SHORT COMMUNICATIONS

Permeation Studies of Marketed Clotrimazole Cream

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Clotrimazole is an effective antifungal agent, mainly marketed as topical preparations. Its high water insolubility may limit its permeation into the skin. Hence, *in vitro* release studies of Clotrimazole from five different marketed cream formulations were carried out through the membrane and without the membrane according to a specially designed protocol. The receptor media used for the permeation studies through the membrane were distilled water, 40% PEG 400 in distilled water, 30% IPA in acetate buffer and IPM, whereas in the membraneless technique IPM was used because of its bipolar properties mimicking the skin. A specially fabricated diffusion cell was used for studies through the membrane and a modified dissolution apparatus was used for the membraneless technique. From the results obtained, it was observed that in the permeability studies through the membrane, the drug release was maximum in IPM compared to the other media in case of all the formulations and the percentage drug release obtained through the membrane was significantly greater than that obtained without the membrane in all the cases ($P<0.001$).

Clotrimazole is a widely used and effective antifungal agent[1]. It is insoluble in water which makes it difficult to obtain meaningful *in vitro* data. Thus, the present work aims at developing a suitable protocol to carry out *in vitro* release studies of the same. The study was conducted in two parts. The first part involved permeation studies in an indigenously fabricated diffusion cell through a membrane. The next part involved permeation studies in a membraneless[2] diffusion cell. Five different marketed formulations namely Translipo-C, Candid, Clotrin, Canestan and Clotrimazole creams were taken for the study and the following procedure was adopted to carry out the permeation studies.

The diffusion studies were carried out according to the following design using rat skin[3] as the permeation barrier. Initially, distilled water was used as the receptor medium. As there was absolutely no release even at the end of 8 h, 40% of PEG 400[4] was incorporated to the same. Even with this, there was no improvement in the release. As the drug was soluble in isopropyl alcohol (IPA), 30% of IPA in pH 5.3 acetate buffer was chosen as the medium (as the pH of the skin is between 5 to 6[5,6]). The drug release was less than 20% with all the formulations tested at the end of 8 h with this system, and hence iso propyl myristate (IPM) was chosen next as the medium because of its bipolar properties mimicking the skin and as the drug was completely soluble in it.

The drug permeation studies were carried out using a diffusion cell consisting of a donor compartment and a receptor compartment. The rat skin was fixed between the donor and the receptor compartments across an area of diameter 2.8 cm and 1 g of the respective cream formulations containing 10 mg of the drug was spread over the membrane. The donor compartment was placed on the receptor compartment containing 75 ml of the medium. The temperature maintained was 37° and the medium was stirred at constant rate (60 rpm) using a magnetic stirrer. At hourly intervals; 5 ml of the receptor

* For Correspondence

Table 1 - Permeation studies through the membrane

Time (h)	% drug release in the medium* (IPM)				
	Translipo-C	Candid	Clotrin	Canestan	Clotrimazole (Plain)
1	-	-	-	-	-
2	9.35	9.37	7.03	4.68	-
3	14.67	12.34	9.84	7.34	7.01
4	20.30	15.46	12.81	12.50	9.37
5	21.55	18.75	15.93	13.30	14.68
6	22.84	19.84	19.22	16.40	15.62
7	24.06	23.40	20.30	17.30	16.56
8	25.31	24.68	21.40	18.25	17.50
Average diffusion coefficient	14.52×10^{-5}/h	13.12×10^{-5}/h	9.64×10^{-5}/h	6.95×10^{-5}/h	6.88×10^{-5}/h

*Average of three determinations

Table 2 - Permeation studies through the membrane

Time (h)	% drug release in the medium* (IPA+buffer pH 5.3)				
	Translipo-C	Candid	Clotrin	Canestan	Clotrimazole (Plain)
1	-	-	-	-	-
2	4.68	-	-	-	-
3	8.02	4.68	4.68	4.68	4.68
4	10.10	9.68	4.99	4.99	7.34
5	12.28	10.31	10.00	5.31	10.15
6	14.58	10.93	10.62	5.62	10.77
7	15.41	11.56	11.25	10.62	11.40
8	16.24	12.18	11.87	11.25	12.02
Average diffusion coefficient	4.93×10^{-5}/h	3.75×10^{-5}/h	2.92×10^{-5}/h	1.93×10^{-5}/h	3.35×10^{-5}/h

* Average of three determinations.

medium was withdrawn using a syringe and replaced immediately with the same amount of fresh medium to maintain the volume of receptor medium constant. Amount of clotrimazole released into the medium was then estimated colorimetrically at 480 nm[7] using spectronic 20.

Cumulative % release was calculated in each case. The experiment was repeated thrice. Diffusion coefficient was calculated in each case using the formula[2]:

$$Q = 2C_0(Dt/\pi)^{1/2}$$

Where 'Q' is the amount of drug absorbed at time 't'

Table 3 - Permeation studies without membrane

Time (h)	Translipo-C	% drug release in IPM medium *			
		Candid	Clotrin	Canestan	Clotrimazole (Plain)
1	-	-	-	-	-
2	-	-	-	-	-
3	3.28	-	-	-	1.05
4	5.03	3.28	3.28	-	3.25
5	6.99	3.49	3.49	3.28	4.12
6	7.43	6.99	3.71	3.49	4.98
7	7.87	7.43	7.21	6.99	5.80
8	8.31	7.87	7.65	7.43	6.06
Average diffusion coefficient	1.20×10^{-5}/h	1.19×10^{-5}/h	0.91×10^{-5}/h	0.93×10^{-5}/h	0.68×10^{-5}/h

* Average of three determinations

per unit area of application, 'Co is initial concentration of the drug in the cream, 'D' is the apparent diffusion coefficient and 't' is the time.

The permeation studies were also carried out using a membraneless technique. One gram of the respective cream formulations was placed at the bottom of a modified dissolution apparatus which was maintained at 37°. A propeller which was positioned 1 cm above the surface of the cream was continuously rotated at the rate of 60 rpm. 75 ml of IPM warmed at the experimental temperature was slowly poured into the apparatus to provide the medium for drug release from the cream. Five millilitre aliquots of IPM were withdrawn at the interval of 1 h for a period of 8 h. Sample was replaced with an equal volume of fresh IPM equilibrated at the experimental temperature. Studies were performed in triplicate and diffusion coefficient was calculated in each case.

The results obtained are presented in tables 1, 2 and 3. The results obtained from the permeation studies through the membrane and without the membrane were subjected to statistical analysis using the student's 't' test.

In the permeability studies through the membrane, IPM proved to be a better receptor medium compared to IPA in all the cases. It was observed that the percentage drug release was significantly greater through the membrane (18.25-25.31%) than without the membrane (7.43-8.31%). The values of diffusion coefficient confirm the above results. The results obtained with the membrane is significantly different in its % drug release from the results obtained in the membraneless technique with $P<0.001$.

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