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IN VITRO RELEASE OF SULCONAZOLE NITRATE FROM OINTMENT BASES

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ABSTRACT

The release rate of sulconazole nitrate, a new antimycotic drug, from 16 ointment formulations has been assessed. The effect of two liquid additives, viz, water and dimethyl sulfoxide (DMSO) on the release rate was investigated. The most enhancing effect was, by far, exhibited by DMSO and was found to be dependent on the additive concentration. This enhancing effect was accounted for the increase in the drug solubility in presence of DMSO rather than water. As regard to the effect of ointment base on the release pattern of the drug, water soluble bases were the superior. This observation is attributed to the fact that sulconazole nitrate is freely soluble in those water soluble bases. The difference in the release rate values exhibited when the drug was formulated in the water soluble bases is almost due to the change in formulations viscosities. It is worthy to note that the release pattern of sulconazole nitrate from all the tested ointment formulations was in agreement with the well known Higuchi diffusional model.

INTRODUCTION

Sulconazole nitrate, 1-[β-("4-chlorobenzylthio)-`2,`4-dichlorophenethyl] imidazol nitrate, is a potential new antimycotic agent developed for human use. Up till now, no attempts have been focused to formulate this drug in ointment.

It is well known that the release of a medicinal substance from an ointment base is influenced, to some extent, by the physicochemical properties of the drug and the base type. The absorption of a drug, applied topically, across the skin has been interpreted as the diffusional mass transfer of the drug starting from a

liquid vehicle, travelling through the skin tissues, and terminating at the blood stream.

Experimental and clinical evidence have been produced to suggest that the vehicle can, appreciably, affect the skin penetration [1-3]. The primary requirement for topical therapy is that a drug, incorporated into the vehicle, reaches the skin surface at adequate rate and in sufficient amounts. So, it is advantageous to choose the vehicles that have low affinity to bind with the medicament strongly, since the drug has to release from the base before it enters the cells.

The *in vitro* studies have shown that the release of a substanse will be favored by the selection of the ointment base which is characterized by having low affinity to the medicament [1&2, 4-8]. The literature regarding the superiority of one type of bases over another is conflicting, yet the efficiency of various vehicles in aiding the penetration of the skin can be reasonably predicted on the basis of their effect on : a) the hydration of stratum corneum or b) the activity of water in the stratum corneum and vehicle partition coefficient.

The effect of penetrant concentration as a factor controlling the rate of permeation of a drug through the membrane can be examined by reference to Fick's law of diffusion which, in essence, states that the driving force causing the transfer of a substance from regions of high concentration to those of low one is proportional to the concentration gradient. The effect of drug concentration on the in vitro release from ointment bases has been extensively investigated [1, 7-9].

The evidence of the role of liquid additives to promote the release of a medicinal material from ointment bases has been explored [4-6 & 10].

The present investigation was carried out to study the influence of the type of ointment base, drug concentration and liquid additives on the in vitro release properties of sulconazole nitrate from different ointment formulations. The utilized liquid additives are : water, propylene glycol and dimethyl sulfoxide. Also, the study concerned with the effect of either stearyl or cetyl alcohlos on the release pattern of the drug.

EXPERIMENTAL

Materials and Methods

Materials

Sulconazole nitrate (SN), kindly supplied by Syntex, (CA., USA). Dimethyl sulfoxide (DMSO), Fisher Sci. Co. (NJ. USA), PEGS 400, 1540, 4000 and 6000 (Ruger Chemical Co., NJ. USA). Span 80 (ICI Inc., Wilmington, Del. USA). Sodium lauryl sulfate, SLS, (BDH; Poole, UK). Cetyl alcohol, (Searle, Chadwell Health, Essex, UK). Propylene glycol (BDH; Poole, UK). Standard cellophane membrane 30/32(Fisher Sci. Co., NJ. USA). All other chemicals used were of pure grade and they were used as supplied.

Preparation of the ointments

All the tested ointment formulations, Table 1, were prepared by the fusion method at low temperature. The warm base was stirred until it cooled so as to achieve homogeneity. The liquids, into which SN was either dispersed or dissolved, were mixed with the specified ointment base prior to use in order to mini-

mize loss by evaporation. All the tested formulations were prepared in such a manner that the drug concentration was 1% w/w.

Release of sulconazole nitrate from ointment bases

The release study was determined using the simple dialysis technique. In this method, 1g of the tested formulation was accurately weighed over the cellophane membrane. The loaded membrane was stretched over one end of a glass tube, donor, with an internal diameter of 2.2 cm. The upper end of the tube was covered with a thinly perforated nylon sheet in order to minimize the possible evaporation of the liquids present in the ointments. The diffusion cell was placed at the center of a 100 ml beaker containing 20 ml of phosphate buffer at pH 6.8. The donor was suspended in the acceptor in such a manner that the membrane was located just below the surface of the sink solution. The whole dialysis unit was placed into a thermostatically controlled water bath shaker operating at 30°C and 25 shake / min. A 1 ml sample was pipetted from the sink solution at suitable time intervals and assayed for its drug content at 230 nm. Equal volume of phosphate buffer, at 30°C, was replaced into the outer sink solution so as to keep the volume constant during the experimental study. Each experiment was done in triplicate and the average was used to plot the data.

RESULTS AND DISCUSSION

The release rate of sulconazole nitrate from the investigated ointment bases was assessed according to the well known diffusional models. When the active substance is mostly dissolved in the ointment base, the release rate was analyzed according to Higuchi model [11], equation 1.

$$q = 2\,C_o \left(\frac{Dt}{\pi}\right)^{1/2} \qquad (1)$$

On the other hand, the equation relating the amount of the medicament released, from an ointment base, in which the drug is dispersed, to time was previously described by Higuchi [12], equation 2.

$$q = (2\,C_o\,D\,C_s\,t)^{1/2} \qquad (2)$$

where q is the amount of the drug released per unit surface area; C_o is the initial total drug concentration in the vehicle; D is the apparent diffusion coefficient; t is the sampling time; π is a constant = 3.14 and C_s is the solubility of the drug in the external phase of the ointment.

According to Eqns. 1 and 2, a linear relationship will be obtained when q is plotted against $t^{1/2}$. Both the release rate and the diffusion coefficient can be assessed from such plots.

The *in vitro* release of sulconazole nitrate from the investigated ointment bases was carried out over a period of 3 h at a concentration of 1% w/w. For all formulations a linear relationship was obtained when the amount of the drug released per unit surface area, q, was plotted against $t^{1/2}$. In no case did the plots pass through the origin. The existence of a lag time reflects the influence of the cellophane membrane that separates the ointment formulation from the release medium. Similar observations were found by other au-

thors [8, 9, 13 & 14]. The slope of each line was calculated using the linear regression analysis and the corresponding release rate was estimated. The data for the release rates are surveyed in Tables 2-4.

The release pattern of SN from absorption bases, B1 and B2, is depicted in Fig. 1. The release was faster from B1 than from B2. The calculated slopes for such plots were found to be 930 x 10^{-5} and 814 x 10^{-5} respectively.

A comparison of the observed release rates for w/o emulsion type, B3 - B6, is given in Fig. 2 and Table 2. From these data it can be observed that the release rates were greater from those bases containing higher proportion of water. It is possible to assume that the presence of water may favor the solubility of the drug in these bases or due to its lowering effect on the viscosity of the tested vehicles. The tested w/o bases can be ranked in the following decreasing order : B6› B5› B4› B3.

Fig.3 and Table 2 show the release of SN from o/w bases, B7 - B10, in presence of 1% sodium lauryl sulfate as an emulsifier. It can be observed that SN release from those vehicles follows the same trend as the previously mentioned vehicles. From the release data it could be possible to conclude that, the ability of these ointment bases to release the drug is, generally, dependent on its water as well as propylene glycol concentration. As the percentage of those ligiud additives was increased the release rate was increased. This finding could be, similarly, explained on the basis of the effect of water and propylene glycol on the drug solubility as well as the vehicle viscosity. The release rate decreased in the following order : B10› B9› B8› B7.

A comparison between the ability of the tested emulsified ointment bases, w/o and o/w, to release sulconazole nitrate, it can be observed that o/w vehicles tend to release the drug faster than the w/o type. The obtained results in this investigation were found to be in agreement with those previously obtained by other authors [4, 5, 15 & 16]. This finding can be explained on the basis that, in case of w/o vehicles, the presence of an oily vehicle as an external phase will result in a formation of an occlusive film on the membrane surface, which will result in a retardation of the permeation of the drug molecules across the membrane, into the sink solution.

Water soluble bases, B11 - B13, which composed of different ratios of PEG 400 and PEG 4000, are shown in Fig.4 and Table 3. The ability of these bases to release the drug is higher than those of absorption or emulsion types, B1 - B10. The release rate was found to be dependent on the base composition. Generally, as the percentage of PEG 400 was increased The release rate was promoted. In these bases the viscosity of the vehicle was decreased with an increase in PEG 400 concentration. The viscosity of B13, B12 and B11 was found to be 88 x 10^3, 176 x 10^3 and 220 x 10^3 cp respectively [17].

The release of sulconazole nitrate from other PEG bases, B14 - B16, was also studied. The data are given in Fig.5 and Table 3. A maximum release rate was at-

tained from those vehicles. The release rate was found to follow the following order : B16› B15› B14. The viscosity of those water soluble bases B16, B15, and B14 was 0.9, 3.5 and 4.7 x 10^4 cp respectively [18]. It is obvious from these results that an increase in the viscosity of the vehicle was accompanied by a reduction in the release rate. This may be explained by the fact that the increase in the viscosity of the tested vehicle will impart a resistance in drug diffusion into the outer effective surface, a phenomenon which is accompanied by retardation in the movement of drug molecules from the bulk of the base into the external mobile diffusion layer and thereby hindered the drug releasing efficacy. This observation is in harmony with that previously reported by Higuchi [19] who pointed out that the diffusion coefficient of the drug is inversely proportional to the viscocity of the vehicle.

Two liquid additives namely; water and DMSO, were incorporated at different concentrations into white petrolatum and a water soluble base # 16, to investigate the release effect of these additives on sulconazole nitrate. Referring to the release rates listed in Table 4 one can observe that DMSO was the most effective in increasing the release of the drug from the corresponding tested bases. The influence of the concentration of each additive on the release rate follows the same trend, Figs.6-8, i.e, an increase in the additive concentration was accompanied by an increase in the value of the release rate. These data are in agreement with those obtained by Whitworth and Stephenson [15] who found that, water and DMSO enhanced the rate of release of atropine sulfate from ointment bases. They attributed this effect to the possible changes in the solubility of atropine sulfate in the bases produced by the additives.

Table 1: Composition of Sulconazole Nitrate Formulations

Ingredient	B1	B2	B3	B4	B5	B6	B7	B8	B9	B10	B11	B12	B13	B14	B15	B16
White petrolatum	95	90	85	75	65	55	60	54	40	20	--	--	--	--	--	--
Wool fat	--	10	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Stearyl alcohol	--	--	--	--	--	--	15	13	10	5	--	--	--	--	--	--
Cetyl alcohol	--	--	--	--	--	--	15	13	10	5	--	--	--	--	--	--
Propylene glycol	--	--	--	--	--	--	2	4	5	8	--	--	--	--	--	--
Span 80	5	--	5	5	5	5	--	--	--	--	--	--	--	--	--	--
Water	--	--	10	20	30	40	7	15	34	61	--	--	--	--	10	10
Sodium lauryl sulfate	--	--	--	--	--	--	1	1	1	1	--	--	--	--	--	--
PEG 400	--	--	--	--	--	--	--	--	--	--	40	50	60	60	60	60
PEG 1540	--	--	--	--	--	--	--	--	--	--	--	--	--	30	--	--
PEG 4000	--	--	--	--	--	--	--	--	--	--	60	50	40	--	--	30
PEG 6000	--	--	--	--	--	--	--	--	--	--	--	--	--	10	30	--

Table 2: Calculated Release Rates of Sulconazole Nitrate from Emulsified Ointment Bases.

FORMULATION	RELEASE RATE X 10^3 (mg / cm^2 / $min^{½}$)
w/o type	
B3	3.19
B4	3.83
B5	4.04
B6	4.91
o/w type	
B7	5.91
B8	8.65
B9	9.71
B10	11.72

Table 3: Calculated Release Rates of Sulconazole Nitrate from Water Soluble Ointment Bases.

FORMULATION	RELEASE RATE X10^3 (mg / cm^2 / $min^{½}$)
B11	64
B12	70
B13	83
B14	92
B15	95
B16	101

Table 4: Effect of DMSO and water Concentrations on the Release Rate of Sulconazole Nitrate from a Water Soluble Base (B16) and White petrolatum.

FORMULATION	RELEASE RATE X 10^3 (mg / cm^2 / $min^{½}$)
B16	101
B16 + 1% DMSO	107
B16 + 3% DMSO	110
B16 + 5% DMSO	118
White petrolatum	10
White petrolatum + 1% DMSO	11
White petrolatum + 2% DMSO	12
White petrolatum + 3% DMSO	15
B16 + 1% water	99
B16 + 5% water	105
B16 + 10% water	111

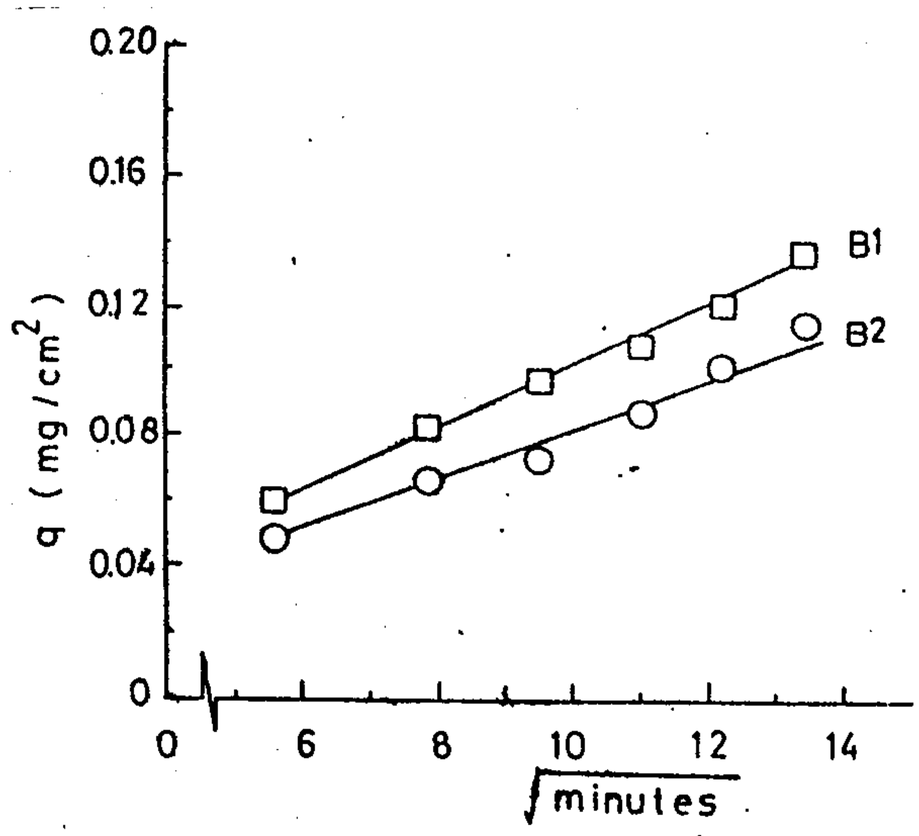

Fig. 1. Release of sulconazole nitrate from absorption bases , B1 and B2 .

In Vitro Release of Sulconazole Nitrate from Ointment Bases

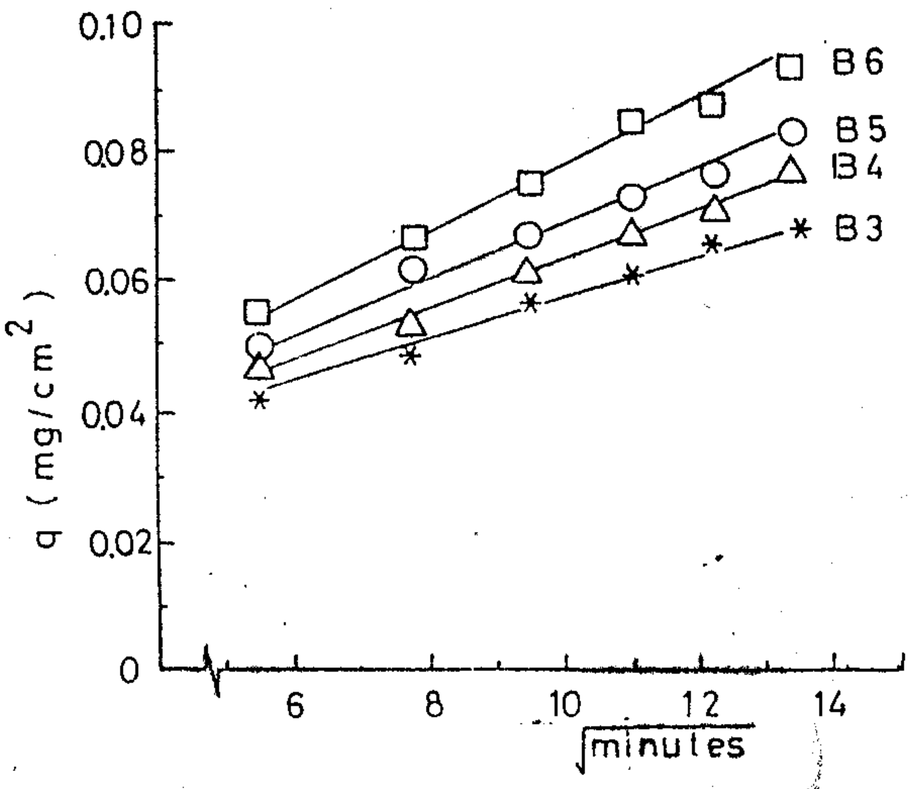

Fig. 2, Release of sulconazole nitrate from emulsion, w/o ointment bases.

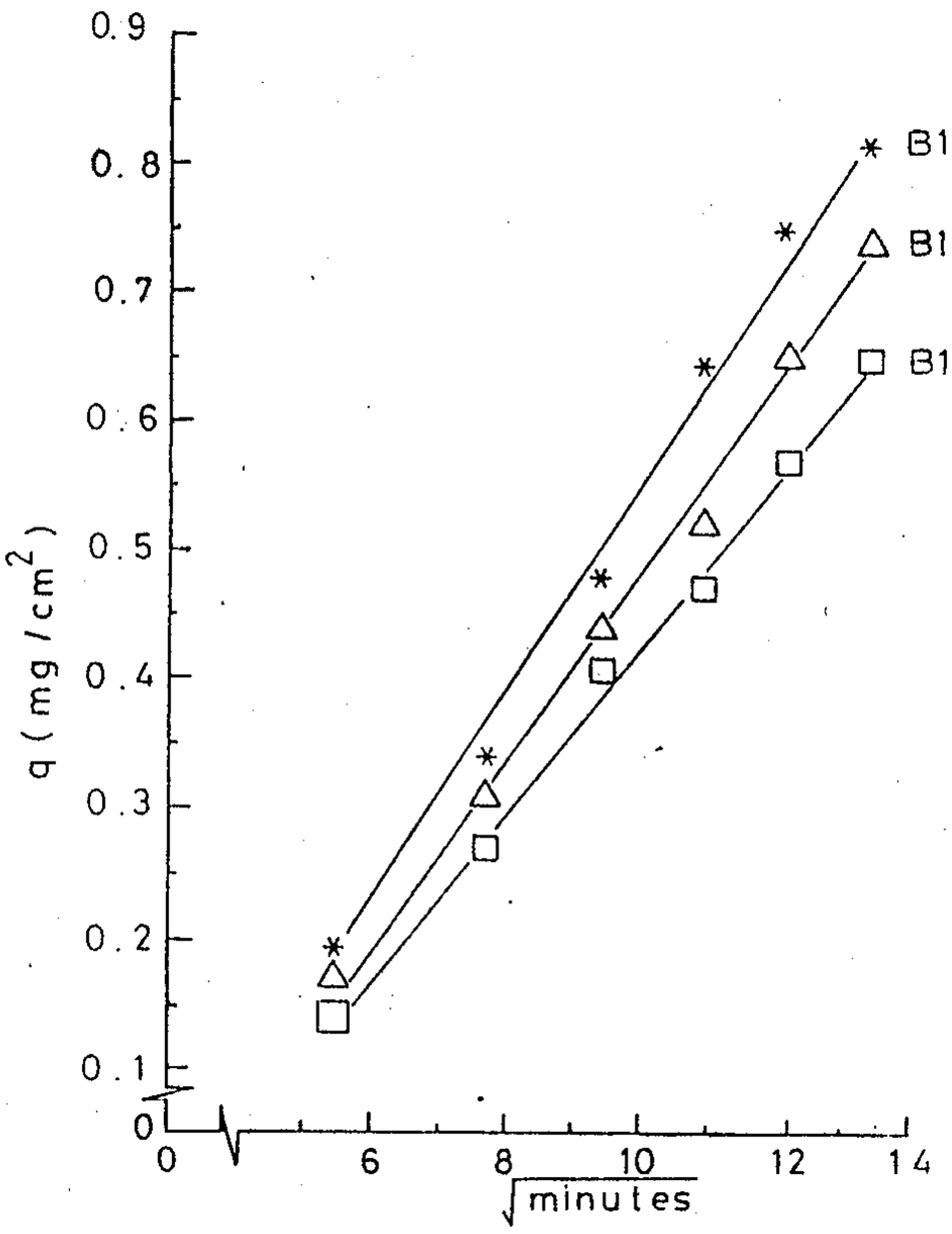

Fig. 4. Release of sulconazole nitrate from some water soluble ointment bases; B 11 - B 13.

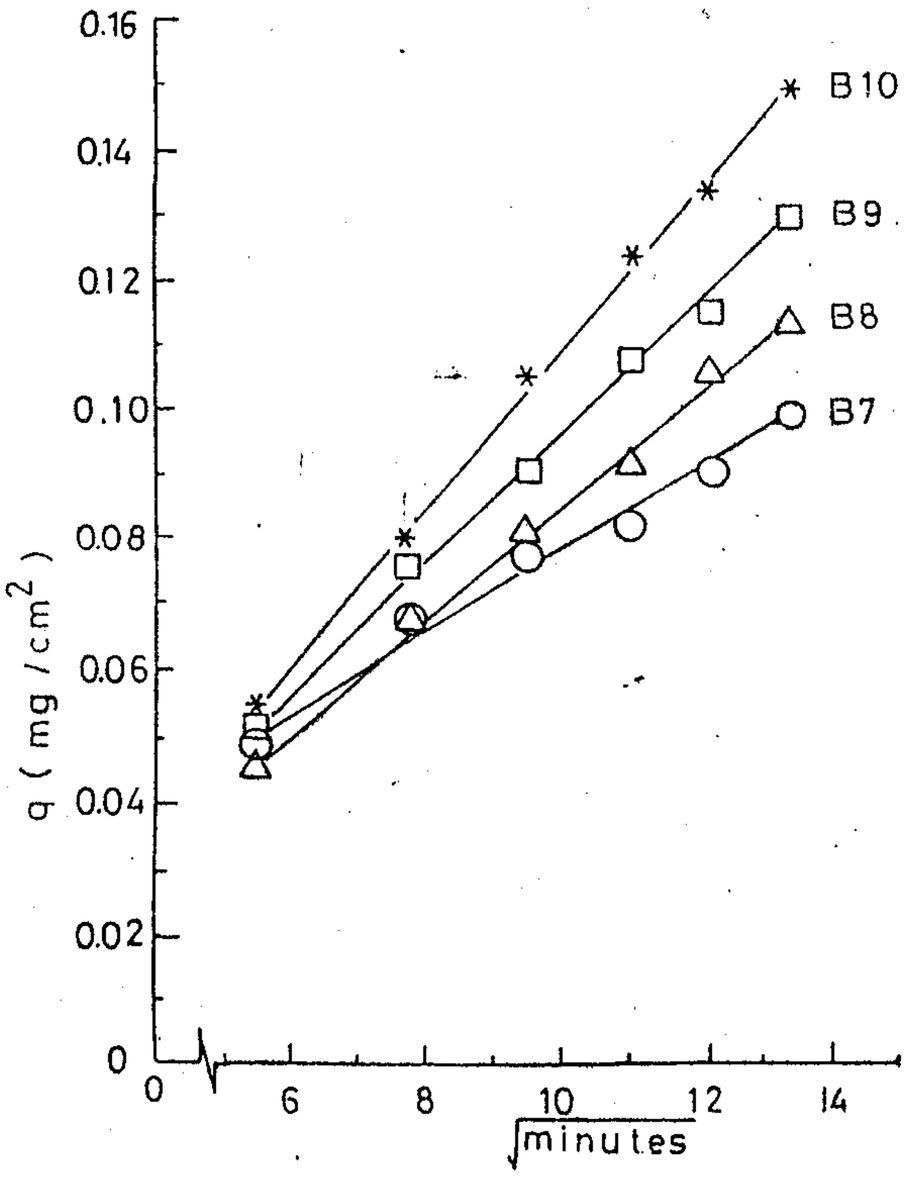

Fig. 3. Release of sulconazole nitrate from emulsion, o/w ointment bases.

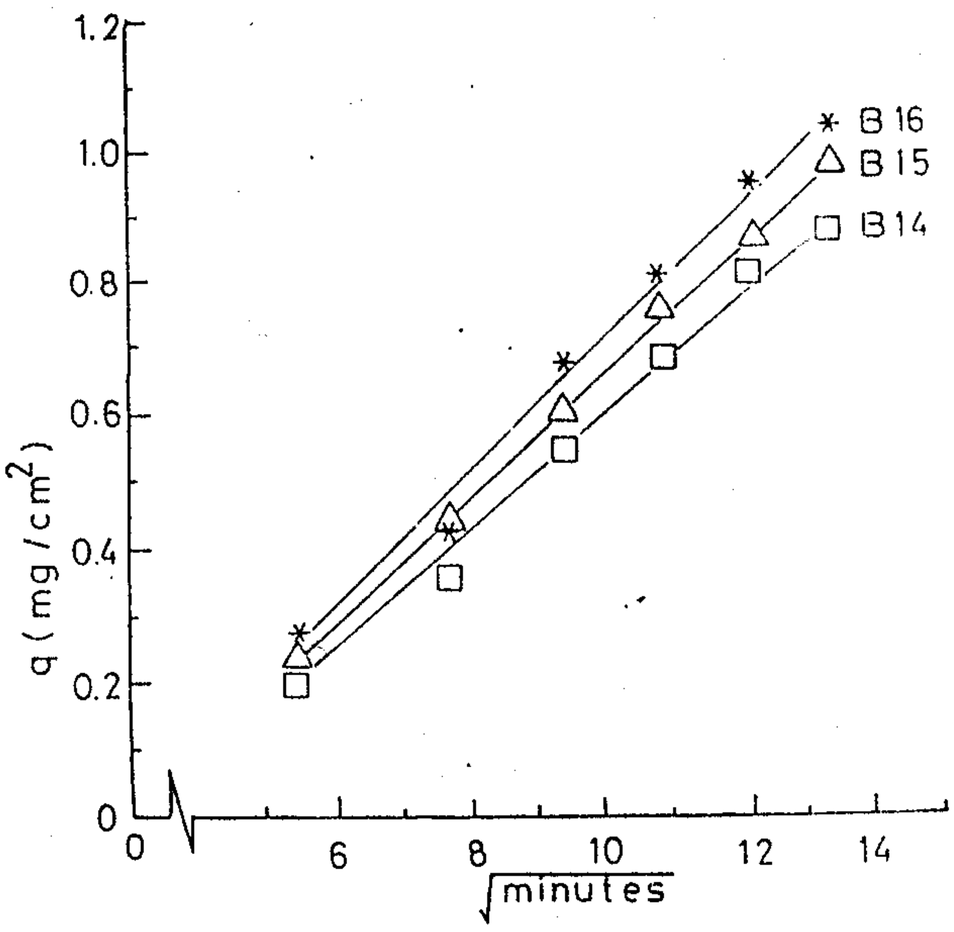

Fig. 5. Release of sulconazole nitrate from some water soluble ointment bases; B 14 - B 16.

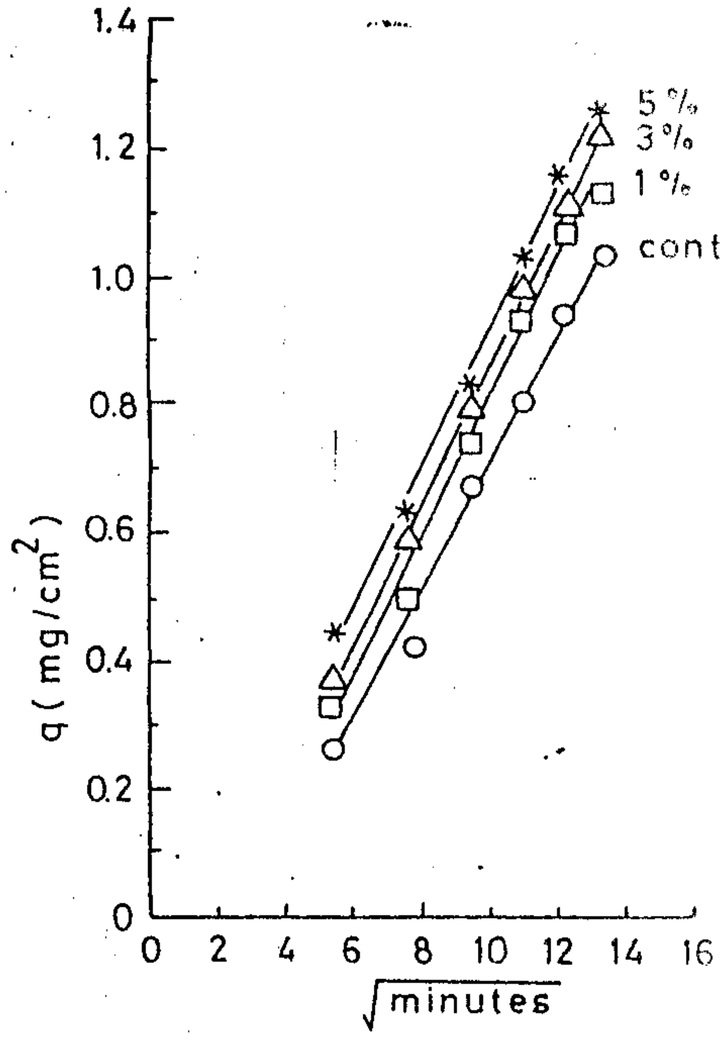

Fig. 6. Effect of different concentrations of DMSO on the release of sulconazole nitrate from a water soluble base; B 16.

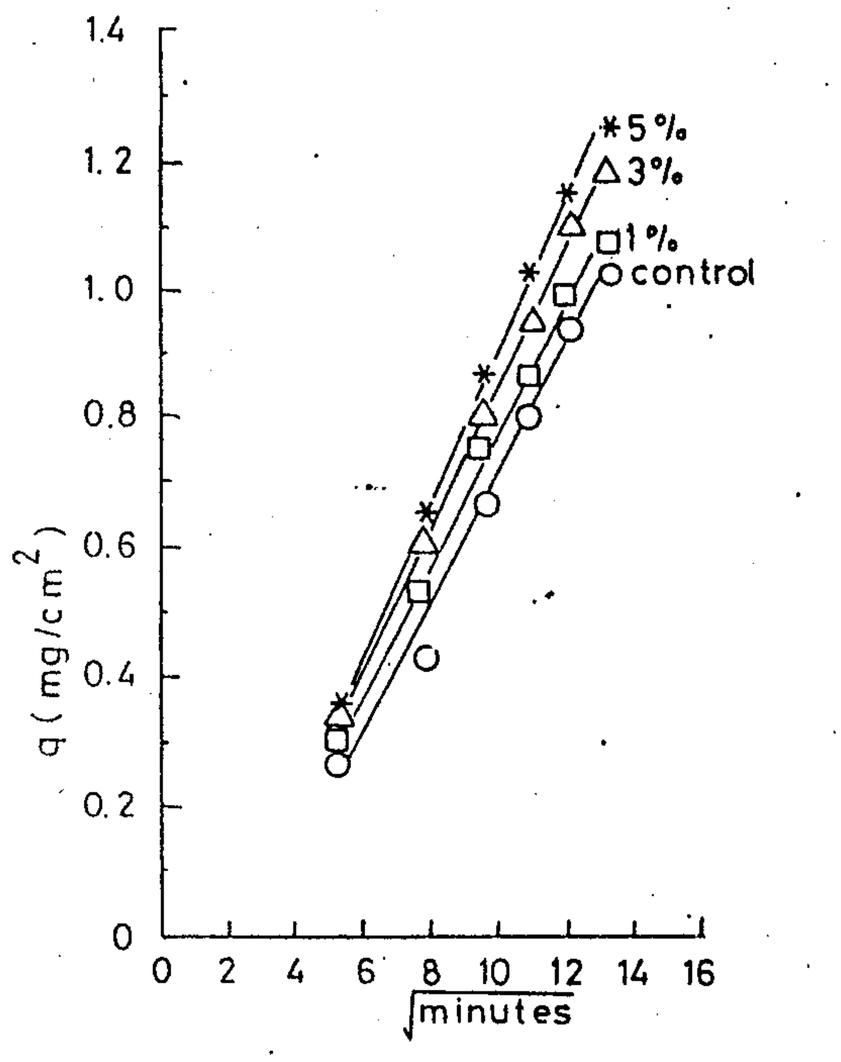

Fig. 8. Effect of water concentrations on the release of sulconazole nitrate from a water soluble base ; B 16.

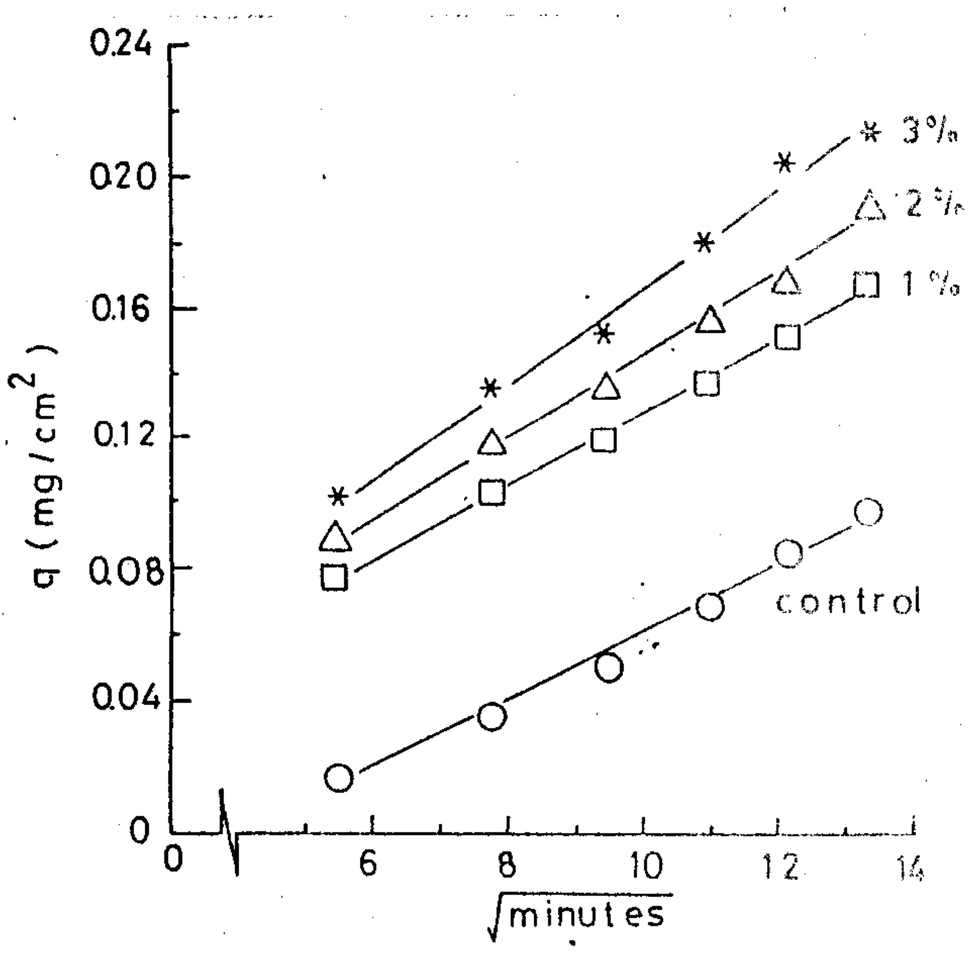

Fig. 7. Effect of different concentrations of DMSO on the release of sulconazole nitrate from white petrolatum.

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انطلاق نيترات السولكانوزول من قواعد المراهم

سيد اسماعيل محمد - عبد الرزاق عبدالمجيد محمد

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تم فى هذا البحث دراسة انطلاق عقار نيترات السولكونازول من ستة عشر صياغة مرهمية مختلفة وتم ايضا دراسة تاثير تركيزات مختلفة من سائلين هما الماء وثنائى ميثيل السلفوكسيد على انطلاق الدواء من بعض الصياغات المرهمية. ولقد وجد ان اعلى معدل للانطلاق قد اعتمد على تركيز ثنائى ميثيل السلفوكسيد فى الصياغة المرهمية. ولقد اعزيت هذه الزيادة فى معدل الانطلاق الى زيادة دوبان العقار فى هذه السوائل.

وبالنسبة لتأثير الصواغات المرهمية المختلفة على معدل انطلاق العقار فلقد اثبتت التجارب العملية أن القواعد القابلة للذوبان فى الماء هى أفضل القواعد المستخدمة. ولقد اختلف معدل انطلاق الدواء من هذه القواعد التى تذوب فى الماء وفسرت النتائج ان هذه الملاحظة ترجع الى اختلاف لزوجة القواعد المستخدمة. فكلما انخفضت اللزوجة كلما زاد معدل انطلاق الدواء.

ولقد أثبتت التجارب أن ديناميكية الانطلاق تتبع نموذج الانتشار البسيط لهيجوشى.

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