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TOPICAL OLEO-HYDROGEL PREPARATIONS OF PIROXICAM WITH ENHANCED SKIN PERMEABILITY AND ANTIINFLAMMATORY ACTIVITY

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ABSTRACT

In an attempt to improve the skin permeation and antiinflammatory activity of piroxicam, various topical formulations including oleo-hydrogels (oleo-gels) were prepared and their in vitro diffusion, skin permeation and in vivo antiinflammatory activities were evaluated. In vitro diffusion and permeation through a standard cellophane membrane and hairless abdominal rat skin were studied using a modified diffusion cell. The diffusion and permeation parameters such as apparent release rate, cumulative amount permeated, steady-state flux, lag time, permeability coefficient, diffusion coefficient and partition coefficient were determined for the prepared formulations in comparison with a commercial piroxicam gel (Feldene gel, Pfizer). The topical antiinflammatory activity of the prepared formulations were compared with the Feledene gel using croton oil-induced inflammation in mice. The results indicate that topical oleo-hydrogels under study improved the diffusion and skin permeation characteristics of piroxicam. In addition, the antiinflammatory activity of piroxicam in the oleo-gel preparations was relatively higher as compared with the commercial piroxicam gel, Feldene-gel.

INTRODUCTION

Piroxicam is one of the most potent nonsteroidal antiinflammatory drugs (NSAIDs). Piroxicam is well absorbed following oral administration; however, its use has been limited by a number of side effects, including gastrointestinal bleeding and ulceration [1]. Transdermal administration of piroxicam can overcome these side effects [2], and higher local concentration can be maintained at the target tissue, which is desirable for antiinflammatory drugs. Transdermal drug delivery systems have additional advantages of avoiding the hepatic first-pass metabolism and providing the controlled delivery of the drug for an extended period [3,4].

In the development of a transdermal drug delivery system, it is desirable to evaluate the in- vitro drug release, skin permeation characteristics as well as the pharmacological activity before carrying out in-vivo studies in human volunteers. It is well known that a number of factors can affect the transdermal permeation of drugs including pH of the formulation, drug concentration, partition coefficient, surfactants, skin permeation enhancers, type of the transdermal vehicle, etc. [5].

The choice of a transdermal base for drug delivery depends upon many factors, such as the action desired, the nature of the medicament to be incorporated and its bioavailability and stability, and requisite shelf-life of the finished product [6]. The optimum base should be selected according to the characteristics of the drug and of the disease state or skin conditions to be treated [7-9]. Recently, Rhee et al.,1999 [10] developed hydrogel system containing an emulsion (topical oleo-hydrogel system) to enhance the skin permeability of ketoprofen.

The objectives of this study were to develop transdermal formulations of piroxicam using the topical oleo-hydrogel systems (oleo-gel) and to evaluate the in vitro drug diffusion, skin permeability and topical antiinflammatory activity of piroxicam in comparison with other transdermal vehicles such as oil in water emulsion ointment base (o/w), polyethylene glycol (PEG base), carbopol gel and sodium carboxymethylcellulose (NaCMC) gel. The comparison also included a conventional topical gel product of piroxicam (Feldene gel, Pfizer).

EXPERIMENTAL

Materials:

Piroxicam B.P. and Carbopol 934 (gifts from the United Pharmaceutical Company, Amman-Jordan), Sodium carboxymethyl-cellulose (CBH Lab. Chemicals, UK), Cetyl alcohol (Sigma, USA), Propylene glycol (Panpeca, Barcelone, Spain), Tween-80 (Riedel-de Haen, Germany), Polyethylene glycol 4000 (Panpeca, Barcelona, Spain). Castor oil (BASF, Germany), Cellophane membrane ($^{30}/_{32}$, Japan), Croton oil (Sigma, USA). All other chemicals were of analytical grade.

Methods

I. Preparation of transdermal (topical) delivery systems

The composition of the prepared transdermal formulations of piroxicam is shown in Table 1 (seven formulations, F1 to F7). All formulations contained 0.5% w/w piroxicam (B.P.). F8, a commercial

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piroxicam gel (0.5% w/w piroxicam) was used as a reference preparation in this study. F1, composed of oil in water emulsion ointment base (o/w base) was prepared by the hot method. The oily and water soluble ingredients were heated separately at 65°C and then mixed with rapid stirring until cooling to about 25°C. F2 composed of water soluble, polyethylene glycol ointment base (PEG base) was prepared by melting PEG and cetyl alcohol at 65°C in water bath, then the aqueous phase contained piroxicam was heated at the same temperature and added to oil phase while hot and mixed with rapid stirring until cooling to about 25°C.

F3, composed of topical oleo-hydrogel transdermal formulation (oleo-gel) and was prepared according to *Rhee et al 1999* [10], as follows: Piroxicam was dispersed in a mixture of propylene glycol, Tween 80 and castor oil to prepare the emulsion. Carbopol was dispersed separately in water with uniform stirring to prepare the hydrogel. The emulsion was then added portionwise to the hydrogel under stirring to prepare the hydrogel emulsion, which was then mixed with the alkalinizing agent, triethanolamine (T.E.A.) to obtain the desired consistency of topical formulation of piroxicam in the form of hydrogel emulsion (oleo-hydrogel) [10]. The final pH of the product was 6.5.

F4 and F5 were composed of carbopol 934 and sodium carboxymethylcellulose (NaCMC) gels respectively, and were prepared by dissolving the gelling agent in a mixture of piroxicam, propylene glycol, Tween 80 and purified water.

F6 and F7 were composed of topical oleo-hydrogel bases, the same as F3 with the addition of linoleic acid (F6) and sodium lauryl sulfate (F7) as skin permeation enhancers. They were prepared by the same procedure of F3.

2. In vitro diffusion and skin permeation studies

In- vitro skin permeation studies using intact hairless abdominal rat skin were performed as follows: full-thickness skin was obtained after shaving the hair from 5-6 week old male rats (200-230 gm) anaesthetized with 25% urethane in saline solution (1.2 g/kg i.p.). The abdominal skin was excised and the adhering subcutaneous fat on the dermal site was removed. Freshly excised full-thickness rat skin was mounted a modified Franz diffusion cell (the effective diffusional area of the cell was 6.15 cm^2, r=1.4 cm) with *stratum corneum* side facing the donor compartment and the dermal side facing the receptor compartment. One gram of the formulation under test was applied to the skin, and the top cell was clamped and covered with parafilm. The receptor compartment contained phosphate buffer (pH 7.4) maintained at 37°C by a circulating water bath. Samples were withdrawn from the receptor compartment at predetermined time intervals and replaced by an equal volume of fresh buffer solution at the same temperature. The samples were filtered using Millipore filters (W-13-2, Toscoh Co., Japan) and analyzed by using a specific high-performance liquid chromatographic method [11]. The same procedure was used when cellophane membrane (30/32, Japan) was used instead of the rat skin. All experiments were carried out on triplicate samples and the mean was reported.

3. Calculation of the permeation parameters

3.1. In-vitro diffusion using cellophane membrane

The drug diffusion data were treated by *Higuchi equation 1962* [12]:

$$Q = 2\,C_o\sqrt{\frac{D_{app}.t}{\pi}} \qquad \textbf{Eq. 1}$$

where Q is the amount of piroxicam released per unit area , C_O is the initial drug concentration in donor compartment, D_{app} is the apparent diffusion coefficient, and t is the time. D_{app} was calculated from the slope of the linear plot of Q versus $(t)^{1/2}$ as shown by equation 2 :

$$D_{app} = \frac{B^2\pi}{4Co^2} \qquad \textbf{Eq. 2}$$

where B is the slope of the linear regression.

3.2. Calculation of the permeation parameters through rat skin

The permeation parameters of piroxicam: lag time t_L, permeability coefficient through the skin k_p, diffusion coefficient within the skin D, and partition coefficient between the skin and the vehicle (K) were calculated according to Chow et al.1984 [13]. The skin permeation profiles were constructed by plotting the cumulative amount of piroxicam permeated versus time [13]. The X-intercept of the extrapolated linear region of the curve gives t_{lag}, D was calculated from t_L with known thickness (0.17 cm) of the penetration barrier L using equation 3. The slope of the linear portion of the profile, determined by linear regression analysis, was the steady-state flux. Jss [13]. k_p was calculated by dividing Jss by the employed concentration of piroxicam, Co (Eq. 4), and k was calculated from Eq. 5.

$$T_{Lag} = \frac{L^2}{6D} \qquad \textbf{Eq. 3}$$

$$Jss = \frac{(K.D.C_o)}{L} = k_p.\,C_o \qquad \textbf{Eq. 4}$$

$$k_p = \frac{K.D}{L} \qquad \textbf{Eq. 5}$$

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4. Topical antiinflammatory activity of different piroxicam formulations

White albino mice (ten for each formulation) 20-25 g weight were used. They were kept under standard conditions [14]. To induce local inflammation 10 µl of croton oil solution [25mg of croton oil dissolved in 1 ml of pyridine/water/diethyl ether (4: 1: 5 v/v/v)] was applied by means of a micropipette to the inner side of the left ear of each mouse ,*Hutter et al.* 1988 [14]. Right ear served as a control. 30 min. after croton oil treatment, topical preparations of piroxicam were used to inflamed ear. Measurements of difference in ear thickness were made at 6, 24 and 48 hours after treatment using micrometer.

5. Statistical analysis of data

The significance of the difference in parameter values was tested by a nonpaired student's test ($p < 0.05$) [14].

RESULTS AND DISCUSSION

Seven topical formulations each containing 0.5% w/w piroxicam (B.P.) were developed (Table 1). Piroxicam is sparingly soluble in water and, therefore, 30% w/w of propylene glycol and 1-4 % w/w surfactant (Tween 80) were added to each formulation to increase the solubility of piroxicam [5].

Permeation through cellophane membrane

Figures (1a and 1b) show the permeation profiles of piroxicam through a standard cellophane membrane from the prepared topical formulations (F1 to F7) in comparison with a commercial piroxicam product, Feledene gel (F8). Linear relationships ($r>0.98$) existed between the amount of piroxicam permeated and the square root of time indicating that the release of piroxicam from the prepared formulations, as well as the commercial product could be described by the diffusional model, and, hence, the rate-controlling step in the permeation process is diffusion of dissolved drug through the matrix vehicle [12].

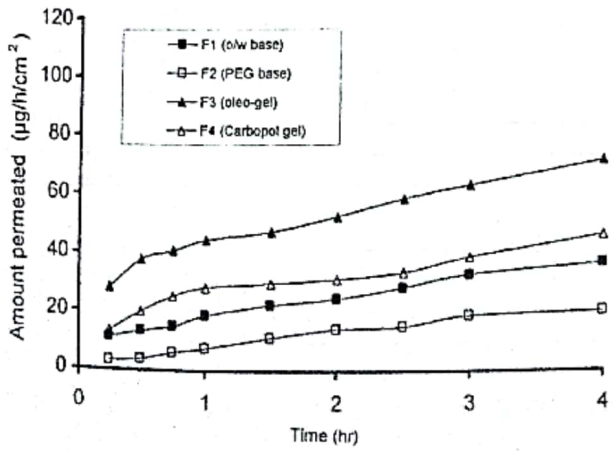

Fig. (1a) : Permeation profiles of piroxicam from various topical formulations throuhg a standard cellophane memt

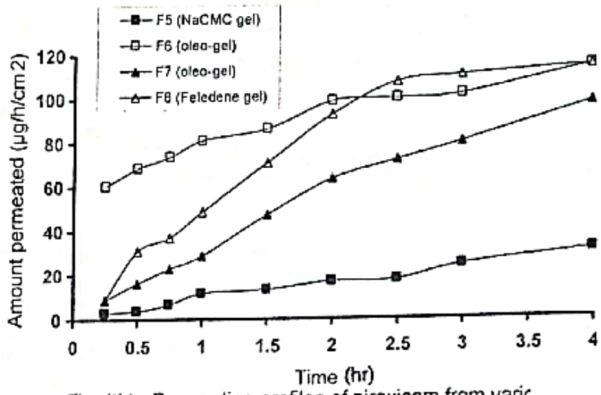

Fig. (1b) : Permeation profiles of piroxicam from varic topical formulations through a standard cellophane membrane.

Table 2 shows the permeation characteristics of piroxicam from various formulations through a standard cellophane membrane. The apparent release rate is given by the following order: F6>F8>F7>F3>F4>F5>F1>F2. Thus, topical oleo-gel of piroxicam containing Tween-80 and linoleic acid (F6) gave the highest release rate (75.5 ± 4.90 µg/cm^2/h) between the prepared formulations which was not significantly different ($p < 0.05$) from F8 ,Feldene gel (75.32 ± 6.50 µg/cm^2/h) and followed by F7 (62.63 ± 4.30 µg/cm^2/h). The apparent diffusion coefficients were 179.36 ± 18.11, 178.22 ± 15.31 and 123.22 ± 11 cm^2/hX10^{-4} for F6, F8 and F7 respectively (Table 2).

Skin permeation studies

Figures 2a and 2b show the permeation profiles of piroxicam across the excised hairless abdominal rat skin from various formulations. The corresponding skin permeation characteristics are shown in Table 3. Table 3 summarizes the cumulative amount permeated per 7 h (Q_{7h}), steady-state fluxes (Jss), lag times (t_{Lag}), permeability coefficients (K_p), diffusion coefficients (D) and the partition coefficients (K) of the prepared formulations in comparison with the commercial piroxicam product, Feldene gel (F8).

Topical oleo-gels, F3, F6 and F7, exhibited higher permeation ratios, steady-state fluxes and permeability

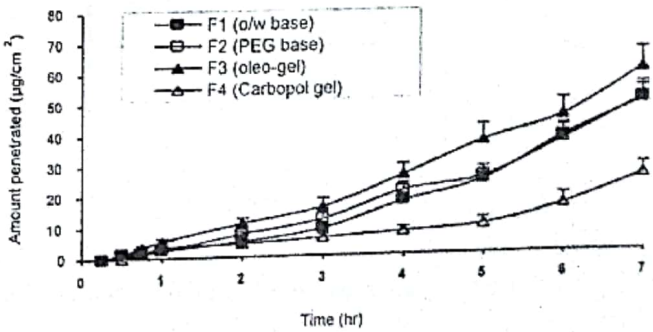

Fig. (2a) : Penetration profiles of piroxicam through full-thickness hairless abdominal rat skin with various formulations.

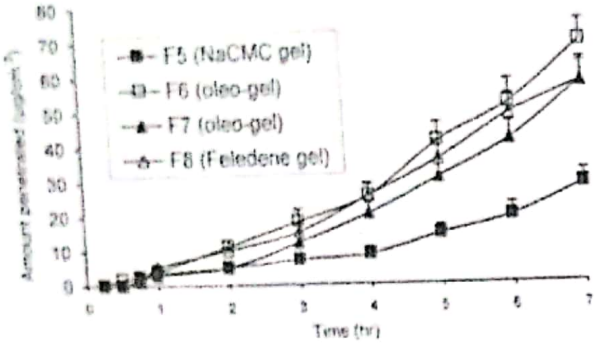

Fig. (2b) : Penetration profiles of piroxicam through full-thickness hairless abdominal rat skin with various formulations

coefficients as compared to the commercial piroxicam gel, F8 (Table 3). However, F6, topical oleo-gel containing 4% Tween-80 and 2.5% linoleic acid exhibited the most improved permeation characteristics as compared to the other topical formulations used in this study (Table 3). The decreased lag time values for the topical oleo-gels would be an advantageous characteristic for the rapid onset of action. On the other hand, the ointment bases (F1 and F2), carbopol gel (F4) and NaCMC gel (F5) exhibited longer lag time values of 2.3±0.11, 2.00±0.5, 3.2±0.50 and 2.5±0.60 hours respectively (Table 3) which could be due to the low thermodynamic activity of piroxicam in these formulations [15]. The improved permeation characteristics of piroxicam by using topical oleo-gel F3, F6 and F7 (Table 3) could be attributed to two possible mechanisms. First, the oleo-gel increased the in vitro release of piroxicam, hence its thermodynamic activity increased in these formulations. Second,the oleo-gel base may interact with the lipid components of the *stratum corneum* and act as a plasticizer with possible enhancement of drug transport. These assumptions are supported by the antiinflammatory activity of piroxicam from topical oleo-gel vehicles [10,15-20].

Antiinflammatory studies

Table 4 summarizes the antiinflammatory activity of different piroxicam formulations. Feledene gel significantly reduced the ear swelling 6, 24, and 48 hours after application of croton oil.

After 6 hours following application of croton oil, maximum antiinflammatory activity of piroxicam was observed with topical oleo-gel, F3, which did not significantly differ ($p < 0.05$) from the commercial product, Feldene gel (F8). The antiinflammatory activity of piroxicam from the oleo-gels, F6 and F7 was better than the other topical formulations, F2, F4 and F5. Other formulations produced antiinflammatory effect less than Feldene gel, F8. Only F6 was not significantly different ($p<0.05$) from the commercial formulation.

It is notable that after 24 hours and 48 hours, maximum antiinflammatory activity of piroxicam was observed with F6 (oleo-gel containing 4% Tween-80 and 2.5% linoleic acid). F6 was superior to commercial Feledene gel. This indicates the enhanced and prolonged activity of piroxicam in this formula (F6) as compared to all other formulations including the commercial formulation (F8) (Table 4) and correlates with the in-vitro permeation studies (Tables 2 and 3).

In summary, the results showed that F3 (oleo gel) had the most rapid onset of action, as was observed 6 hours after induction of inflammation, while F4 and F6 had the most prolonged activity as seen after 24 hours and 48 hours after croton oil-induced inflammation (Table 4). F6 was even much more effective as compared to the commercial piroxicam gel, F8 (Feldene gel).

Table (1): Composition (% w/w) of the prepared topical formulations of piroxicam.

Ingredient	Formulation							
	F1 o/w base	F2 PEG base	F3 oleo-gel	F4 carbopol gel	F5 NaCMC gel	F6 oleo-gel	F7 oleo-gel	F8* Feledene
Piroxicam	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Cetyl alcohol	20	24	-	-	-	-	-	-
Mineral oil	15	-	-	-	-	-	-	-
Propylene glyol	30	30	30	30	30	30	30	-
Tween 80	1	1	4	1	1	4	4	-
PEG 4000	-	20	-	-	-	-	-	-
SLS	-	1	-	-	-	-	-	-
Carbopol 934	-	-	2	2	-	2	2	-
Castor oil	-	-	10	-	-	10	10	-
T.E.A.	-	-	1	-	-	1	1	-
NaCMC	-	-	-	-	2	-	-	-
Linoleic acid	-	-	-	-	-	2.5	-	-
Purified water	33.5	23.5	52.50	66.5	66.5	50	50	-

* *Feldene*: Commercial piroxicam gel containing 0.5% w/w piroxicam (B.P.).

Table (2): Permeation characteristics of piroxicam from different topical formulations through a standard cellophane membrane.

Formula	Q 4h (μg/cm²/h)	Correlation coefficient (r)	Apparent release rate (μg/cm²/h)	Diffusion coefficient. D (cm²/hX10⁻⁴)
F1	36.10±3.1	0.993	17.38±1.50	9.48±0.53
F2	29.81±2.1	0.991	12.45±1.70	4.86±0.35
F3	70.73±7.1	0.993	26.54±2.50	22.12±3.20
F4	45.90±5.1	0.987	18.67±1.97	10.95±1.50
F5	30.41±4.1	0.982	18.40±1.60	10.63±1.30
F6	114.92±9.11*	0.992	75.56±4.90*	179.36±18.11*
F7	97.99±8.5	0.994	62.63±4.30	123.22±13.11
F8	114.62±6.5	0.981	75.32±6.50	178.22±15.31

* No significant difference from the commercial formulation F8 ($P < 0.05$).

Table (3): Skin penetration parameters of piroxicam through full-thickness hairless abdominal rat skin with various topical formulations.

Formula No.	Cumulative amount at 7h (Q 7h, μg/cm²)	Flux (Jss, μg/cm²/h)	Lag time (t_{Lag}, h)	Permeability coefficient (kp, cm/hX10⁻⁶)	Diffusion coefficient (D, cm²/hX10⁻⁷)	Partition coefficient (K)
F1	49.50 ± 7.50	11.80 ± 2.11	2.3 ± 0.11	6.11 ± 0.11	5.81 ± 0.61	1.78 ± 0.05
F2	50.10 ± 8.30	9.60 ± 2.50	2.00 ± 0.50	5.33 ± 0.12	6.68 ± 0.73	1.41 ± 0.11
F3	55.87 ± 6.30	11.40 ± 1.80	1.0 ± 0.21	6.33 ± 0.13	13.37 ± 1.31	0.83 ± 0.01
F4	25.10 ± 4.50	5.89 ± 1.60	3.2 ± 0.50	3.22 ± 0.16	4.18 ± 0.51	1.36 ± 0.05
F5	27.10 ± 7.70	6.15 ± 1.30	2.5 ± 0.60	3.41 ± 0.17	5.55 ± 0.31	1.12 ± 0.06
F6	66.07 ± 6.30	12.10 ± 1.60	1.5 ± 0.31	6.72 ± 0.18	8.91 ± 0.41	1.33 ± 0.03
F7	55.93 ± 5.50	11.50 ± 2.30	1.8 ± 0.41	6.59 ± 0.11	7.43 ± 0.51	1.52 ± 0.11
F8	55.73 ± 4.31	10.20 ± 1.20	1.4 ± 0.31	5.67 ± 0.11	9.55 ± 0.61	1.05 ± 0.04

Table (4): Effect of topical piroxicam preparations on croton oil-induced inflammation in mice.

Formulation	Difference in ear thickness, mmX10⁻³ (Mean ± SE) after		
	6 h	24 h	48 h
Control (no treatment)	2.857±0.240	3.000±0.001	6.500±0.433
F1 (Piroxicam, o/w)	0.643±0.042 +	0.901±0.041 +	2.000±0.066 +
F2 (Piroxicam, PEG)	1.429±0.092 +	3.286±0.241 +	3.600±0.200 +
F3 Piroxicam, oleo-gel)	0.001±0.0001	1.000±0.001 +	1.144±0.074
F4 (Carbopol gel)	6.000±0.966 +	0.126±0.013	0.501±0.050 +
F5 (NaCMC gel)	1.625±0.05 +	1.751±0.142 +	3.000±0.347 +
F6 (oleo-gel)	0.715±0.07 +	0.201±0.020	0.001±0.0001 +
F7 (oleo-gel)	0.751±0.13 +	0.723±0.022 +	0.572±0.030 +
F8 (Feldene)*	0.001±0.0001*	0.251±0.025*	1.001±0.071*

Note: * $p < 0.05$ compared to control. + $p < 0.05$ compared to Feledene gel (F8).

CONCLUSION

In an attempt to obtain an optimal composition of a topical piroxicam preparation, various oleo-gel vehicles were formulated and compared to other prepared transdermal (topical) vehicles such as ointment and gel bases or a standard commercial gel of piroxicam (Feledene gel, Pfizer). The reported data for diffusion, skin permeation and antiinflammatory studies indicate that the preparation of piroxicam in form of topical – oleo hydrogel (oleo-gel) could improve the diffusion and skin permeation characteristics as well as the antiinflammatory activity of piroxicam as compared to commonly used transdermal (topical) delivery systems.

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مستحضرات موضوعية مكونة من جل مائى - زيتى لعقار البيروكسكام ذات قدرة محسنة على اختراق الجلد وعلاج الالتهاب

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فى محاولة لتحسين قدرة عقار البيروكسكام على اختراق الجلد وعلاج الالتهاب تم تحضير صيغ مختلفة ضمنها جل مائى - زيتى . وقد تم تقييم هذه الصيغ من حيث معدل الانتشار ومعدل الاختراق الجلدى باستخدام خلايا الانتشار المحسنة المزودة بغشاء السليوفان او جلد الفئران.

وقد تم تعيين عوامل الانتشار والاختراق الجلدى وذلك بالمقارنة مع صيغة مطروحة بالسوق لعقار البيروكسكام وهى فلدين جل من إنتاج شركة فايزر.

وأوضحت النتائج أن مستحضرات الجل المائى - الزيتى حسنت خصائص الانتشار والاختراق لعقار البيروكسكام . وكذلك القدرة على علاج الالتهاب الموضعى فى أذن الفئران وذلك بالمقارنة مع المستحضر الموجود بالسوق (فلدين جل) .