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# DRUG RELEASE FROM PLURONIC GELS

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الغرض من هذه الدراسة هو دراسة انطلاق بعض الهرمونات مثل بروجستيرون، ايثينيل استراديول وديكساميثازون وعقار آخر هو الفا – ميثيل دوبا من مستحضرات بلورونك الهلاميه.

وفي هذا المجال تم بحث تأثير اختلاف تركيز الهرمونات والفا ميثيل دوبا في الهلاميات المحضرة من ١٢٧–ف عند درجة حرارة ٣٠ درجة مئوية وكما تم دراسة تأثير اختلاف تركيز المادة الهلامية ١٢٧–ف ونوع المادة الهلامية من ناحية الوزن الجزيئى على انطلاق الادوية. وكذلك تم دراسة تأثير ارتفاع درجة الحرارة عن معدل انطلاق الادوية من المستحضرات الهلامية ١٢٧–ف.

وبدراسة النتائج وجد أن معدل انطلاق العقار يتبع نظام الانتشار وانه يزداد مع زيادة تركيز البروجستيرون ويقل مع زيادة تركيز الفا ميثيل دوبا وكذلك يقل مع زيادة درجة الحرارة ومع زيادة تركيز المادة الهلامية ويزداد المعدل كلما زاد الوزن الجزيئى للمادة الهلاية.

*The release rate of progesterone, dexamethasone, ethinylestradiol and α-methyldopa$^{(MD)}$ was determined in aqueous gels of pluronic surfactants (F-65, F-127, F-123) and the effects of concentration and temperature were investigated. The release of drugs from pluronic F-127 could be described by the diffusional model and the rate-controlling stage in the release process is diffusion of the dispersed drug through the matrix continuum. The release-rate decreased as the concentration of pluronic F-127 increased for both dexamethasone and progesterone; and increased as the molecular weight of the pluronic type increased (F-65 < F-123 < F-127) for ethinylestradiol.*

*While, the release rate of α-methyldopa$^{(MD)}$; dexamethasone and ethinylestradiol decreased as increasing concentration of the drug and increasing the temperature, we found that increasing progesterone concentration and temperature; increased the release rate.*

## INTRODUCTION

The poloxamer polyols are series of closely related block copolymers whose molecular weights range from 1100 to over 14000. All are chemically similar in composition, differing only in the relative amounts of propylene and ethylene oxides. Their physical and surface active properties vary over a wide range[1].

Poloxamer 188 is one of a series of poly (oxyethylene) poly (oxypropylene) block polymers; pluronic F-127 (PF-127) Containing approximately 70% oxyethylene with nominal molecular weight of 11500[2].

Due to its unique molecular structure, PF-127 forms micelles in aqueous solution[3-4] and exhibits reverse thermal gelation in concentrations above 20%[2], good release characteristics and low toxicity[5].

Owing to its gelation characteristics, in association with its nontoxic nature[5], pluronic F-127 appears to have good potential for use in topical drug controlled or improved delivery systems. Pluronic F-127 has been evaluated as a vehicle for novel dosage forms, either for dermatological use [6] or ophthalmic application[5].

Morikawa *et al.*[6] have tested the feasibility of PF-127 as sustained-release vehicle for subcutaneous administration of interleukin. Miyazaki *et al.*,[7-8] suggested that indomethacin and tegafur preparations based on PF-127 aqueous gel may be practically useful as a rectal

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preparations with prolonged action and reduced side effects.

In recent years, PF-127 gels have been used for topical delivery as microemulsions[9] of indomethacin, diclofenac sodium, Lidocaine[4], Pilocarpine nitrate[7-8] hydrocortisone[10], $xfl^Xxrouracil and adriamycin[3]. Also, the release characteristics of PF-127 gels have been investigated by employing barbiturates[11] and benzoic acid derivatives[12] as model compounds.

Since PF-127 gels are assumed to consist of large populations of micelles[3-4], the solute release from the gels should be modified by the interaction of the solute with the micelles.

Previous work[13-15] demonstrated that hydrogels are excellent candidates for use in controlled-release drug delivery systems. The major advantages of these polymers for this purpose are biocompatibility[16] and the potential for controlling release characteristics.

The importance of the solute molecular volume on permeation characteristics has been demonstrated. A number of investigators[17] are developing PVA hydrogels for biomedical applications, particularly transdermal drug delivery systems, because of inherent low toxicity, good biocompatibility and desirable physical properties such as rubbery or elastic nature and high degree of swelling in water.

Anti-inflammatory drugs e.g. dexamethasone; progestational hormones as progesterone which has been used in the treatment of dysmenorrhea[18] and ethinylestradiol which is one of the most active estrogens, all the three drugs were selected to examine the release characteristics of them in pluronic F-127 gel. Estrogens are used as substitution therapy when menopausal symptoms occur after cessation of ovarian function and also useful in the treatment of atrophic or senile vaginitis, vulvo vaginitis or cervicitis resulting from hypoestrogenesis[18]. Another drug selected to the release study is α-methyldopa which is one of the centrally acting antihypertensive drugs used in the treatment of moderate to severe essential hypertension, including malignant hypertension[18].

The aim of this study is to extend the usefulness of pluronic F-127 gels for the topical delivery of the anti-inflammatory; the progestational hormones, and the anti-hypertensive drug to avoid the side effects following oral administration of those drugs. The in-vitro release characteristics of such drugs were investigated in relation to the effect of pluronic F-127 concentration and type, drug concentration and effect of temperature on the release rate.

## EXPERIMENTAL

### Material and Apparatus

- Dexamethasone (SIGMA Co. St. Louis, U.S.A.)
- Ethinylestradiol (Mead Johnson Co., U.S.A.)
- Progesterone (Biochemical Searle Comp. Opkin and Williams; England).
- α-methyldopa (Merck Sharp Co., Germany).
- Poloxamer F-123, 127, 68( A gift from BASF Wyandotte Corporation (N.J.; U.S.A).
- All other chemicals and solvents were of laboratory reagents.
- Spectrophotometer, UV/VIS - 150 - 02, Shimadzu (Japan).
- Thermostated Waterbath with Shaker (Unitronic 320 OR Selecta).
- Standard Cellophane membrane 32/36 (Fischer; England).

Methods

### 1- Preparation of PF.127 gels:

The required amount of PF-127 or PF-123 was placed in a beaker and dispersed in 0.05 M phosphate buffer PH 6.8 under constant agitation at 5°C[2]. The beaker was left over night in refrigerator to ensure complete dissolution. Upon complete dissolution of the pluronic eventually, a clear, viscous solution was formed; an appropriate amount of either of the drugs was added to the beaker. The solution was then brought to volume with the buffer and thoroughly mixed with a magnetic stirring bar while cold. Upon warming the mixture to room temperature, a clear viscous gel was formed.

**2- Determination of the release rate from pluronic gels.**

In-Vitro drug release from PF-127 gels was evaluated using standard cellophane membrane stretched at the end of the dialysis cell (2.5 cm in diameter and 10 cm *in* length)that used as a gel container (donor compartment). The acceptor compartment composed of glass beaker (250 ml) contains 150 ml phosphate buffer pH 6.8 as the releasing medium. Samples (5 ml) were determined by ultraviolet absorption spectrophotometrically at maximum wave length 247 nm; for progesterone; dexamethasone; ethinylestradiol and 289 nm for methyldopa. The presence of poloxamer did not interfere with the readings. Use control (plain gel) against the tested samples all over the release time. All experiments were carried out in triplicate and average values were plotted.

## RESULTS AND DISCUSSION

**Effect of PF-127 concentration on drug release:**

Figs. 1,2 (A and B) show the release of dexamethasone; progesterone and methyldopa as a function of the square root of time from 25% and 30% w/v pluronic F.127 gels at 30°C and 40 in phosphate buffer of pH 6.8. The initial concentration of each drug in gels was 0.25%; 0.5% and 1.25% w/v.

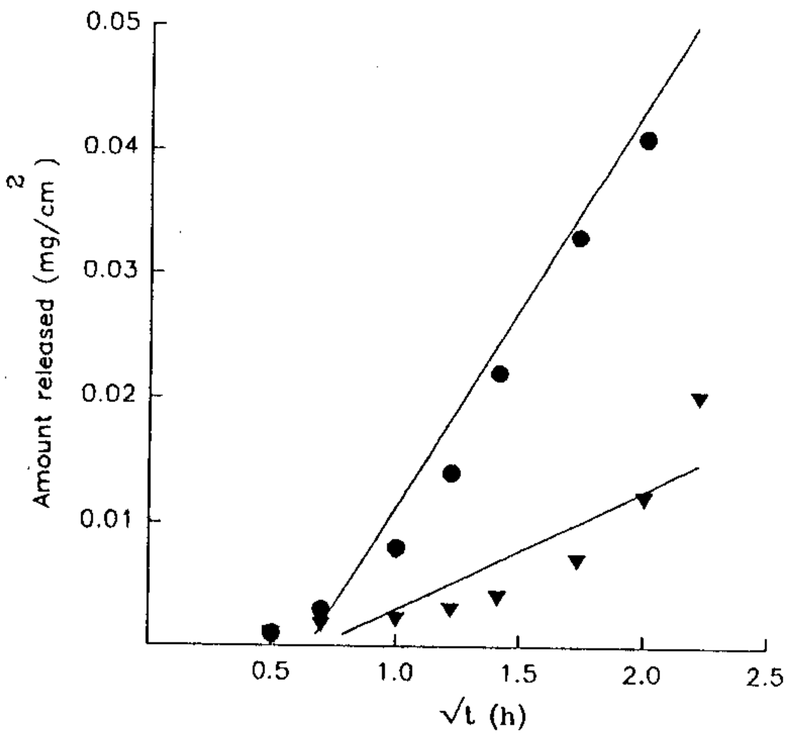



Fig. 1A: Release of progesterone from ( ▼ ) 30%, ( ● ) 25% w/v pluronic F−127 at 30°C.

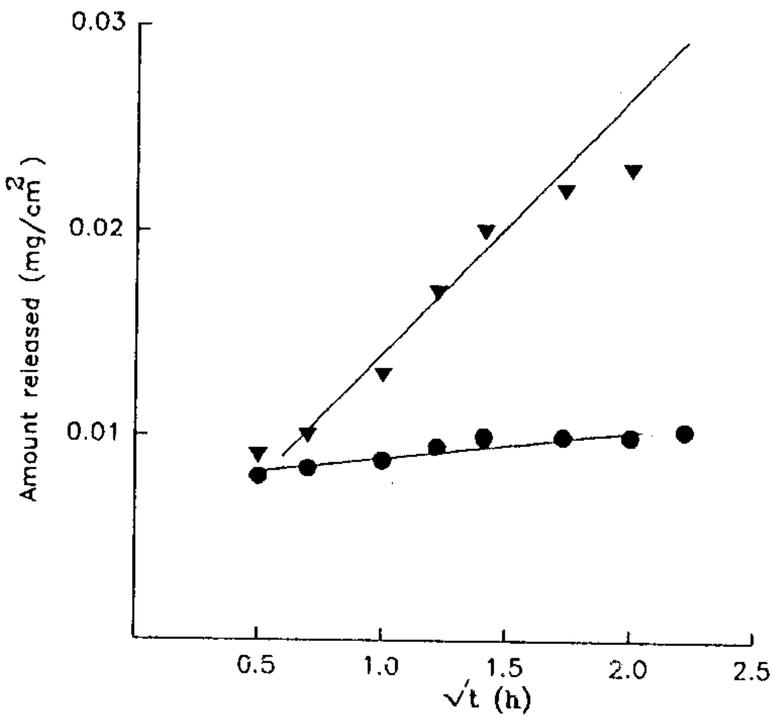



Fig. 1B: Release of dexamethasone from ( ▼ ) 30%, ( ● ) 25% w/v pluronic F−127 gel at 40°C.

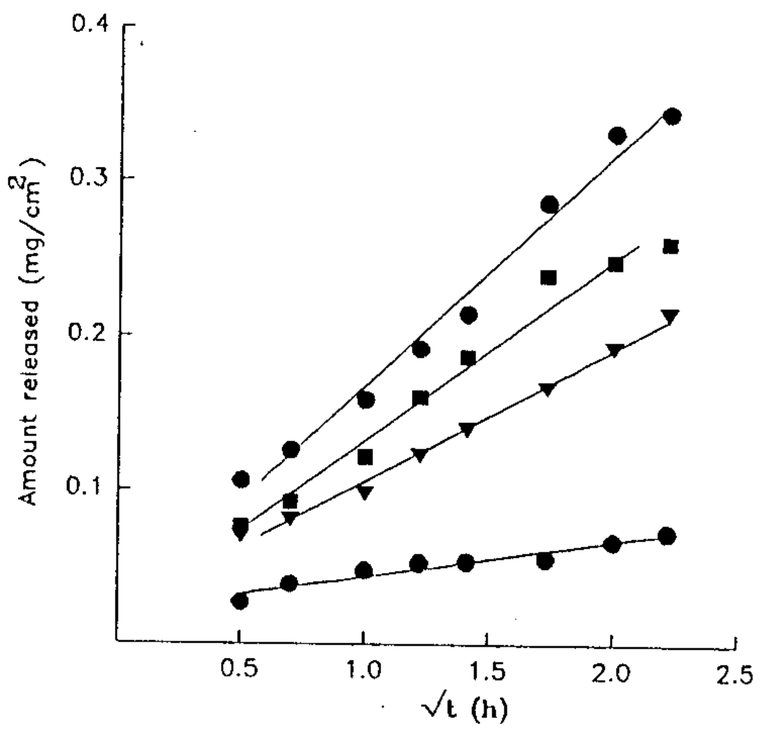



Fig. 2A: Release of α−methyldopa ( ● ) 0.25%; ( ■ ) 0.50%; ( ▼ ) 1.25% w/w and ( ● ) 1.50% from pluronic F−127 gel 30% w/v at 30°C.

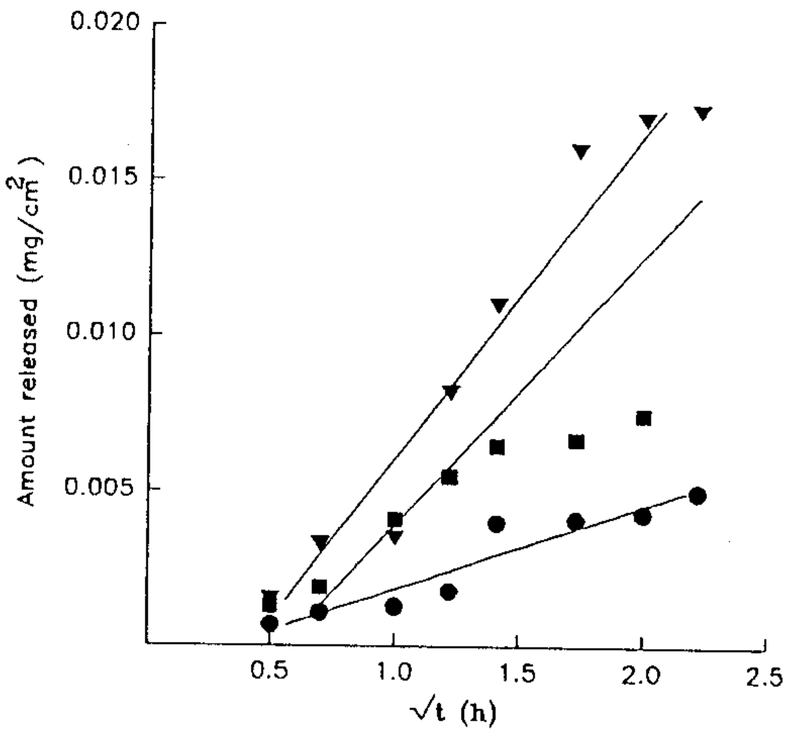



Fig. 2B: Release of progesterone from 30% pluronic F−127 gel at 30°C ( ● ) 0.25%; ( ■ ) 0.05%; ( ▼ ) 1.25% w/w.

**Table 1**: Effect of Pluronic F-127 concentration on drug Release at 30°C.

| Type of drug | Conc. of pluronic F-127 | Rlease-rate Slope | Intrecept | Correlation coefficient (r) |
|---|---|---|---|---|
| *Progesterone | 25 % | 0.0379 | $1.2574 \times 10^{-3}$ | 0.9511 |
| | 30 % | 0.0104 | $4.2881 \times 10^{-3}$ | 0.9729 |
| *Dexamethasone | 25 % | 0.0445 | 0.0478 | 0.9407 |
| | 30 % | 0.0166 | 0.0345 | 0.9859 |

Table (1) and fig. 1 (A and B) show the linear relationship between Q (cumulative amount of drug released per unit surface area) and the square root of time existed for dexamethasone and progesterone drugs.

The results indicate that the drug release from PF-127 gels could be described by the diffusional model and hence the rate controlling stage in the release process is diffusion of dispersed drug through the matrix continuum[19-20]

It can be seen in Figs 1,2 that, as the concentration of PF-127 increased, the release rate decreased, which agrees with the findings of earlier workers[7-12].

As, postulated, the mechanism for the reduced release-rate may be due in part to reductions in the numbers and dimensions of the aqueous channels through which solute diffuse[7].

In addition, since the PF-127 gels are believed to consist of large populations of micelles[7], the increased solubilization by the micelles resulting in a reduced concentration of diffusible solute is also highly probable.

**Effect of initial drug concentration on the release**

The effect of initial drug concentration on the release from 30% w/v PF-127 gels was studied at various drug concentrations (Table 2 (A and B) and Fig. 3).

Table 2 show the apparent release rate of methods defined by the slope of Q versus t plot, against the initial drug concentration in the gels. Also, from Table 2, we can see that as the concentration of progesterone increased, the corresponding release rate increased and the opposite was observed for α-MD due to the difference in solubility between the drugs in the gel base.

**Table 2A**: Effect of α-methyldopa concentration on the Release rate from pluronic F-127 gel (30% w/v) at 30°C.

| Conc. % w/w | Rlease-rate Slope | Intrecept | Correlation coefficient (r) |
|---|---|---|---|
| 0.25 | 0.1675 | 0.0374 | 0.9934 |
| 0.50 | 0.1482 | 0.0202 | 0.9923 |
| 1.25 | 0.1166 | 0.0161 | 0.9869 |
| 1.50 | 0.0855 | 0.0205 | 0.9967 |

**Table 2B**: Effect of progesterone concentration on the Release rate from pluronic F-127 (30% w/v) at 30°C.

| Conc. % w/w | Rlease-rate Slope | Intrecept | Correlation coefficient (r) |
|---|---|---|---|
| 0.25 | 0.00265 | 7.9813 | 0.9507 |
| 0.50 | 0.0104 | 4.2881 | 0.9729 |
| 1.25 | 0.0622 | 0.0439 | 0.9851 |

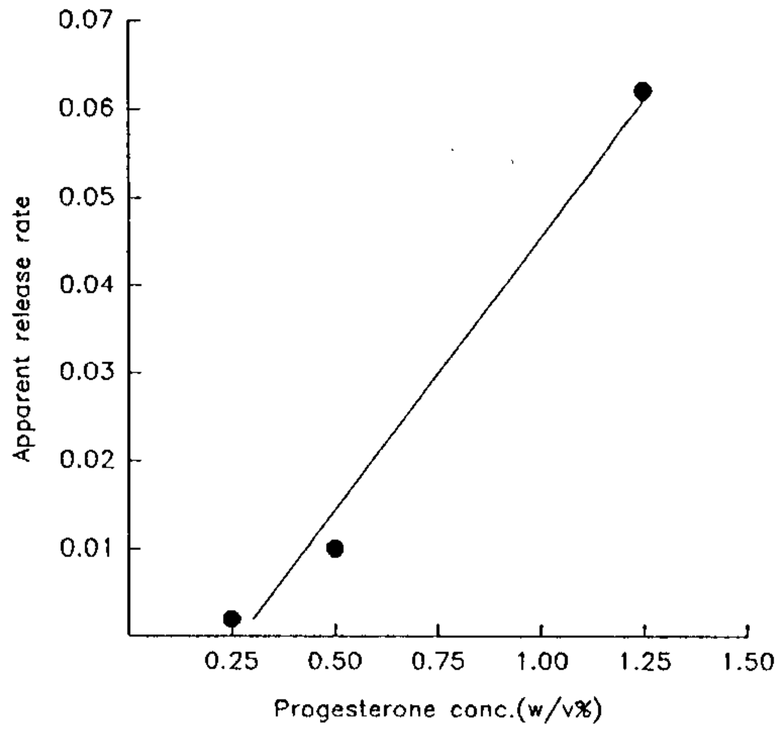



Fig. 3: Relationship between the apparent release rate of progesterone and the initial drug concentration in 30% w/v pluronic F-127 gels.

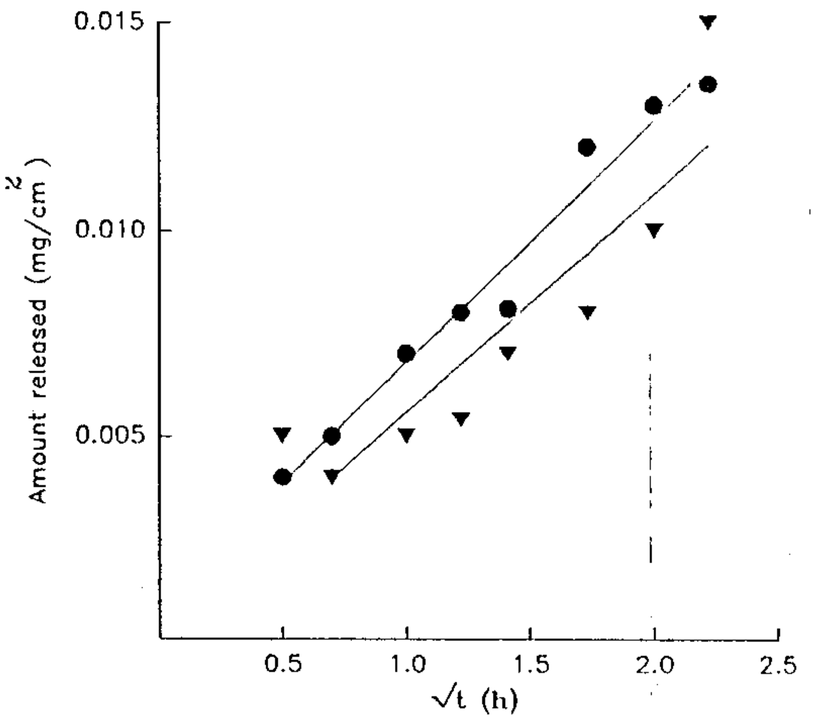



Fig. 2: Release of dexamethasone at 30°C from ( ● ) pluronic F-127 (25%) w/w; ( ▼ ) pluronic F-123 (25%).

**Table 3**: Effect of pulronic type gels on drug release rate at 30°C.

| Type of pluronic | % w/v | release-rate (slope) | Intercept | Corr. coeff. (r) |
|---|---|---|---|---|
| (A) Dexamethasone | | | | |
| pluronic F-127 | 30 % | 0.00680 | $5.8130 \times 10^{-5}$ | 0.9679 |
| pluronic F-123 | 30 % | 0.00496 | $3.5868 \times 10^{-5}$ | 0.9299 |
| (B) % progesterone | | | | |
| pluronic F-65 | 30 % | 0.002299 | $1.1211 \times 10^{-3}$ | 0.9506 |
| pluronic F-127 | 30 % | 0.005085 | $7.4578 \times 10^{-5}$ | 0.9532 |
| (C) Ethinylestradiol | | | | |
| pluronic F-127 | 30 % | 0.8261 | 0.3062 | 0.9811 |
| pluronic F-123 | 30 % | 0.8169 | 0.1601 | 0.9811 |

**Effect of pluronic type gels on drug release rate:**

The aim of the in_vitro studies were to examine possible changes in the release of drugs from gels containing different pluronic molecular weights. It was found from Table 3 and Fig. 4 that the drug was greatly affected with pluronic type gel and affected on the release rate in case of all the three drugs. A strongly prolonged in vitro release from pluronic-gels could be proven by using pluronic F-123 or pluronic F-65 30% w/w. This diminution in the release rate was, however, insignificant in each case. The results indicate that release rate of dexamethasone; progesterone and ethinylestradiol increased with the increase in chain length of polyoxyethylene of poloxamer surfactant.

**Effect of temperature on drug release**

The drug release from 30% w/v PF-127 gels was measured at 20,30 and 40°C.

It is found that the release rate decreases with increasing the temperature (in case of dexamethasone and α-MD ). Figs. 5 (a,b,c), 6

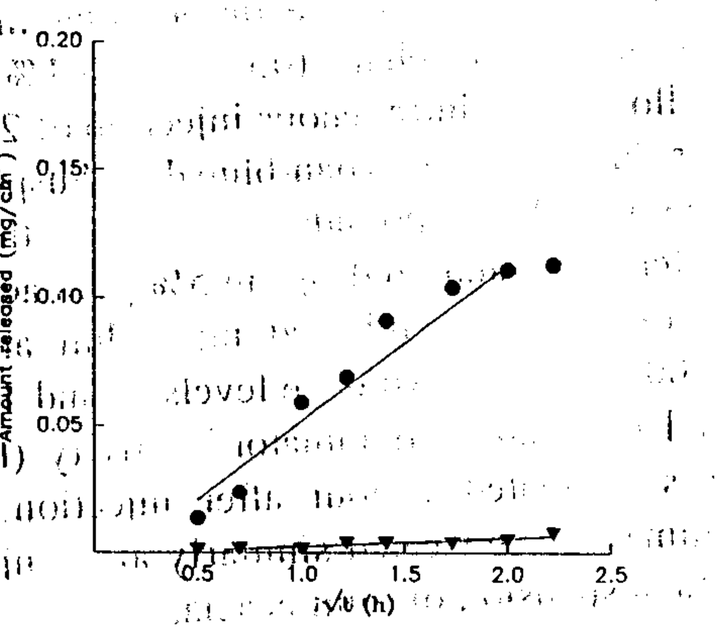



Fig. 5A: Release of progesterone as a function of the square root of time at ( ▼ ) 40°C; ( ● ) 30°C from 30% w/v pluronic F-127 gel.

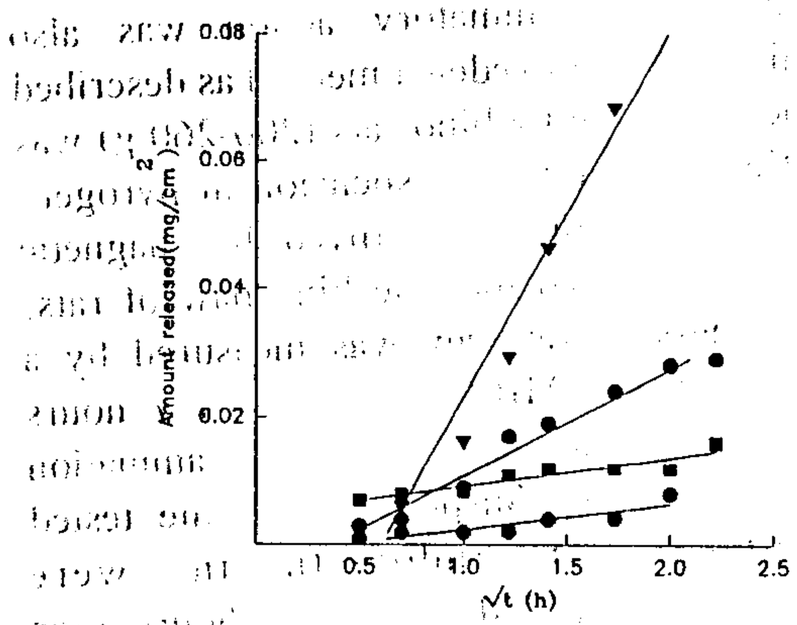



Fig. 5B: Release of dexamethasone at 30°C from ( ● ) 30% pluronic F-127 gel and ( ▼ ) at 20°C at 25% of the gel at ( ● ) 30°C and ( ■ ) at 20°C.

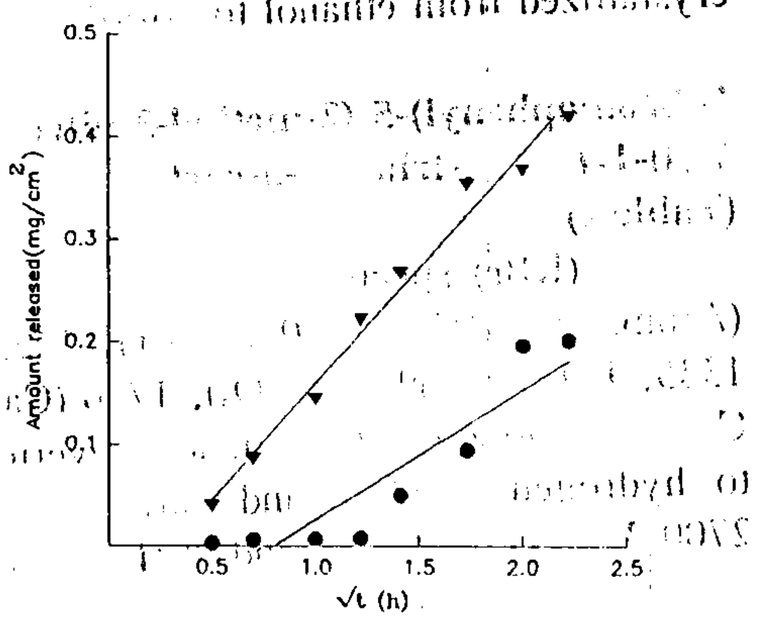



Fig. 5C: Release of α-methyldopa from 25% w/v pluronic F-127 gel at ( ▼ ) 20°C; ( ● ) 30°C.

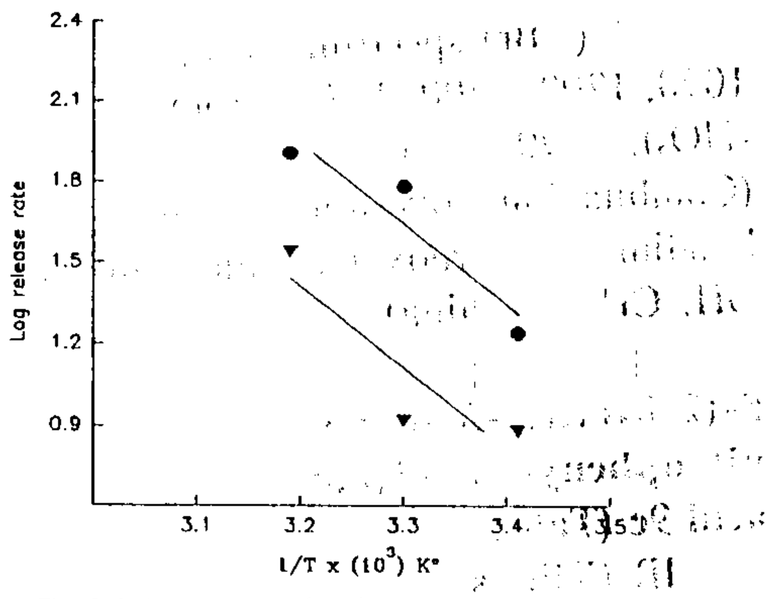



Fig. 6: Release rate of ( ● ) dexamethasone and ( ▼ ) α-methyldopa release from 30% w/v pluronic F-127 gel as a function of absolute temperature.

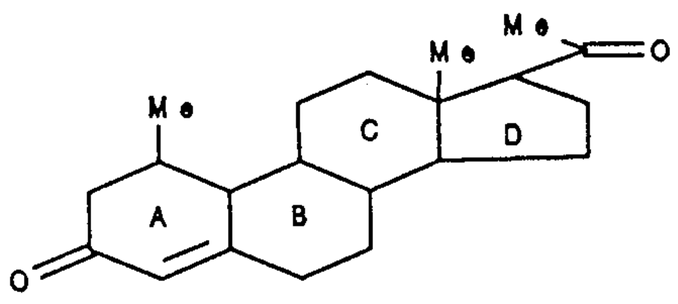
**Table 4**: Effect of temperature on drug release rate from pluronic F-127 30% w/w gels.

| Type of drug | Temp. °C | release-rate (Slope) | Intercept | Corr. coeff. (r) |
|---|---|---|---|---|
| A. Progesterone | 20-<br>30-<br>40- | 0.0037<br>0.0043<br>0.0607 | 0.00125<br>0.0104<br>0.0877 | 0.9511<br>0.9729<br>0.9668 |
| B. Dexamethasone | 20-<br>30<br>40- | 0.0575<br>0.0166<br>0.0125 | 0.0345<br>0.0058<br>0.0015 | 0.9851<br>0.9859<br>0.9641 |
| Ethinylestradiol | 30-<br>40- | 0.8161<br>0.1731 | 0.3062<br>0.1374 | 0.9811<br>0.9596 |
| C. α-methyldopa | 20-<br>30-<br>40- | 0.1317<br>0.1206<br>0.0289 | 0.0774<br>0.0175<br>0.0207 | 0.9798<br>0.9449<br>0.9696 |

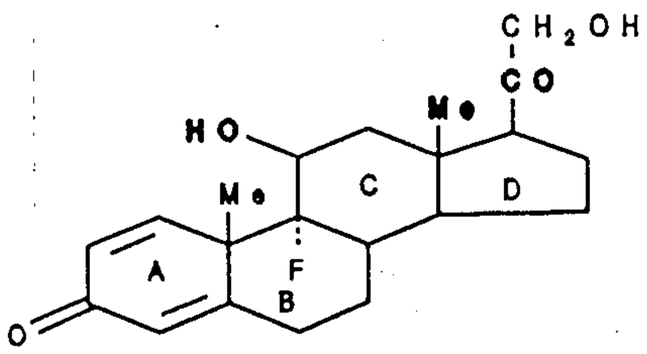
and Table 4. When the apparent release rate was plotted as a function of absolute temperature on an Arrhenius-type plot[21], a good linear relationship is observed with both drugs.

From the data presented it would seem that, when the drug included in PF-127 gels; the gel concentration and the temperature has an enhancing effect on water-insoluble drugs, other workers said that the most important factor in controlling the drug release-rate from PF-127 is the pH.

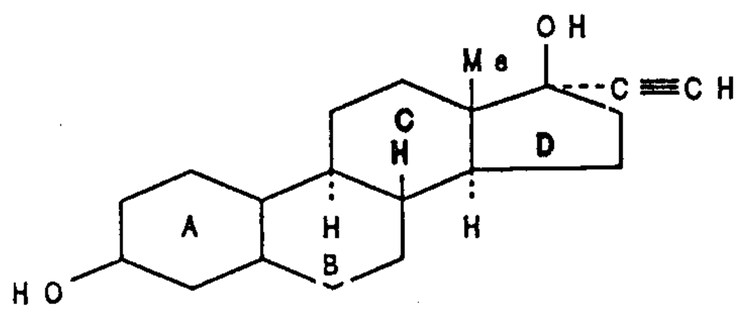
**Effect of steroid structure on the release from poloxamer gels.**




Progesterone




Dexamethasone




Ethinylestradiol

The natural hormone, progesterone, is used for different indications in human therapy such as insufficient corpus luteum function and threatened abortion[18]. It is not used orally because of a high first pass effect due to an extensive liver metabolism[22]

In order to develop a rectal formulation of progesterone with higher bioavailability[23] than known so far, poloxamer gel containing progesterone was prepared.

Several studies[24] demonstrated the effects of molecular structure on solute permeation. The release of progesterone (M.W. 314.47); dexamethasone (M.W. 392.4) and ethinyl estradiol were studied in release medium of phosphate buffer (pH 6.8).

As can be seen from Table 4, the apparent release rate of dexamethasone is slightly higher than that of progesterone released from pluronic F-127 30% w/v. (non-ionic surfactant) and ethinyl estradiol have the highest rate under the same concentration.

Since, those steroids are nonionic in nature , so, as expected from the inherent nature of the diffusion permeation, structural alterations in steroidal solutes can affect diffusion and the hydroxyl groups (dexamethasone and ethinyl estradiol) increases diffusibility.

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