampicin released was spectrophotometrically measured at 475.

B - Disc Technique:

The design of the apparatus was as previously reported by Brian (2).

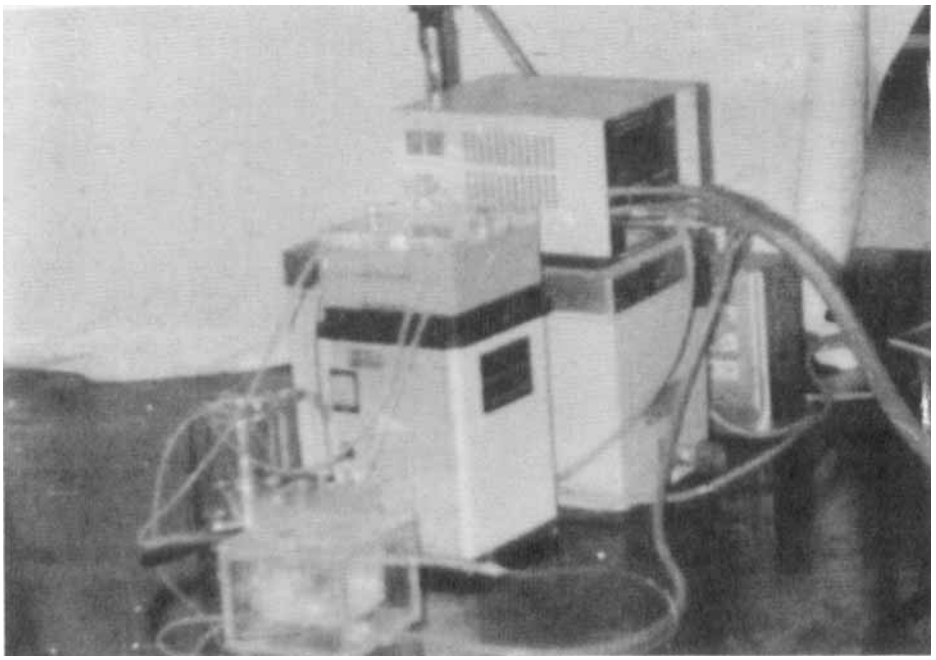

FIGURE 2
Diffusion cell apparatus
(Photographic Picture)

C - Skin Simulation Technique:

Similar to that used by Busse et al (4) to study the release of corticosteroids from model ointment systems.

D - Intact Skin Technique:

This test was conducted by marking circles of 3 cm diameter and 7 cm^2 surface area on each arm of human volunteers (25-29 years old). Half gm ointment was spread on each of eigh circles, covered with a plastic plug to prevent another spreading of the ointment and absorption by the bandage.

The remaining antibiotic in the applied ointment was determined by means of the jet surface sampler using 200

TABLE I

Effect of Different Techniques on the Release of Rifampicin from Ointment Formulations

Time (hours)	Amount Drug Released (mg/ml)															
	Formula a				Formula b				Formula c				Formula d			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
0.25	4.2	6.7	1.2	1.1	11.3	10.2	3.5	1.2	11.2	5.7	2.1	0.6	6.6	5.2	3.6	1.1
0.30	5.6	8.3	3.6	1.5	20.7	15.3	5.6	2.3	15.3	8.6	4.3	0.9	7.3	7.4	5.3	2.3
1.00	8.9	11.9	6.8	2.7	25.2	20.1	8.2	2.9	19.7	15.3	5.6	1.0	8.2	14.8	9.1	3.6
1.50	9.3	13.8	10.1	3.8	28.9	24.6	10.3	3.9	21.3	19.6	8.2	2.1	10.7	15.6	11.7	4.7
2.00			11.7	3.9			11.2	4.0			11.1	3.6			12.6	5.8
3.00			13.1	4.6			12.6	7.8			12.3	4.0			14.8	6.1
4.00			14.2	5.8			13.8	9.6			15.7	5.6			15.3	7.4
48.00				12.9				26.1				15.2				11.8

A : Disc Technique

B : Diffusion cell Technique

C : Skin Simulation Technique

D : Intact Skin Technique

ml chloroform-petroleum ether 1:1 as a solvent followed by evaporation, boiling water extraction, dilution and drug assay.

RESULTS AND DISCUSSION

The results obtained are presented in Table 1. The difference between the techniques is reflected on the amount of drug released. In case of Beeswax-triolein mixture and Dehymuls-k the disc technique exhibited the highest release rates followed by the proposed diffusion cell, intact skin and then skin simulation techniques. This order differs in case of Amphocerin-E base, and becomes: proposed diffusion cell $>$ intact skin $>$ simulation $>$ disc technique. In case of simple ointment base, the skin simulation technique possessed the highest release rates followed by proposed diffusion cell, intact skin and finally the disc technique.

On comparing the proposed diffusion cell technique with the intact skin technique, it is clear that there is a great similarity regarding the amount and the pattern of the antibiotic release. Such similarity may be explained on the basis that the proposed diffusion cell is more or less simulating the conditions of the intact skin. This similarity was established by using the membrane in the proposed apparatus. Such vertical membrane design ensures that air bubbles do not readily lodge beneath the membrane which may decrease the diffusional flux, and no hydrostatic head distorts which possibly ruptures the membrane as well as the receptor and donor phases are present in a constant temperature.

The correlation between the in-vitro release from ointment determined by various techniques and that of intact skin showed that a linear correlation is present. The mean correlation coefficient values were 0.92, 0.913

and 0.927 in the case of disc, skin simulation and proposed diffusion cell techniques respectively.

In all the tested in-vitro techniques, a significant ($P < 0.05$) correlation of the amount of Rifampicin released by the intact skin method with that of the in vitro release technique has been proved.

From the reported results, it is clear that the proposed diffusion cell techniques has showed promising findings because the release rate results obtained showed closer results of the intact skin technique. This might be attributed to the homogenity of the drug release from the surface of the ointment and the withdrawal of samples from the diffusion layer just touching the ointment surface. This can exclude the errors which may occur due to the improper mixing of the release medium. In addition, the manufacture of such diffusion cell is not so complicated.

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