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FORMULATION AND EVALUATION OF SOME TOPICAL ANTIMYCOTICS 3-EFFECT OF PROMOTORS ON THE IN VITRO AND IN VIVO EFFICACY OF CLOTRIMAZOLE OIMTMENT.

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ABSTRACT

Dimethyl sulphoxide (DMSO), linoleic acid (LOA) and propylene glycol(PG) glyceryl monostearate (GMS), dioctyl sodium sulphosuccinate and Brij 35 were tested as enhancers for clotrimazole permeation.

The results revealed that, incorporation of the tested promotors in the oleagenous base increased the in vitro release rate of the drug and also its antimycotic activity against candida albicans. Contrast results were obtained for the water soluble base.

The amount of clotrimazole determined in rabbit skin, was more pronounced when the additives were incorporated in the water soluble base. The histological studies of rabbit skin, showed variable degrees of penetration and no harmfull changes of the skin tissues were observed.

INTRODUCTION

It is well known that the skin itself presents an effective barrier to topically applied drugs. The development of penetration promotors are becoming important in overcoming the low permeability of drugs across the skin.

Many substances have been reported as promotors for subcutaneous absorption of drugs [1-16] Viz; Azone[1-4], DMSO [5,6], PG [6,7], LOA [1], oleic acid[7-9] lauric acid[6,8] and surfactants[6,10,11]. Moreover, ethyl acetate was found to be an effective promotor for a number of drugs[12-14]. The promoting effect of cyclic monoterpenes have been recently investigated[15]. Since d-limonene has been found as the main constituent in orange and lemon oils, its toxicity or irritancy to the skin is considered to be low[15].

Clotrimazole is used generally for the superficial fungus infection. It is essentially prescribed for the topical treatment of Tinea capitis at the same time of the systemic treatment by griseofulvin tablets. Since, the causative organism of T.capitis is present in deep keratinized layer of the skin, addition of promotors seems important to enhance penetration and hence, increase the efficacy of the drug.

In the preceding work the authors[17] recommended that 1% clotrimazole in either the water soluble or oleagenous base achieved good clinical efficacy. In the present study, these formulations were selected to investigate the effect of various promotors on the *in vitro* drug release. *in vitro* antimycotic activity, and penetration of the drug into the skin. As well as their effect on skin tissues.

EXPERIMENTAL

Materials:

Clotrimazole (kindly supplied by the Arab Drug Company, Cairo, Egypt), PEG 400, 4000 (Fluka, AG, Switzerland), Brij35 (ICI Am. Inc, Atlas Chem. Div., Willimington, Delaware Co.), dioctyl sodium sulphosuccinate (Sargen-Welch Scient. Co.), glyceryl monostearate, dimethyl sulphoxide,(BDH Chem., Ltd., Pool, England), Linoleic acid (Morgan Chem. Co. Cairo, Egypt).

Semipermeable Fischer Cellophane membrane (30/32). (Fischer. Sci. Co. Lond.,U.K.) and all other ingredients were of Pharmaceutical grade samples and were used as received.

Methods:

The procedure of ointment preparation, *in vitro* release through cellophane membrane as well as the antimycotic activity of the drug using the cup-diffusion method, were described in our previous study[17].

Determination of Clotrimazole in Rabbit Skin :

The following ointment formulations each containing 1% w/w clotrimazole were selected.

-Oleagenous ointment (A).
-Oleagenous ointment containing combination of 20% DMSO, 7% LOA and 3% GMSO (B).
-Water soluble Ointment (C).
-Water soluble ointment containing combination of 20% DMSO, 7% LOA and 3% GMS (D).

Male healthy rabbits, weighing about 1 -2kg were used. The rabbits were fed a regular diet with no restriction on food and water. The hair of an area of 4 x 6 cm was shaved on the back of the rabbit. This area was selected so as to prevent the rabbit from ingesting any ointment by bicking the treated area. 5 gm-sample was applied once daily for one week. The treated area was covered with aluminium foil that was tied by a rubber bandage. At the end of this experiment, the skin surface was cleaned from any adhering ointment. Three rabbits, were used for each formula as well as for the control (untreated rabbit).

An area of the treated skin equivalent to about 1 gm was cut out. The dermal surface was cleared from any adhering solution and throughly homogenized.

The homogenized skin samples were stirred magnetically each with 200 ml chloroform for 24 hours. The chloroformic extract was evaporated, then the obtained residue was dissolved in perchloric acid. The developed bright yellow colour was measured colorimetrically at 436 nm[18]. The control skin samples were similarly treated and used as a blank experiment.

Histological Study :

The following ointment formulations were tested using each of the water soluble and the oleagenous bases.

1-Plain Base.
2-Ointment containing 1% clotrimazole.
3-Ointment containing 20% DMSO.
4-Ointment containing 20% LOA.
5-Ointment containing combination of 20% DMSO, 7% LOA, and 3% GMS.

After the end of the test period mentioned above under determination of clotrimazole in rabbit skin, the animals were sacrified. The treated parts was then cut into thin slices (10 um in thickness), fixed in formaline and processed to obtain paraffin sections. The sections were stained with haematoxylin and eosin for general histological studies. The stained sections were examined microscopically and photographed.

RESULTS AND DISCUSSION

1-*In Vitro* release through cellophane membrane:

The effect of promotors and their combination on the *in vitro* release of clotrimazole from the water soluble and oleagenous bases was investigated.

Enhancer effect was found to be related to its structure and concentration as well as to composition of the ointment base used(Table 1and 2)

The data presented in Table 1 showed that incorporation of either liquid promotors or surfactants in water soluble base invariably decreased the *in vitro* release of the drug except for LOA at 20% concentration which enhanced the release of the drug from the same base.

Incorporation of DMSO and PG at 5,10, or 20% w/w into the base, may increase the affinity of the drug to the base with subsequent reduction in its release[19]. Kundu et al [20] reported that DMSO at 5,10 and 15% w/w, has no effect on the *in vitro* release of nitrofurazone from PEG base. At 5%, DMSO did not affect the release of testosterone from washable base[21]. Green and Hadgraft[22], reported that fatty acids enhanced the release of propranolol, metopranolol or exprenolol through cellophane membrane.

The effect of surfactants on the *in vitro* release of clotrimazole from the water soluble base can be arranged as follows: Brij35 (HLB=16) > GMS (HLB=11) > DOSS (HLB=1.2). It can be seen that higher *in vitro* release of the drug was obtained with Brij35 of the higher HLB value and of longer polyoxyethylene chain length.

On using the oleagenous base, (Table 2), all the tested promotors enhanced the release rate of the drug depending on the type and concentration of the enhancer. The enhancing effect of DMSO or PG was found to be more pronounced at the lower concentration (5% w/w).

Incorporation of 20% DMSO or PG to the oleagenous base resulted in the separation of the preparation. Whiles 20% LOA still showed the promising enhancing effect.

Two combinations of the tested promotors were selected from a variety of combinations tried.

Composition of Additive Combination		
Combination No.	Composition	% w/w
I	DMSO	20
	LOA	7
	GMS	3
II	LOA	20
	DMSO	7
	GMS	3

The oleagenous base was selected to study the influence of these combinations on the *in vitro* drug release. It is clear from Table 4 that the use of combination of promotors was found to be highly effective as compared to each promotor alone. However, the release was higher on using combination I. This may be attributed to the higher concentration of LOA.

2-*In Vitro* antimycotic activity :

The effect of promotors on the *in vitro* antimycotic efficacy of clotrimazole formulated in either the oleagenous or the water soluble PEG base was investigated by using the agar-cup diffusion method and C. albicans as test organism. The results for each base are presented in Table 5. It is apparent that, DMSO, PG or LOA at all the tested concentrations (5-20% w/w) reduced the an-

timycotic efficacy of the drug when they are incorporated in the water soluble base. The effect is predominent with LOA which is considered as a source of carbon for the organism (C.albicans), facilitating its proliferation[23]. However, higher antimycotic activity has been observed with Brij35. This can be explained by the suggestion that Brij35 may increase the membrane permeability of the cell and hence inactivate the organism [23].

Table 5 shows also the effect of the tested promotors on the antimycotic efficacy of 1% clotrimazole using the oleagenous base. It is clear that DMSO or PG were of no effect on the extent of inhibition, whereas LOA at all concentrations decreased the efficacy of the drug against C. albicans.

As shown in Table 5, combination of promotors reduced the extent of antimycotic activity of the drug mainly due to the presence of LOA in the formulation. As expected, combination II that containing higher proportion of LOA showed particularly lower activity of the drug as compared to combination I. Consequently, if LOA is to be a useful additive for the percutaneous absorption of clotrimazole, it is necessary to take into account, that the product must not be prescribed for candiases.

3-Determination of clotrimazole in rabbit skin :

The amount of clotrimazole penetrated the skin was determined. The results are shown in Table 6.

It is clear that, the amount of clotrimazole penetrated the skin was to some extent greater from the PEG base than from the oleagenous base. The effect of PEG base on increasing skin permeability is barrier specific and related to altration of skin structure and mass flow of water[24]. This observation appeared to be in agreement with those reported by Ayers and Lasker[25] showing that penetration of benzocaine into the human stratum corneum is much greater from the water soluble bases than from other bases. Further, Sasaki *et al* [26] found that the vehicle not only influence drug penetration but also the enhancer penetration.

Incorporating combination of 20% LOA and 3% GMS in the PEG base increase drug permeability 3-fold its control "C", and 4-fold on using the oleagenous ointment "A".

The increased permeability obtained can be attributed in one hand, to DMSO which altered the conformation of keratin and leads to disruption of water structure and increase the membrane permeability thereby creating holes in the membrane[27,28]. On the other hand, LOA being a fatty acid, it modifies the skin barrier properties by its fluidizing action on lipids of the stratum corneum[29]. Moreover, the similarity of LOA to the free fatty acids in the stratum corneum[30]. facilitates its miscibility and penetration through the skin.

The synergism obtained by combination of a number of promotors was studied by many investigators[31-34]. Two component systems consisting of PG and OA or LOA were found to be more effective penetration enhancers as compared with PG, OA or LOA alone[31]. A maximum penetration of triamicinolone acetonide with 10% azone-ethanol combination was reported[32]. Moreover addition of 10% non-ionic surfactant increased the absorption of flufenamic acid from petrolatum base. On using combination of DMSO (5%) and 10% surfactant in the base, the percutaneous absorption of the drug was further increased due to the formation of high activity co efficient complex [33].

Bennett et al[34] reported combination of PG and azone acts as a cosolvent to increase the thermodynamic activity of betamethazone-17-benzoate and hence its bioavailability[34].

Histological study :

It has been reported[23] that the penetration enhancing effect are via alteration of the normal skin structure and could be expected to be associated with an inflammatory response. Hence, the effect of the selected ointment formulations on skin tissues seems to be essential practice to evaluate their safety.

Photographs of rabbit skin after 7 days of treatment are illustrated (Figures 1,2 and 3). Figure. 1.a. the normal rabbit skin (control). It shows two distinct layers. the superficial epidermal layer (E) and the deep connective tissue layer (dermis).

The dermis, is the thick dense connective tissue layer. It contains the sweat and sebaceous glands as well as hair follicles. Blood vessels (BV) are also embeded.
Sweat glands are hardly observed in rabbit skin, whereas sebaceous glands are associated with hair follicles. The latter is connected to the surface of skin.

Figure. 1.b. shows the skin after treatment with the plain water soluble base. No histological changes were observed except, separation of the horny layers (HL) and the connective tissue fibres (Ctf) into thin distinct strands. These changes may be attributed to the hygroscopic properties of PEG base that lead to withdrawal of water and its accumulation within the connective tissue fibres of dermis and superficial horny layers.

Figure. 1.c. & d. shows the skin after treatment with water soluble ointment containing 1% clotrimazole, proliferation of the prickle cell layer (acnathosis) and thickening of the horny layer (hyperkeratosis) were observed. There is a marked increase in the number of hair follicles (HF) which were seen in groups separated by loose connective tissue fibres. The dermis also became highly cellular and showed many empty spaces.

Figure. 1.e. shows the skin after treatment with PEG ointment containing 1% clotrimazole and 20% LOA. A distinct changes including, marked swelling, vesiculation of epidermal cells (PCL) and degenerative changes in hair follicles were observed. In addition, an occasional accumulation of inflammatory cells, mostly lymphocytes and infilteration of the underlying connective tissue with the same type of cells were observed. The dermis on the other hand, showed oedema, an increase in the number of degenerative hair follicle (HF) and a decrease in the amount of connective tissue fibres (CTF).

Figure. 1.f. shows that 20% DMSO incorporated in the water soluble base did not alter the normal appearance of the skin. However, new hair formation as indicated by the appearance of small hair follicles in the dermis was observed. Also, an increase in the number of hair follicles, presence of fine connective tissue fibres and clear spaces among these fibres. The latter may be due to accumulation of the penetrated promotors containing the absorbed drug.

Figure 2 shows rabbit skin treated with water soluble ointment containing 1% clotrimazole and combination, 20% DMSO, 7% LOA and 3% GMS. This combination leads to some histological changes in epidermis including; parakeratosis (Figure 2a) and disturbed horny layer (HL) in sites where parakeratosis is absent.

The dermis shows fine connective tissue fibres, numerous dilated blood vessels (BV) and accumulation of tissue fluid especially around hair follicles (HF) (Figure $2a_2$). These changes may be attributed to the presence of GMS in the formulation.

Malkinson[35] reported that hyper- and parakeratosis as well as keratinization of the hair follicles were associated with the application of ionic surfactants which are essential for the penetration of some drugs.

The improvement in skin appearance and absence of inflammatory changes on using combination of promotors, may be related to the use of lower concentration (7% w/w) of LOA.

Regarding the oleagenous base, Figure.3a illustrated the rabbit skin treated with plain oleagenous base. The skin is normal and to some extent, similar to that of the control.

Figure. 3b shows rabbit skin after treatment with oleagenous base containing 1% clotrimazole. The most notable changes evoked by the drug are proliferation of hair follicles (HF), and dilatation of blood vessels (BV). From Figures. 3c and d. it is clear that the changes induced by LOA or DMSO were more or less similar to those obtained with the water soluble base.

Finally, Figure. 3e shows rabbit skin treated with the oleagenous base containing 1% clotrimazole and combination of 20% DMSO, 7% LOA and 3% GMS. It is evident that combination of these promotors leads to acnathosis, hyperkeratosis and marked increase in number of mature hair follicles. However, the epidermis appears intact all over the treated area.

Of the tested additives, DMSO even at higher concentration (20%) was found to be preferable since, it exhibited no harmful effect on skin tissues. However, LOA, Caused reduction of the antimycotic activity of the drug against C. albicans, in addition, at concentration 20% w/w it exhibited undesirable histological changes.

Although combination of 20% DMSO, 7% LOA and 3% GMS in PEG base showed effective enhancing effect on the penetration of clotrimazole, additional work is necessary for the development of useful antimycotic delivery system for the topical treatment of T. capitis in Egypt. In future work, we intend to investigate the enhancing effect of various promotors on the skin penetration of griseofulvin. Furthermore, formulation of griseofulvin-clotrimazole combination should be also studied.

Table 1 : Effect of Promotors on the *Ir Vitro* Release Characteristics of Clotrimazole (1% w/w) from Water Soluble Base.

Additive used	Conc.n (% w/w)	r	K(hr)$^{-1}$	t (hr).
Control	-	0.990	0.2 04	3.40
DMSO	5	0.993	0.1 13	6.14
	10	0.999	0.0 27	0.46
	20	0.999	0.1 32	5.28
PG				
	5	0.999	0.0 99	6.97
	10	0.999	0.1 03	6.71
	20	0.999	0.1 26	5.54
LOA				
	5	0.998	0.1 92	3.63
	10	0.999	0.1 81	3.83
	20	0.985	0.4 22	1.65
DOSS				
	1	0.999	0.1 10	6.34
	3	0.998	0.0 99	7.03
	6	0.996	0.0 48	14.68
$Brij_{35}$				
	1	0.999	0.1 25	5.54
	3	0.976	0.2 1	3.30
	6	0.999	0.1 26	5.50
GMS				
	1	0.985	0.1 27	5.46
	3	0.99	0.0 92	7.53
	6	0.993	0.0 83	8.35

Control : Water Soluble Ointment Containing 1% Clotrimazole

Table 2 : Effect of Promotors on the Release Characteristics of Clotrimazole (1% w/w) from Oleagenous Base.

Additive used	Conc.n 5 w/w	r	K(hr)$^{-1}$	t (hr)
Control	-	0.999	0.0 33	20.9
DMSO	5	0.996	0.0 78	8.85
	10	0.994	0.0 69	10.03
	20	-	-	-
PG				
	5	0.993	0.0 990	6.99
	10	0.985	0.0 48	14.33
	20	-	-	-
LOA				
	5	0.999	0.0 55	12.54
	10	0.992	0.0 94	7.34
	20	0.995	0.2 99	2.32
DOSS				
	1	0.995	0.0 67	10.38
	3	0.931	0.0 90	7.72
	6	0.988	0.0 76	9.12
$Brij_{35}$				
	1	0.998	0.0 44	15.84
	3	0.989	0.0 42	16.72
	6	0.990	0.0 69	10.03
GMS				
	1	0.998	0.0 900	7.77
	3	0.996	0.0 360	19.25
	6	0.989	0.0 35	19.80

Control : Oleagenous Ointment Containing 1% Clotrimazole

Table 3 : Effect of Additive Combination on the *In Vitro* Release Characteristics of Clotrimazole(1% w/w) From Oleagenous Base.

Combination No.	r	$K(hr)^{-1}$	t (hr)
Control*	0.998	0.0 33	20.9
I	0.960	0.2 46	2.82
II	0.995	0.4 23	1.64

* Oleagenous Ointment Containing 1% Clotrimazole

Table 4 : Effect of Promotors on the *In Vitro* Antimycotic Efficacy of Clotrimazole (1% w/w) from Oleagenous and Water Soluble Ointment Using Agar-Cup Method and Candida Albicans as Test Organism.

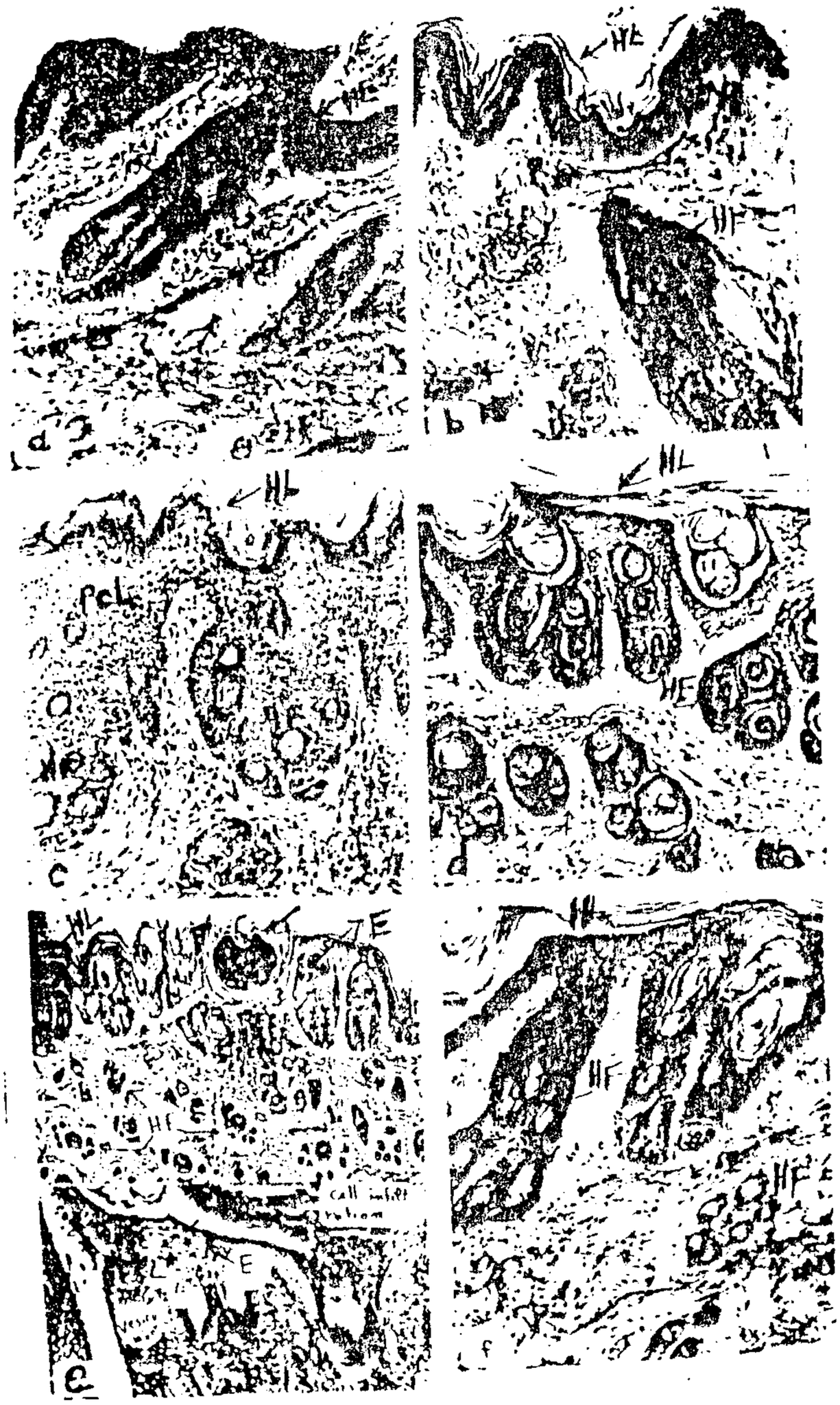
Additive used	Conc.n (%w/w)	Inhibition zone diameter (mm)	
		Oleagenous	Water soluble
Control*	-	37	54.7
DMSO	5	37.5	53.33
	10	32.2	44.77
	20	-	44.90
PG	5	38.0	44.0
	10	34.9	44.5
	20	-	45.25
LOA	5	29.25	20.0
	10	35.5	19.2
	20	25.35	19.0
DOSS	6	39.00	32.4
$Brij_{35}$	6	45.3	60.00
Combination No. II		30.2	30.0
III		29.4	-

* Ointment Containing 1% Clotrimazole

Table 5 : Determination of Clotrimazole Permeated From its Tested Preparations in Rabbit Skin.

The tested preparation	Amount of Clotrimazole determined (ug)
A	21.6
B	24.00
C	25.00
D	80.64

Fig. 1



Figures (a-f): The shin of untreated rabbit (ontrol) (a), rabbit skin treated with plain PEG base (b), PEG base cont. 1% clot. (c,d), PEG base cont. 1% clotr. and 20% LOA (e), and PEG base cont. 1% clot. and 20% DMSO(f).

Key :

Epidermis	(E)
Dermis	(D)
Connective tissue fibre	(Ctf)
Hair follicle	(HF)
Stratum corneum	(SC)
Horny layer	(HL)
Blood vesseles	(BV)

Fig. 2(a_1,a_2): Skin of rabbit treated with water soluble base comtaining 1% clotrimazole and combination of 20% DMSo, 7% LOA and 3% GMS.

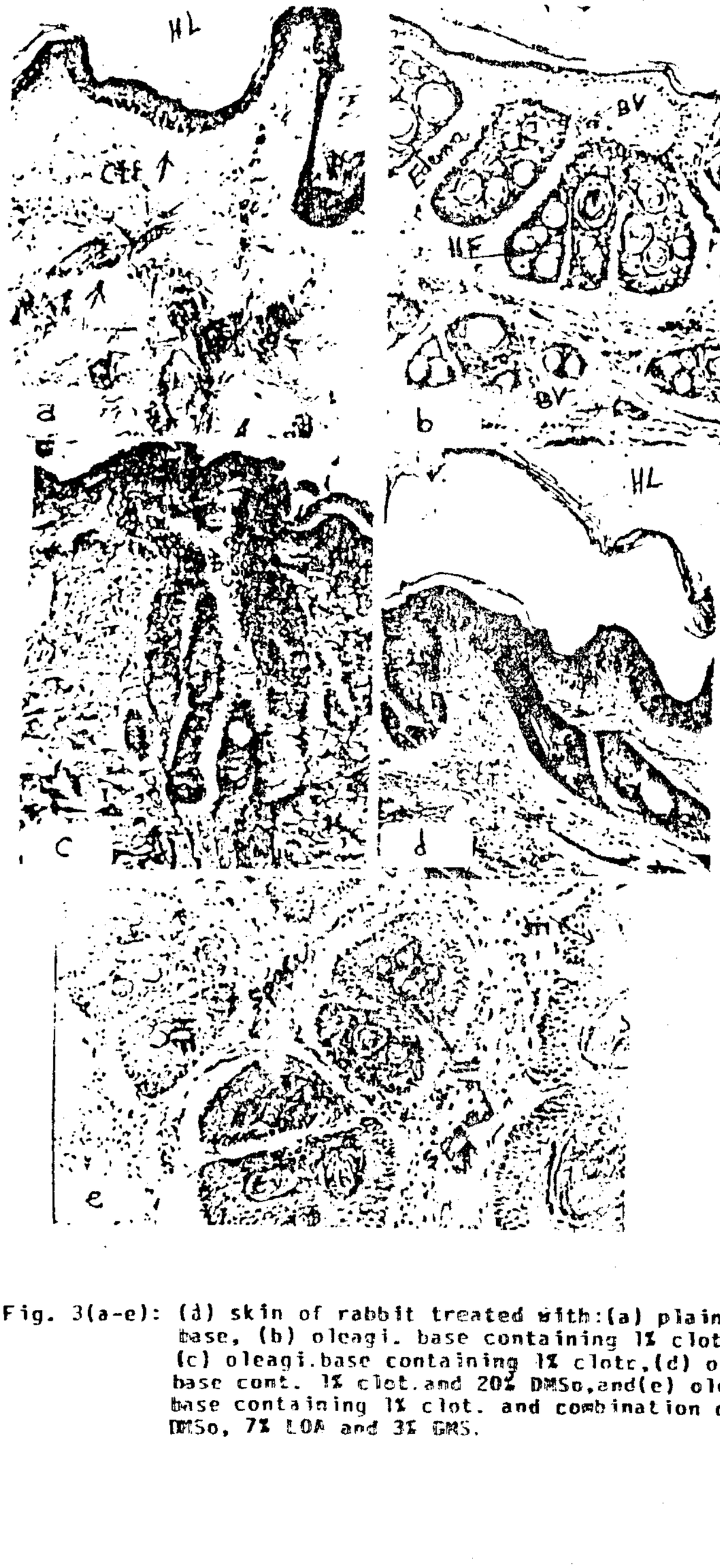


Fig. 3(a-e): (d) skin of rabbit treated with:(a) plain oleagi. base, (b) oleagi. base containing 1% clot., (c) oleagi.base containing 1% clotr,(d) oleagi. base cont. 1% clot.and 20% DMSo,and(e) oleagi. base containing 1% clot. and combination of 20% DMSo, 7% LOA and 3% GMS.

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تأثير معجلات الامتصاص على كفاءة مرهم الكلوتريمازول

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فى هذا البحث تم اختيار القاعدتين الذائبة فى الماء والدهنية على ضوء الدراسات السابقة وذلك لدراسة تأثير اضافة بعض معجلات الامتصاص مثل منشطات السطوح وبعض المعجلات السائلة على كفاءة مرهم الكوتريمازول

وقد تبين من الدراسة أن تأثير هذه المعجلات على زيادة الاتاحة المعملية للمادة الدوائية له علاقة وثيقة بالتركيب الكيميائى للمادة المضافة كذلك تركيزه وتبين ايضا أن جميع المعجلات تزيد من اتاحة العقار من القاعدة الدهنية .

وقد تم ايضا اختيار تأثيرهذه المعجلات على امتصاص العقار داخل جلد الأرنب وتأثيرها ايضا على انسجة الجلد بالدراسة الهستولوجية .

وتبين أن المواد المضافة أدت الى زيادة كمية العقار الممتصة داخل جلد الأرنب وانه ليس لها تأثير واضح على انسجة الجلد ماعدا حمض اللينولييك الذى أوضح تغييرفى انسجة الجسم عند تركيز ٢٠ ٪ .

ومن الدراسة يتضح أن استخدام خليط من ٢٠ ٪ من داى ميثيل سلفوكسيد، ٧ ٪ حامض لينولييك ، ٣ ٪ من منشط السطح جليسرول أحادى الايبريت يعطى أفضل النتائج .

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