

FORMULATION AND EVALUATION OF CERTAIN ANTI-INFLAMMATORY DRUGS
FOR TOPICAL APPLICATION. 1- OINTMENT FORMS

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ABSTRACT

The influence of type of vehicle on the in-vitro and anti-inflammatory effect of flufenamic and mefenamic acids has been studied. The vehicle investigated consisted of: water soluble base, an absorption base and two emulsion bases (O/W and W/O).

In-vitro release was evaluated using a diffusion assembly fitted with Fischer cellulose membrane (30/32) as diffusion barrier. Phosphate buffer of pH 6.8 at 35°C (+2) was used as release medium.

The results revealed that, the rate and amount of drug released was greatly affected by the type of base and nature of drug. The ointment bases can be arranged according to in-vitro release for both flufenamic and mefenamic acids as follows: water-soluble base > water-in oil emulsion base > oil-in-water emulsion base > absorption base. Anti-inflammatory effect was studied on inflamed tissue of albino rabbit. The selected ointment bases were uniformly spread over the shaved inflamed back skin of rabbit for several days. The ointment bases can be arranged in descending order according to anti-inflammatory effect after topical application to inflamed tissue as follows: Absorption base > water in-oil emulsion base > oil-in-water emulsion base >

water soluble base. Trials to find out any correlation between in-vitro release and anti-inflammatory effect for both flufenamic and mefenamic acids were carried out. It was found that there is only correlation between in-vitro release and anti-inflammatory effect for emulsion base (W/O, O/W) for both flufenamic and mefenamic acids.

INTRODUCTION

From the standpoint of therapeutics, one important attribute of an ointment is its ability to release its active ingredient. Vehicle should act as inert carrier for the active substance, however it may also influence the release and drug absorption processes¹⁻⁶.

So the role of a vehicle in the transport of the drug through the skin is of fundamental importance for the rational development of topical formulation. Relevant works dealing with this problem have been reviewed by Idson and Katz and Poulsen^{8,9}.

The effect of formulation additive on drug permeation through skin has been investigated¹⁰⁻¹². The penetration rate of topical agent may be influenced by drug-vehicle, drug-skin and vehicle-skin interaction. So, in the clinical assessment of a topical agent, the vehicle may significantly affect drug release and skin penetration, thereby altering biological activity¹³⁻¹⁵.

The anti-inflammatory and analgesic actions of flufenamic and mefenamic acids have been reported¹⁶⁻¹⁹. Percutaneous absorption of flufenamic and mefenamic acids and resulting anti-inflammatory activity has been shown using animal and human models²⁰⁻²³.

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Cutaneous application of flufenamic and mefenamic acids for rheumatic disorders could have numerous advantages. The active ingredients diffuse directly through the skin at the application site avoiding the side effects associated with oral administration. So the objective of this work was to investigate the effect of ointment base type on in-vitro release and in-vivo anti-inflammatory effect of flufenamic and mefenamic acids.

EXPERIMENTAL

Materials:

Flufenamic and mefenamic acids (obtained from El-Nile Company, Egypt) white soft paraffin, liquid paraffin, cetyl alcohol, lanoline, propylene glycol, Tween 80, span 20, polyethylene glycol 400 and 4000, disodium hydrogen phosphate and mono-sodium dihydrogen phosphate and Fischer cellulose membrane (30/32) were of analytical or pharmaceuticals grades and were used as obtained.

The following formulation of various ointment bases were prepared

I- Absorption Base:

Wool fat		15 gm.
Liquid paraffin		15 gm.
White soft paraffin		70 gm.

II- Water Soluble Base:

Polyethylene glycol	400	50 gm.
Polyethylene glycol	4000	50 gm.

III- Emulsion Base (O/W):

White soft paraffin	50 gm.
Liquid paraffin	12 gm.
Cetyl alcohol	25 gm.
Tween 80	5 gm.
Distilled water	33 gm.

IV- Emulsion Base (W/O):

White soft paraffin	30 g.
Liquid paraffin	15 g.
Propylene glycol	20 g.
Span 20	5 g.
Distilled water	30 gm.

Method:Preparation of Ointment:

The flufenamic and mefenamic acids were formulated with absorption and water-soluble ointment bases according to the composition above. The drug was incorporated with melted base. The ointment was continuously stirred until cold in order to achieve homogeneity of the drug in the base. The emulsion types of ointment (O/W, W/O) were prepared by dispersing the drug in the aqueous phase then warming and adding to the melted oleagenous phase of ointment base. The concentration of both drugs in all the ointment bases was 5 % w/w.

In-Vitro Release of Drug From Various Ointment Bases:

The ointment (1 g) was accurately weighed and placed on semipermeable Fischer cellulose membrane (30/32) to occupy a circle of 2 cm in diameter. The loaded membrane with the ointment was stretched over the open end of a

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glass tube, 2 cm in diameter, which was made water-tight by rubber band. The inverted tube was suspended so that the membrane was just below the surface of a predetermined quantity of 30 ml phosphate buffer (pH 6.8) at 35°C (+ 2) contained in 250 ml wide mouth beaker. Samples, each of 5 ml were withdrawn from the beaker at 1,2,3,4,5, and 6 hours.

The samples were assayed spectrophotometrically at 287 nm²⁴ for flufenamic acid and 288 nm for mefenamic acid after appropriate dilution. Equal amount of buffer was added to the beaker in order to maintain a constant volume.

In-Vivo Studies:

Male albino rabbits; 1½ - 2 kg were fed a regular diet with no restriction on food and water consumption. Each rabbit was used for one formula; the hair of an area of 8x12 cm was shaved on both side of the back of the rabbit with depilatory cream (opilca). This locations were selected to prevent the rabbits from ingesting any ointment by licking the application area.

The cream was then washed out from the skin²⁵. The shaved area was exposed to chemical inflammation (5% p. cresol). One gram of medicated ointments was applied to a shaved inflamed area, the other inflamed area of the rabbit was used as control through application of the respective ointment base. The treatment was repeated every day for ten days.

RESULTS AND DISCUSSION

In-Vitro Release Studies:

Figures 1,2 represent release rate of flufenamic and mefenamic acid from investigated ointment bases. From the figures it is clearly abovious that the release rate pattern of flufenamic acid is much higher than that obtained with mefenamic acid. However, the sequence of the release rate pattern of flufenamic and

mefenamic acid^d was observed to be the same from the various ointment bases. The higher release of flufenamic acid may be attributed to its higher water-solubility compared to mefenamic acid. From the kinetic data it is generally noticed that, the release rate of both drugs from the investigated ointment bases was found to follow the first order kinetics.

The results also revealed that, polyethylene glycol base showed the highest release value than emulsion and absorption ointment bases for both flufenamic and mefenamic acids. These highest release values may be attributed to the rapid dissolution of the base in water and the possible solubilizing effect of the base component on these water-insoluble drugs^{26,27}.

Incorporation of flufenamic and mefenamic acids in emulsion ointment bases showed intermediate release values. However, the release of both drugs from W/O emulsion base was higher than that obtained in case of O/W emulsion bases. This may be due to the possible oil solubility of both drugs and the effect of the surfactant on the permeability of the membrane which may be higher in case of span rather than tween²⁸.

Release rate of flufenamic and mefenamic acids from absorption ointment base was lower than those obtained from the other investigated ointment bases. This may be attributed to the hydrophobic nature of the absorption base which renders them immiscible with the surrounding aqueous medium, and thus allowing only a poor contact between the two phases. These results are in agreement with the finding of Macht²⁹ who stated that, the drug incorporated in fatty base exhibited the least drug-releasing property among other types of bases.

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In-Vivo Anti-inflammatory Effect:

Anti-inflammatory effect of flufenamic and mefenamic acids released from investigated ointment bases was evaluated as the extent of decrease in redness of the inflamed area. The results shown in figures 3.4.5 indicated that incorporation of both drugs in absorption base enhanced the anti-inflammatory effect and significantly inhibited inflammation on the treated skin at a rate higher than the other ointment bases, although the effect was almost the same for both absorption and W/O emulsion bases at the first three days.

The higher anti-inflammatory effect from absorption base may be attributed to the occlusive nature of base which facilitates the penetration of drugs.

It was also found that anti-inflammatory effect of drugs from water-in-oil emulsion base was higher than that from oil-in-water system. This may be explained by the fact that in case of W/O emulsion; the drug resided almost totally within the oil phase, and was easily released from the base to the skin while in case of O/W emulsion system the drug resided totally within the dispersed phase; hence the release was decreased. Further; W/O emulsion base performed an occlusive effect on the skin thus facilitated drug penetration through the skin. The water-soluble base showed the lowest anti-inflammatory effect and a longer time for complete healing than that obtained with other ointment bases. This may be due to the nature of water-soluble base retarding the drug penetration from the ointment base.

From the previous results it can be concluded that the anti-inflammatory effect of flufenamic and mefenamic acids can be controlled by the type of ointment base.

The investigated ointment bases can be arranged in a decreaseing order according to the anti-inflammatory effect after topical application of either drugs to the inflamed skin as follows: Absorption base > W/O emulsion base > O/W emulsion base > water-soluble base.

Trials to find out any correlation between in-vitro and anti-inflammatory effect of both drugs from different ointment bases under investigation showed that there is only a correlation between the in-vitro release from emulsion ointment base (W/O-O/W) and anti-inflammatory effect, thus showing the limitation of the in-vitro release studies to predict the in-vivo efficiency of drug in ointment forms.

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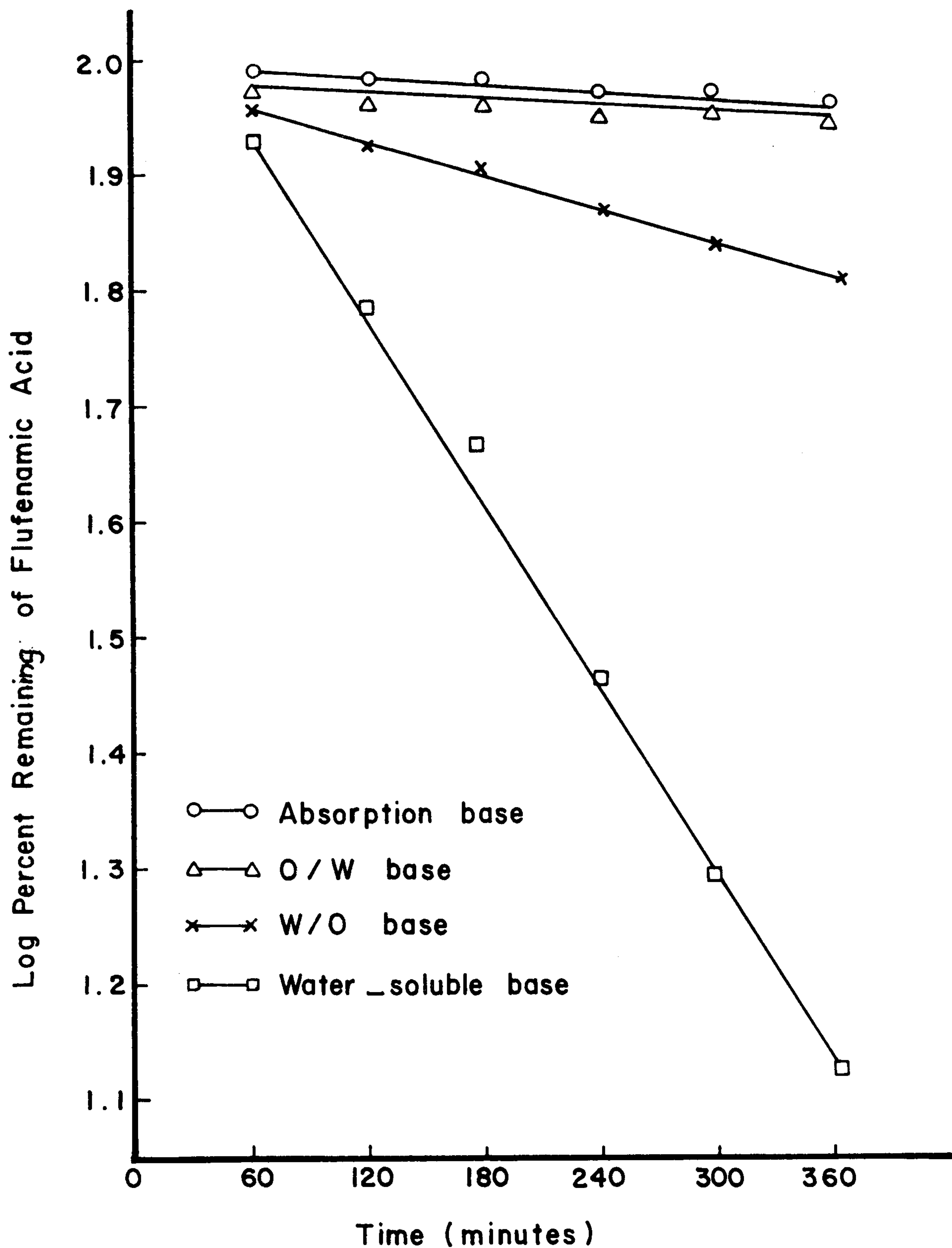


Fig.(1): Release Rate of Flufenamic Acid From Different Ointment Bases.

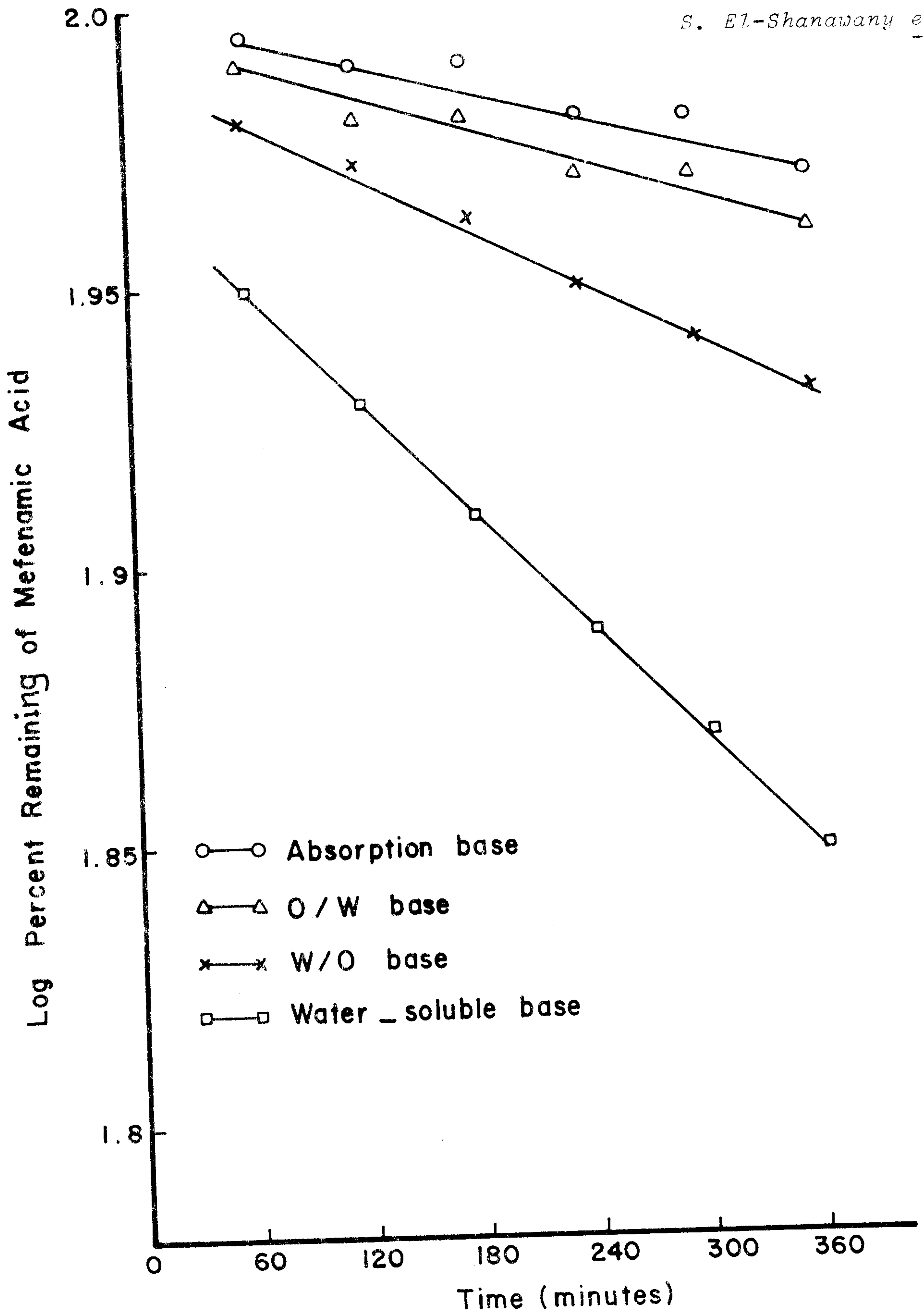


Fig.(2): Release Rate of Mefenamic Acid From Different Ointment Bases .

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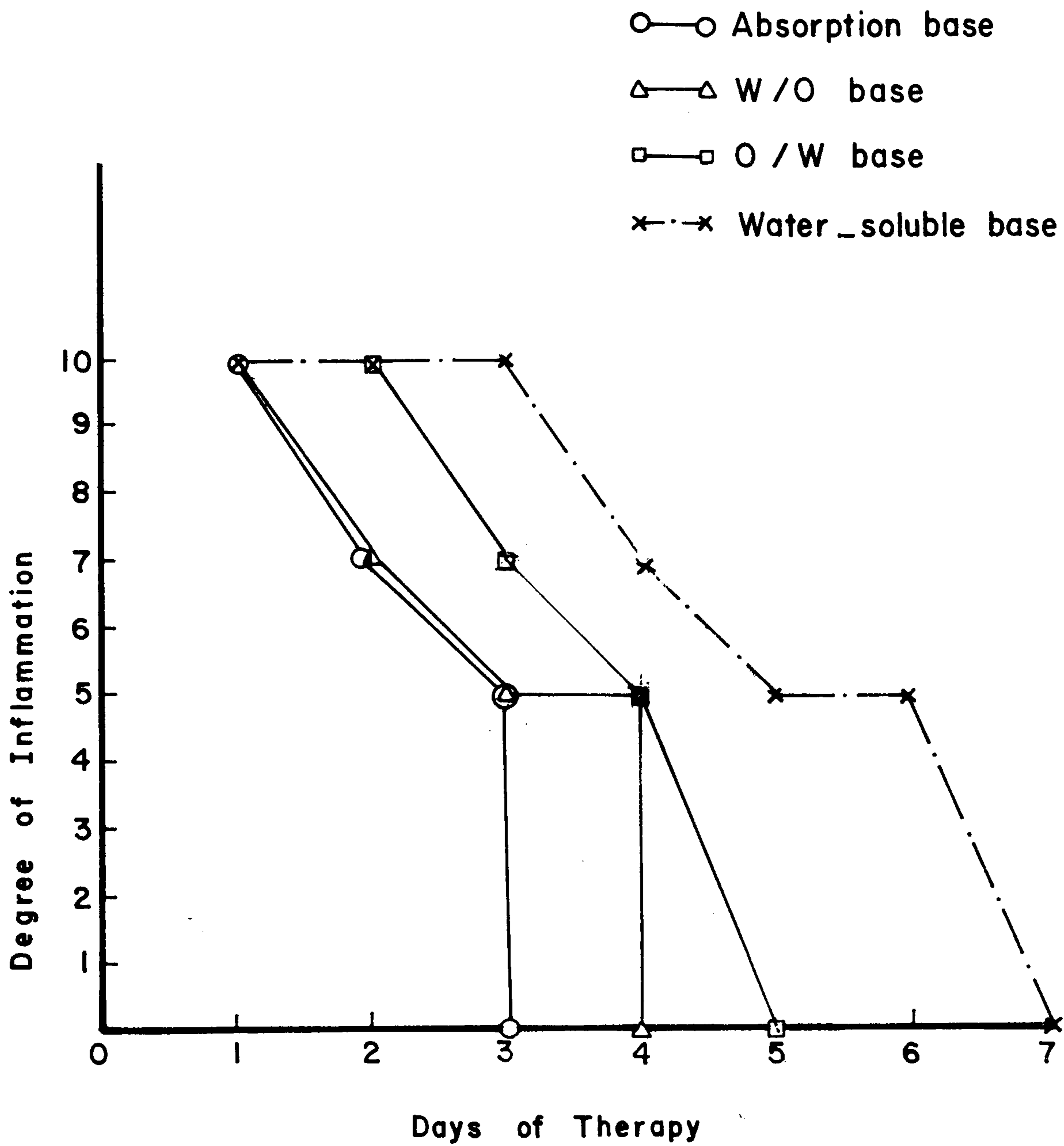


Fig.(3): Effect of Flufenamic Acid Ointment Applied Topically on Inflamed Rabbit Skin.

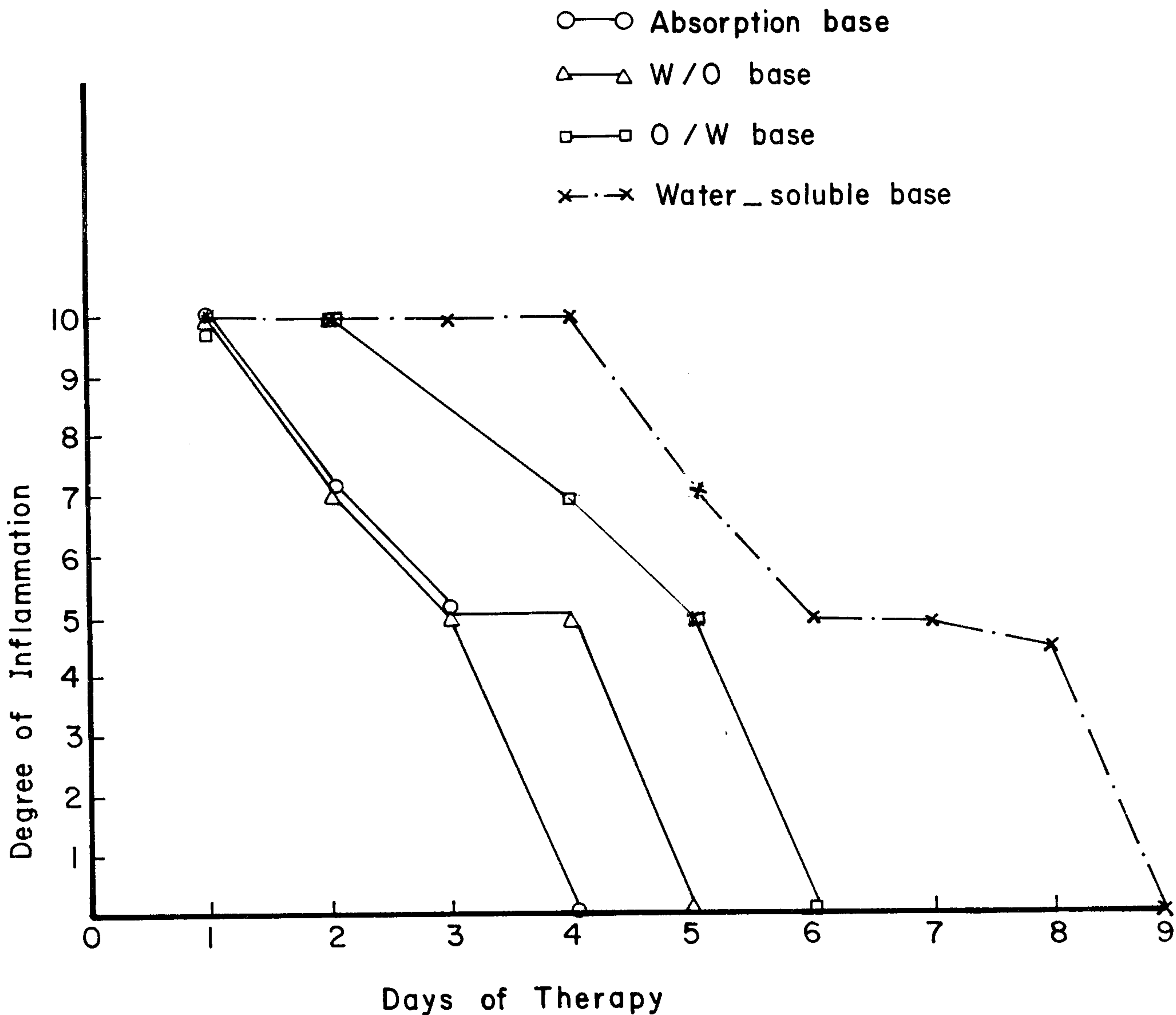


Fig.(4):Effect of Mefenamic Acid Ointment Applied Topically on Inflamed Rabbit Skin.

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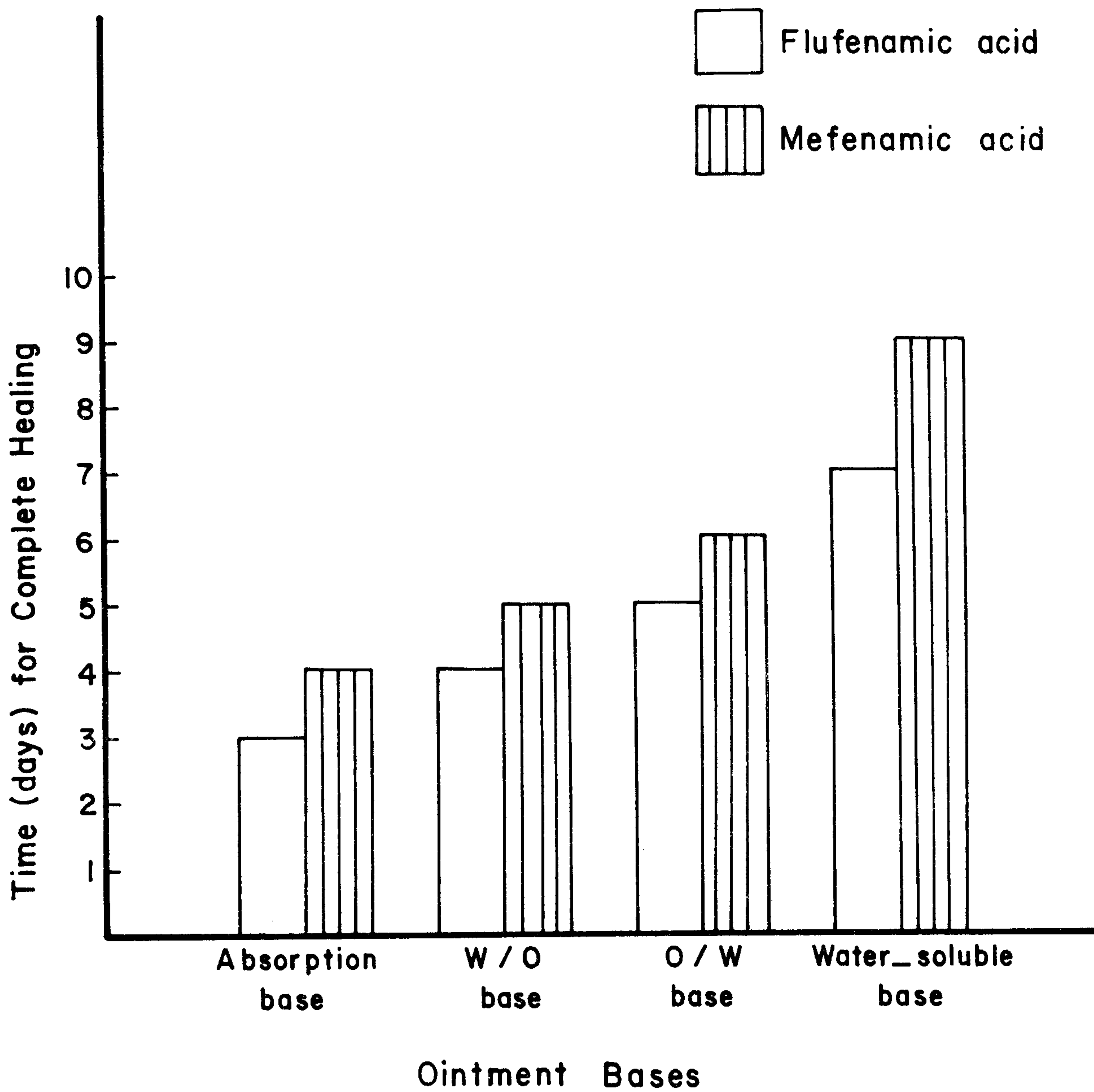


Fig.(5):Effect of ointment Bases on Healing of Inflamed Rabbit Skin .

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" صياغة وتقييم بعض الأدوية المضادة للالتهابات
للاستعمالات السطحية "

١ - المراهم

سهير الشنوانى - سلوى صفوت - السيد على ابراهيم
قسم الصيدلانيات - كلية الصيدلة - جامعة أسيوط .

فى هذا البحث تم دراسة تأثير نوع قاعدة المرهم على الانطلاق
المعملى والتأثير المضاد للالتهابات لكل من حمض الفلوفيناميك وميفيناميك .
وكانت قواعد المراهم المستخدمة هى قاعدة مرهم تذوب فى الماء وقاعدة ممتصة
للماء ومستحلب الزيت فى الماء ومستحلب ماء فى الزيت .

وقد أثبتت النتائج الآتى :-

- ١ - ان معدل وكمية الانطلاق المعملى للعقارين تتأثر كثيرا بنوع قاعدة
المرهم وطبيعة الدواء المستخدم وأمكن ترتيب قواعد المراهم حسب
انطلاق كل من حمض فلوفيناميك وميفيناميك منها الى القاعدة التى
تذوب فى الماء ، قاعدة ممتصة للماء ، مستحلب ماء فى الزيت .
- ٢ - من نتائج التأثير المضاد للالتهابات لكل من العقارين وذلك بوضع
المرهم لعدة أيام على أنسجة جلد الأرانب الملتهبة (كيميائيا)
باستخدام ٥% كريسول أمكن ترتيب قواعد المراهم ترتيبا تنازليا
حسب تأثيرها المضاد الى :-
قاعدة ممتصة للماء ، مستحلب الماء فى الزيت ، مستحلب الزيت فى الماء
قاعدة تذوب فى الماء .
- ٣ - ولقد أجريت محاولات لايجاد علاقة بين الانطلاق المعملى والتأثير
المضاد للالتهابات لكل من الفلوفيناميك والميفيناميك ووجدت علاقة
فقط قاعدة مستحلب الزيت فى الماء والماء فى الزيت .