

RELEASE STUDY OF DEXAMETHASONE FROM DIFFERENT OINTMENT BASES

F.S.Habib and S.M.El-Shanawany

*Department of Pharmaceutics, Faculty of Pharmacy,
Assiut University, Assiut, Egypt.*

ABSTRACT

The effect of various additives on the release of dexamethasone from different ointment bases was investigated. It was found that the rate of dexamethasone release was greater from water-soluble base and oil-in-water emulsion ointment base than from oleaginous, absorption or water-in-oil emulsion bases. Propylene glycol followed by glycerin exhibited the best effect on the amount of drug release with the different concentrations used. The incorporation of water in the water-in-oil emulsion base decreased the rate of drug release (even less than the control) than any of the other additives. It was also concluded that the best release of dexamethasone was obtained from the bases which were of similar nature to the diffusion medium. Other factors such as the characteristics of bases and the additives as well as their effect upon the solubility of the drug in the mixture may play a part.

INTRODUCTION

The in-vitro release of dexamethasone, an anti-inflammatory drug, from topical vehicles may offer useful information on some physicochemical factors involved in the in-vivo absorption. Such important parameters as the diffusion coefficient and solubility of a drug in a vehicle can be calculated by relatively simple equations, derived from mathematical models describing the process of in-vitro release of drugs dissolved¹⁻³ or suspended^{1,4-7} in ointment bases. In practice, these equations are used rarely, since their use is restricted by theoretical requirements whose fulfilment are difficult to realize and to verify in most experimental systems^{3,8-10}.

Many in-vitro procedures have been widely used to study the drug release from various types of pharmaceutical preparations, especially ointments^{2,9}. The diffusion method has been widely used for investigating heterogeneous preparations such as ointments¹¹ and emulsions¹².

It was found that the rate of release and the degree of penetration of the drug through the site of application depend mainly upon its solubility in the body fluids^{13,14}, the base¹⁵ or the other incorporated active ingredients^{16,17}.

The purpose of this work was to study the in-vitro release of dexamethasone from an oleaginous, absorption, two emulsion types (o/w and w/o) and a water soluble base (polyethylene glycol 400 with veegum). The effect of different additives on the drug release was also studied. The release of dexamethasone from each base without additives was considered as the control.

EXPERIMENTAL

Materials

Dexamethasone (Sigma Chemicals, St., Louis, USA), White soft paraffin, liquid paraffin, and glycerin (BDH, Poole, England), cetyl alcohol and Tween 80 (Merck, Darmstadt, GFR), Propylene glycol (Carl Roth, W.Germany), 1-octanol (Prolabo). Semipermeable Fischer cellulose membrane 30/32 (Fischer Scientific Co., London, England). All other chemicals are of reagent grade.

Methods

The following formulations of the various ointment bases were prepared (% w/w) :

- Oleaginous base : white soft paraffin 100
- Absorption base : wool fat 10, liquid paraffin 10, white soft paraffin 80.

Release Study of Dexamethasone From Different Ointment Bases.

- Water soluble base : PEG 400 37, veegum 8, water 5.
- Emulsion base : water-in-oil : white petrolatum 64, Span 65, water to 100.
Oil-in-water : Cetyl alcohol 25, white soft paraffin 25, glycerin 12, Tween 80 5, distilled water 33.

The additives used were : water, propylene glycol, glycerin and cetyl alcohol in concentrations : 2.5, 5 and 10 % w/w of each.

Solubility Determination :

The solubility of dexamethasone was determined in water at 37°. About 100 mg of dexamethasone was placed in 20 ml of water, in 50 ml screw capped tubes. The tubes were placed horizontally on a shaker in a water-bath, and shaken at 100 r.p.m. until the equilibrium was reached. This stage was determined by repetitive sampling. The concentration determination was made by UV absorption measurement at 239 nm.

Solubility of dexamethasone in PEG 400 and liquid paraffin was determined because it is the major component of different types of ointment bases, and the solubility of dexamethasone in these vehicles could give an indication of its solubility in other similar semisolid or solid components of the ointments used. These solubility determinations were made by incorporating known amounts of material in increasing amounts in a known quantity of solvent. The solubility values of dexamethasone in the PEG 400 and liquid paraffin were accepted as the highest concentrations that could be solubilized in the referred solvents.

Partition coefficient determination :

10 ml of water (containing 1 mg dexamethasone) was added to 10 ml octanol, in 50 ml screw capped tubes. The tubes were shaken on a horizontal shaker at 37° until no difference was observed between the repetitive sampling. The water and octanol phases were separated and assayed for dexamethasone concentration. The results of these experiments are shown in Table 1.

Preparation of Ointments :

The ointments were prepared by fusion on a water-bath. White soft paraffin was used as supplied. The drug was added to the warm base and the mixture was stirred until cooled. Water, glycerin, propylene glycol and cetyl alcohol were mixed with the ointments just prior to use to minimize loss by evaporation. The ointments incorporated with the additives (water, glycerin, propylene glycol or cetyl alcohol (2.5, 5 or 10% w/v) were still semisolid. Water-soluble base was prepared by soaking veegum in the specified amount of water. PEG 400 was added with stirring until homogeneity. The concentration of dexamethasone was 0.1 % w/w in all bases. The prepared ointments were subjected to drug release evaluation using the dialysis method¹⁶. All the ointments prepared were of suspension type (drug particle size : 90-120 μ)

In-vitro Release of Dexamethasone from Various Ointment Bases :

The ointment (1 g) was accurately weighed and placed on a semipermeable Fischer cellulose membrane 30/32 and the method was completed as reported by Attia et al., 1981¹⁷. The samples withdrawn were assayed spectrophotometrically at 239 nm after appropriate dilutions equal amount of water was returned to the beaker in order to maintain a constant volume. Dexamethasone was found to obey Beer's law in the concentration range found in the diffusion medium.

Although viscosity measurements were not carried out in these ointment bases the quantities added to the various bases were so small and therefore they were expected to have little effect upon their viscosities and consequently the in-vitro release of dexamethasone

Release Study of Dexamethasone From Different Ointment Bases.

RESULTS AND DISCUSSION

Oleaginous Base :

The release of dexamethasone from white soft paraffin is given in Fig. 1. The effect of different concentrations of additives on the released amount of dexamethasone is clearly seen in this Figure. It was noticed that the diffusion of dexamethasone from white soft paraffin base proceeded very slowly and gave the least amount released if compared with the other bases under investigation. On the other hand, the four liquid additives used were found to increase the rate of release of this drug. The effect of propylene glycol was greater than glycerin and the latter was better than both water or cetyl alcohol. It was also observed that the increase in concentration of additives achieved a progressive increase in the amount of drug diffused. On the other hand. The increased concentration of each liquid did not exhibit the same increased rate of release as shown in (Fig. 1).²

Absorption Base :

It was found that all the liquid additives significantly increased the diffusion of dexamethasone from this base. The addition of propylene glycol was found to have a more pronounced effect on the diffusion of this drug especially on using 10% w/w concentration as shown in Fig. 1, followed by glycerin which was better than water or cetyl alcohol.

Water-soluble base :

Generally all the used additives increased the diffusion of dexamethasone from this base, but propylene glycol in all its concentrations significantly increased the release of this drug from the base as shown in Fig. 3. 10% w/w propylene glycol produced the best results.

Glycerin was also found to have a pronounced effect of the diffusion of the drug especially on using 10% w/w concentration. Although water and cetyl alcohol increased the diffusion of the drug from the base, the increase was minor.

W/O Emulsion base :

Propylene glycol was found to exhibit the best effect on the amount of drug release with the different concentrations used. This effect was more pronounced especially on using 10% w/w concentration. It was noticed that water in all added proportions decreased the amount of drug release from the base if compared with the control .

On the other hand the incorporation of 2.5% w/w cetyl alcohol in the base markedly decreased the diffusion of the drug. While 5 and 10% (w/w) concentration increased the release of the drug from the base. Glycerin in all proportions increased the amount of drug released (Fig. 2).

O/W Emulsion base :

It was found that all the liquid additives increased the diffusion of dexamethasone from this base. Propylene glycol exhibited the best effect on the amount of drug release with different concentrations used (Fig. 2). On the other hand, glycerin in all the concentrations used markedly increased the diffusion of the drug followed by water and lastly cetyl alcohol. There was no considerable difference in drug release of 1% (w/w) of cetyl alcohol was incorporated with the base. Also there no difference if 2.5 or 5% (w/w) of water was incorporated as shown in Fig. 2 .

From the previous results it can be concluded the rate of diffusion of dexamethasone was mainly affected by the type of the base. Water-soluble base followed by o/w emulsion base

Release Study of Dexamethasone From Different Ointment Bases.

were the best for exhibiting considerable release than the other used bases. This may be due to the hydrophilic character reflected by PEG and veegum which build up channels of water sufficient to drug dexamethazone out of the ointment with regard to the o/w type the miscibility of the external phase (water) in the emulsion with the external diffusion medium lead to an increase in the amount of drug released in case o/w or oleaginous base the external phase is non polar and immiscible with the polar diffusion medium and hence the observed retardation in drug release.

Absorption base was capable to increase the amount of drug release to be approximately twice that released from the oleaginous base due to its ability to allow water to penetrate in for extracting the drug out of the ointment if compared with the oleaginous base. The solubility of the drug in the ointment base undoubtedly plays a major role in its diffusion from the base. Some investigators used liquids to simulate the single components ointment bases and correlated the rate of diffusion from them with that occurred from the bases¹⁷.

Mixing of the different liquid additives with the base can also affect the rate of release of the drug. In the case of dexamethasone, it was found that the incorporation of water and cetyl alcohol with all bases studied was found to give slower rate of release than did propylene glycol and glycerin. On the other hand the base which is of similar nature to the diffusion medium e.g. water-soluble base and o/w emulsion base afforded a relatively greater rate of release.

The results were found to be in accordance with those reported by Whitworth and Stephenson⁹. They have mentioned that the diffusion measurements showed no apparent correlation to the solubility of atropine in the base. The present results also show that the rate of release of dexamethasone was dependent on both characteristics of the base, the additives and

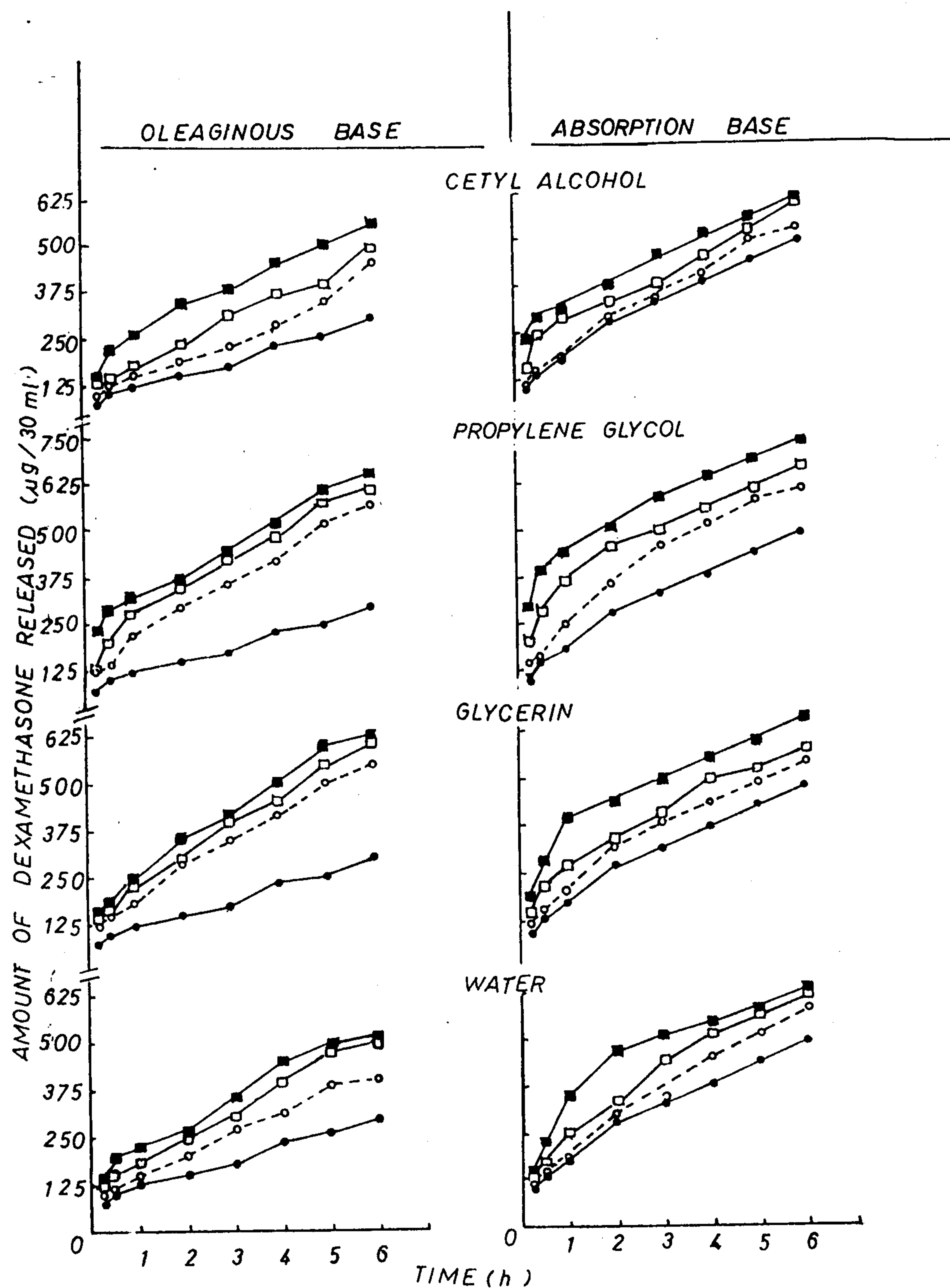
this solubility of the drug in the mixtures (Table 1). This was in agreement with Whitworth¹⁸ who investigated the effect of liquid on the release of atropine sulphate from other ointment bases.

In conclusion, the release of dexamethasone from the test ointment bases is dependent on its situation in external or internal phase, the hydrophilic nature of the base as reflected by additives, and the solubility of the drug in the base. Although, the effect of these factors seems intermingled, yet the main criterion is the building up of water channels in the base that allows for the extraction of the drug out of the base. Nevertheless, prolonged release dexamethasone ointments could be formulated via the build of minor channels. Meanwhile, quickly released base, could be formulated using greater channels for the drug embedded in external hydrophilic, base. The use of a solvent e.g., propylene glycol in the base helps dragging of the drug according to its concentration i.e. its capability of dissolving dexamethasone.

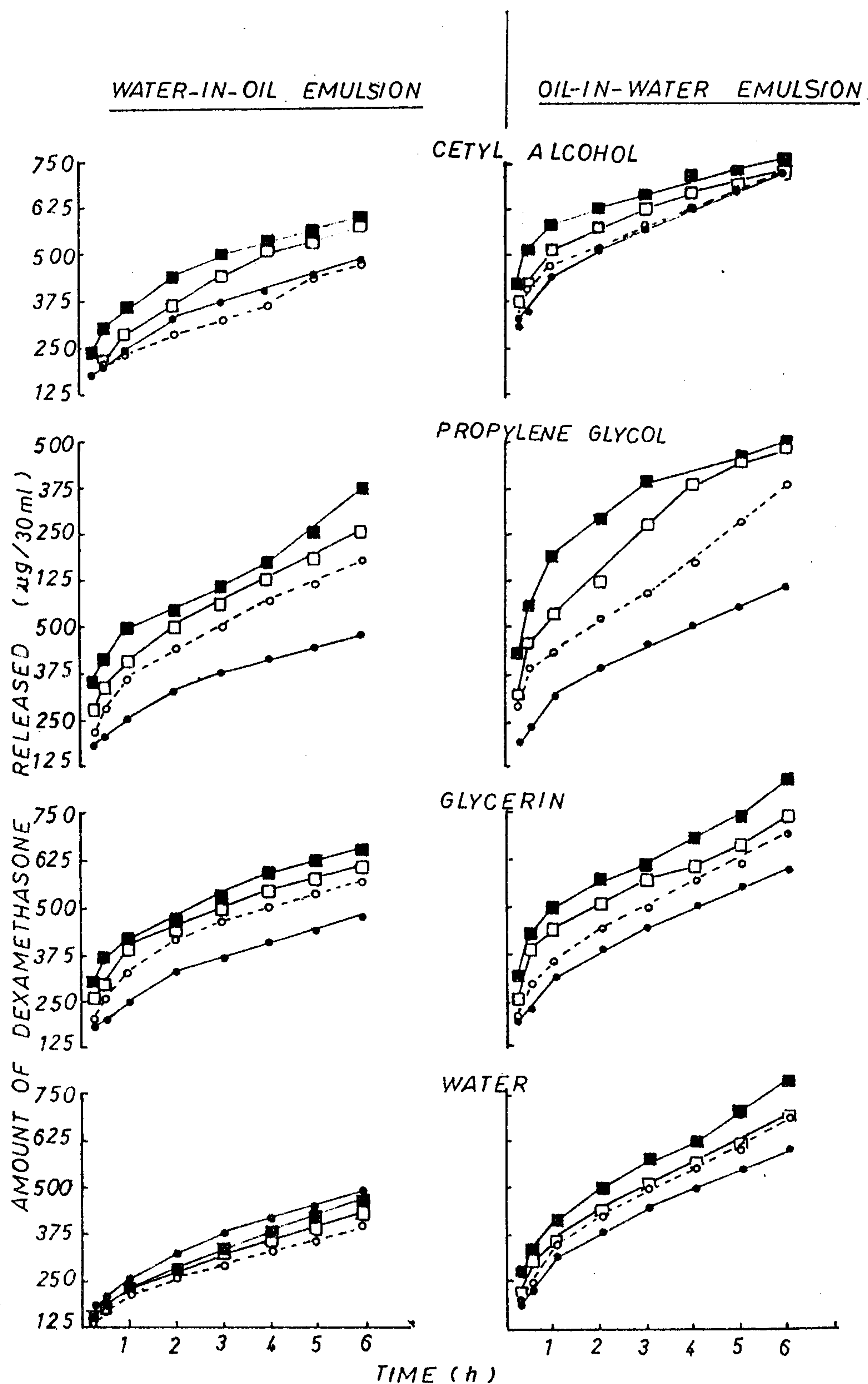
Table. 1. Some Physicochemical Properties of Dexamethasone.

-	<u>Solubility :</u>	
	In water (37°)	0.109 mg/ml
	In PEG 400 (37°)	3.400 mg/ml
	In Liq. paraffin (37°)	0.095 mg/100 ml
-	Partition coefficient(octanol/ water).	0.377

Release Study of Dexamethasone from Different Ointment Bases

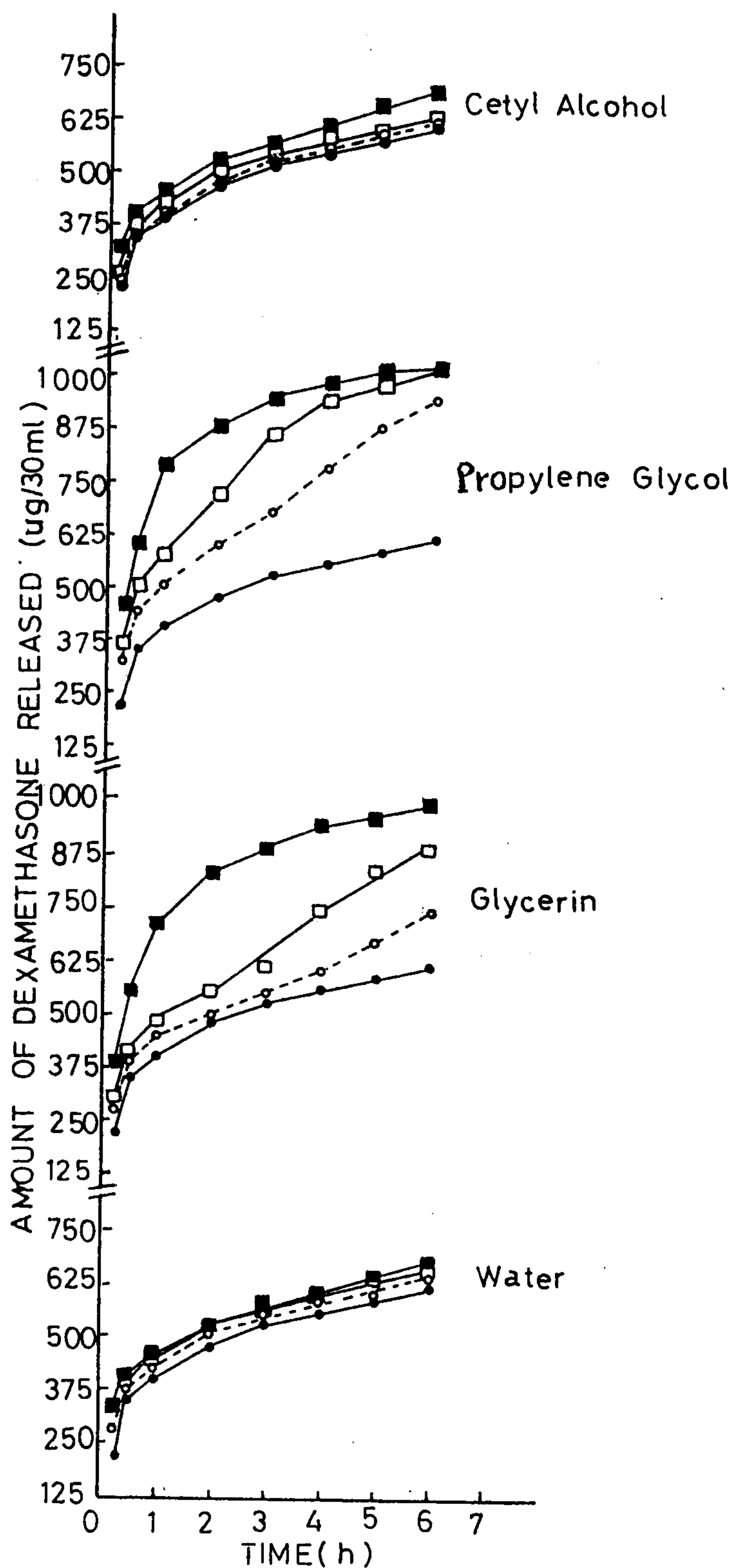


Fig(1) Release of Dexamethasone from Oleaginous and Absorption Bases Containing Various Additives.
 Key: \bullet , Control; \circ , 2.5%(w/w); \square , 5%; \blacksquare , 10% Additives.
 (each point represents the mean of three readings.)



FIG(2) RELEASE OF DEXAMETHASONE FROM EMULSION (water in-oil-and oil-in-water) BASES CONTAINING VARIOUS ADDITIVES. Key: \bullet , Control; \circ , 2.5% (w/w); \square , 5%; \blacksquare , 10% Additives. (each point represents the mean of three readings.)

Release Study of Dexamethasone from Different Ointment Bases



FIG(3) RELEASE OF DEXAMETHASONE FROM WATER SOLUBLE BASE CONTAINING VARIOUS ADDITIVES.

Key: ●, Control; ○, 2.5% (w/w); □, 5%; ■, 10% Additives.
(each point represents the mean of three readings.)

REFERENCES

- 1) T.Higuchi, J. Soc. Cosmet. Chem., 11, 85 (1960).
- 2) W.I.Higuchi, J. Pharm. Sci., 51, 802 (1962).
- 3) Idem, 56, 315 (1967).
- 4) Idem, 50, 874 (1961).
- 5) Idem, 52, 1145 (1963).
- 6) T.J.Roseman, and W.I.Higuchi, J. Pharm. Sci., 59, 353 (1970).
- 7) T.J.Roseman, Ibid., 61, 56 (1972).
- 8) A.L.Weiss and B.J.Sciarrone, Ibid., 58, 980 (1969).
- 9) C.W.Whitworth and R.E.Stephenson, Ibid., 60, 48 (1971).
- 10) J.Haleblan, R.Runkel, N.Mueller, J. Christopherson and K.NG., Ibid., 60, 541 (1971).
- 11) K.C.Patel, G.S.Banker and H.G.Dekay, J. Pharm. Sci., 50, 300 (1961).
- 12) T.Kouizumi and W.I.Higuchi, J. Pharm Sci., 57, 87 (1968).
- 13) J.B.Shelwire, Arch. Dermatol., 82, 24 (1960).
- 14) D.E.Wurstr and S.F.Kramer, J, Pharm. Sci., 50, 288 (1961).
- 15) W.Clyde and E.Robert, J. Pharm. Sci., 60, 48 (1971).
- 16) M.A.Attia, Ph.D.Thesis, First Medical Institute, Moscow (1978).
- 17) M.A.Attia, A.E.Aboutaleb and F.S.Habibb, Pharmazie 36, 4.1 (1981).
- 18) C.W.Whitworth and R.E.Stephenson, Canad. J. Pharm. Sci., 10, 89 (1975).

فوزية سيد حبيب - سهر مصطفى الشنوانى
قسم الصيدلانيات - كلية الصيدلة - جامعة أسيوط

تم فى هذا البحث دراسة تأثير الاضافات المختلفة على معدل انطلاق العقار من قواعد المراهم المختلفة . وقد وجد أن معدل انطلاق العقار كان أعلى ما يمكن من القاعدة التى تذوب فى الماء وقاعدة الاستحلاب زيت فى ماء وذلك بالمقارنه بالقاعدة الدهنية أو قاعدة الامتصاص أو قاعدة الاستحلاب ماء فى زيت .

وقد أبدى جليكول البروبيلين ثم الجلسترين أحسن تأثير على كمية العقار المنطلقة في كل التركيزات التي استعملت فيها .

وقد اتضح أن إضافة الماء الى قاعدة الاستحلاب ماء فى زيت قللت من معدل انطلاق العقار (حتى أقل من الكنترول نفسه) أكثر من أى إضافة أخرى . وقد استنتج أيضا أن القواعد ذات الطبيعة المتشابهة للوسط المحيط أعطت أفضل انطلاق للعقار كما وجدت عوامل أخرى مثل مواصفات القواعد والإضافات الى جانب تأثير كل منهم على ذوبان العقار فى المخلوط لعبوا أيضا دور آخر فى معدل انطلاق العقار .