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IN VITRO RELEASE PROPERTIES OF CAFFEINE. II. EFFECT OF TYPE OF PETROLATUM AND SODIUM BENZOATE

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ABSTRACT

Petrolatum is widely used for the preparation of topically applied pharmaceutical forms, like ointments. The physico - chemical characteristics of petrolatum largely depends on the source of crude petrolatum which is obtained.

The purpose of this study is to investigate whether any difference exists in release characteristics of two different batches of petrolatum, named as A and B, and to look into the effect of sodium benzoate as a complexing agent on the release properties of caffeine from petrolatum and PEG bases. It is found that the released amount of caffeine from both petrolatums for each concentration is significantly different. It is also established that the use of sodium benzoate increased the released amount of caffeine from petrolatum and PEG bases significantly

INTRODUCTION

Petrolatum is widely employed in the field of pharmaceutics, especially for the preparation of topically applied pharmaceutical

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forms, like ointments. There are several therapeutic agents like bacitracin, sulphur and zinc oxide which appear at USP, French National Formulary and BPC officially as petrolatum ointments. Petrolatum was also found as a suitable base for the release of sulfanilamide (1) and salicylic acid (2,3).

It is well known that, the physico-chemical characteristics of petrolatum largely depends on the source of crude petrolatum which is obtained and the type and degree of purification. Therefore, the properties of different batches of petrolatum may vary considerably, although they may all suit the desired pharmacopea requirements as far as melting point, acidity, alkalinity etc. are concerned. Hence, the differences in the in vitro release properties of different petrolatums can also be expected. Therefore it would be interesting to find out whether there is a difference in released amounts of caffeine from two different batches of petrolatum.

Although caffeine is a drug generally for oral and parenteral use, recently some patents of topical preparations have been seen in the literature for the treatment of trichophytia and eczema (4), acne, baldness and skin wrinkling (5). Zesch et al. (6) investigated the quantitative distribution of percutaneously applied caffeine in the human skin.

In addition, it has been shown that caffeine can be used to cure atopic dermatitis (7,8,9). By local application , it increases skin levels of cyclic adenosine monophosphate (c-AMP) by inhibiting cyclic nucleotide phosphodiesterase. This increment therefore eases the symtomps of atopic dermatitis (10). In the first part of this paper (11), petrolatum was found to release caffeine in minimum amounts compared to a w/o emulsifying ointment, hydrophilic ointment and a PEG ointment. But the most underlined relationship between the concentration and the amount released was also from petrolatum, between 1.0 and 30.0 % (w/w) of caffeine. Additionally, caffeine appeared to react with petrolatum minimallly in comparison with other bases and this is a favorable property for an ointment base in order to investigate the effect of an additional agent on

release. In fact, it is found in the literature that the release of benzocaine increased by the addition of sodium saliyclate (12). In in vitro permeation studies (13), drug-complex formations were found to change the diffusion characteristics of several drugs like caffeine and salicylic acid. Since it is well-known that, the solubility of caffeine can be increased by benzoic acid and its salts (14), it might also be expected an increment in the release of caffeine from different types of ointment bases.

Within the frame of introduction given above, the purpose of this study is to investigate whether any difference exists in release characteristics of two different batches of petrolatum. And if a difference is found, choosing the base which releases caffeine better, to look into the effect of sodium benzoate on release properties at 1.0 to 30.0 %(w/w) concentrations. If sodium benzoate will be found to change the release of caffeine significantly, then the effect of it on caffeine release from PEG ointment will also be investigated.

EXPERIMENTAL

Materials

The same materials reported in the previous paper (11) were used throughout the experiments. Two different batches of petrolatum, named as petrolatum A and petrolatum B, were of unknown sources. Both petrolatum A and petrolatum B were controlled according to USP requirements for colour, solubility, taste, odour, acidity, alkalinity, foreing organic matter, sulphated ash, fixed oils, fats and rosin and they both were found to be suitable to pharmacopeia requirements. Sodium benzoate[1] was used as supplied.

Preparation of Petrolatum Ointments

Both petrolatums were used as supplied. They were added on to caffeine in a mortar by geometric dilution, to give previously determined concentrations, in weight percentages. Caffeine was mixed with petrolatum thoroughly until a homogenous mixture was

obtained. It was used at 1,5,10,20 and 30 % (w/w) concentrations in both petrolatum A and B. The mixtures were left at the ambient temperature for sixteen hours before the release experiments.

Preparation of Caffeine Complexes

Two different preparation techniques were used:

The first method was the one given in the Merck Index (15). According to this method equal amounts of caffeine and sodium benzoate were mixed and thoroughly grinded in a mortar. This mixture is called as Complex I.

In a second method of preparation, caffeine was mixed with an equal amount of sodium benzoate. With the addition of sufficient amount of alcohol a smooth paste was obtained. This paste was dried at the ambient temperature and powdered. It was called as Complex II (16). Both complexes were incorporated in petrolatum and PEG bases with routine methods to give a total of 20% (w/w) concentration 10% of which was caffeine.

Apparatus and Method of Measurement

Diffusion cells used were described in the first part of this paper (11). The filling procedure and the measuring technique were the same as before. Caffeine released into distilled water was measured spectrophotometrically at 272 nm with a spectrophotometer[2].

In order to minimise a possible interference on measurements which might be induced by sodium benzoate, petrolatum B and PEG ointments containing only 10% sodium benzoate were also prepared. Release experiments were carried out with this "blanks" and caffeine released into water phase was measured against the diffusate from these blanks.

RESULTS and DISCUSSION

Release From Petrolatums

Figure 1, shows the release of caffeine from two types of petrolatum bases, petrolatum A and petrolatum B for 1,10 and 30 % (w/w) concentrations.

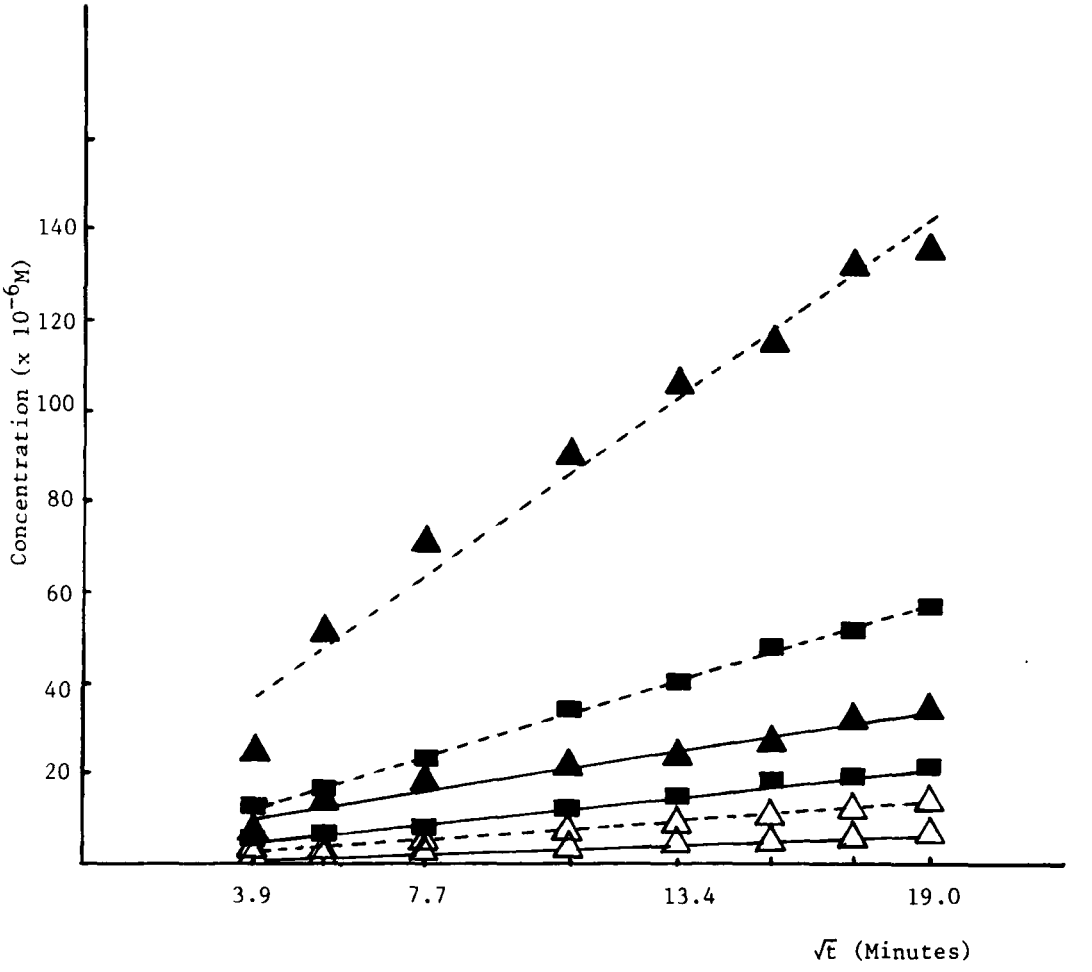

FIGURE 1

Release of Caffeine From Petrolatum A and Petrolatum B.
Key:-△-, 1 %(w/w);-■-, 10 %;-▲-, 30 % Caffeine From Petrolatum A.
---△---,1 %(w/w);--- ■ ---, 10 %;---▲---, 30 % Caffeine From Petrolatum B.

The released amounts of caffeine and release rates for each concentration were found to be significantly different from each other as Figure 1 shows. On the other hand, a positive correlation between the released amounts and the concentration is obvious for each concentration in both bases. Although both petrolatums were

TABLE I

Release Rates ($x10^{-6}$) of Caffeine From Two Petrolatum Bases at Varying Concentrations

Ointment Base	Percentage Caffeine Concentration (w/w)				
	1.0	5.0	10.0	20.0	30.0
Petrolatum A	0.37	0.92	1.08	1.57	1.61
Petrolatum B	0.67	1.73	2.95	5.05	7.01

suitable to USP XVIII requirements, petrolatum B released caffeine in higher amounts comparing to petrolatum A for each concentration. Table I shows the difference between the release rates of each petrolatum which were calculated from slopes of lines obtained by plotting the released amounts of caffeine against $\sqrt{t}$.

If the release rates given in Table I are plotted against concentrations, stright lines are obtained which indicate a linear relationship between the concentration and the release rates. The difference of release from both petrolatums can be attributed to the different structural characteristics of these bases. In order to check this point, both petrolatums were investigated under a polarising microscope. However, no apparent difference between the crystal structure was observed(Fig.2).Also, X-ray diffraction studies of both bases showed no difference between the Debye-Sherrer patterns of both bases (Fig.3). Further the DTA investigations of them also exhibited the same inversion points by heating and cooling the samples. The melting temperatures of both bases were 56.5° C and the crystallisation temperatures were of 53.5-54° C. Finally, viscosity measurements were carried out to see whether a possible difference between the viscosities of petrolatums exists. A rotational cone and plate viscometer[3] used for this purpose. The petrolatums both exhibited plastic viscosities.

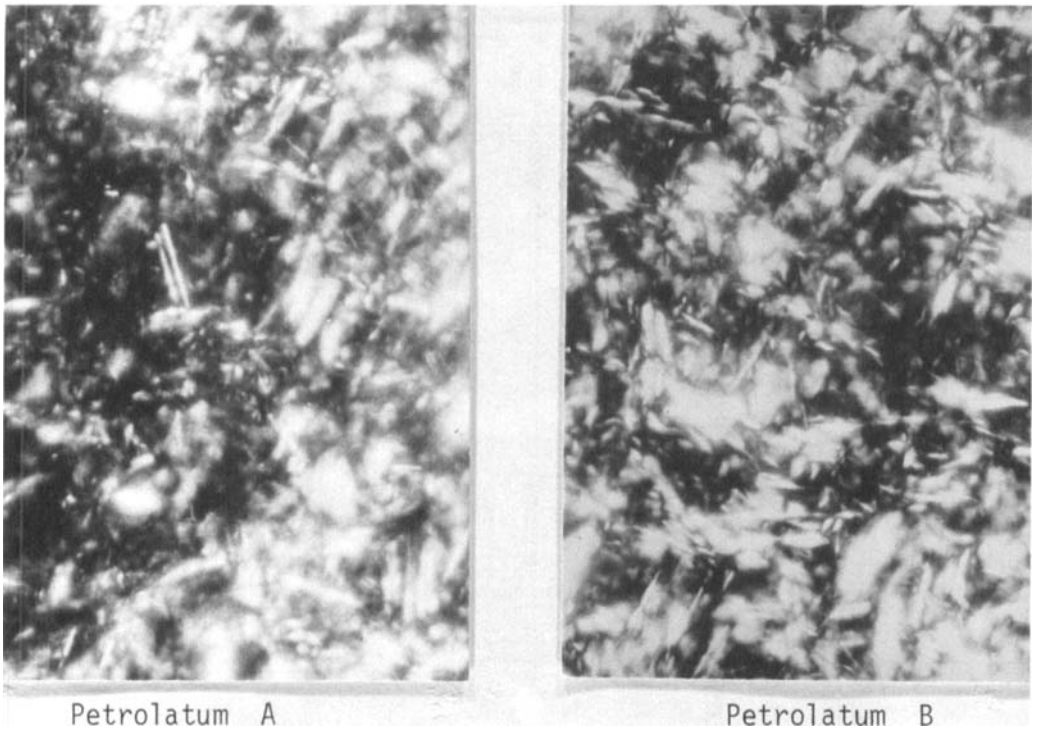

FIGURE 2

Microscopical Appearences of Petrolatum A and Petrolatum B (Magnification : x 143).

The viscosity of petrolatum A was higher than of petrolatum B for all the shear rates studied. Petrolatum A also exhibited a thixotropic behaviour, whereas petrolatum B did not show a similar effect.

The apparent viscosities of both samples were determined from the apex of upcurves, obtained when shear stresses were plotted against shear rates. The apparent viscosity of petrolatum A was 1.85 and petrolatum B of 0.69 poise at 37° C.

Since there is an inverse relationship between the viscosity and the diffusion coefficient as formulated with Stokes-Einstein equation, a higher release from a less viscous sample can be

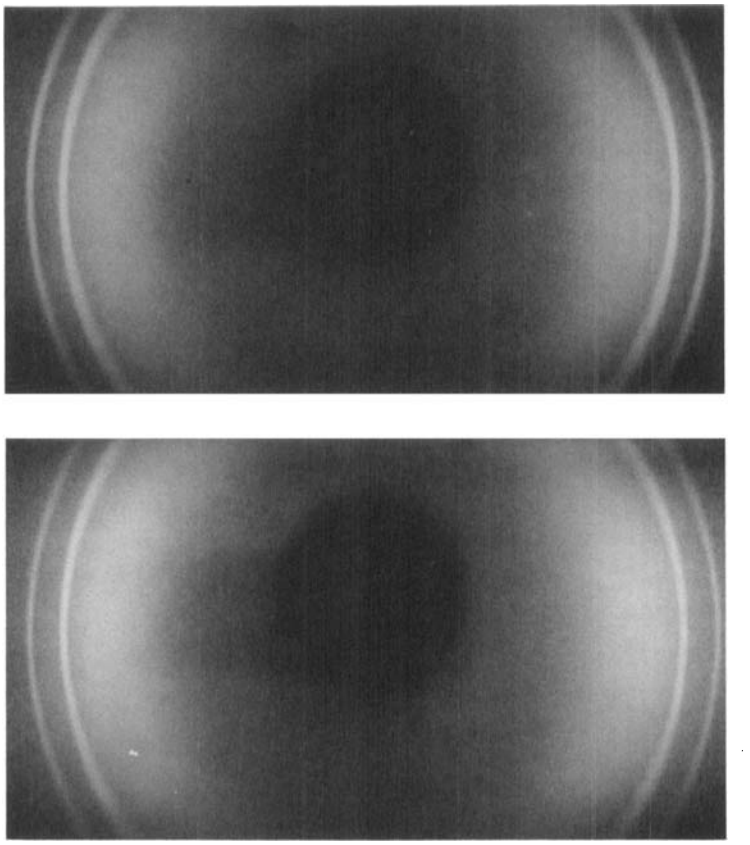

FIGURE 3

X - Ray Diffraction Analysis of Petrolatum A and Petrolatum B.

expected. Although this relationship may not hold rigidly for the complex structure of the ointments, it can be assumed that the decrement in viscosity would yield an increased diffusion coefficient for the drug in the ointment base. Davis and Khanderia (17) showed the effect of viscoelastic properties of the ointment bases to in vitro release and in vivo absorption properties of salicylic acid. Boylan (18) observed slight rheological differences between the viscosities of NF and USP petrolatums. Later Barry and Grace (19) examining the grade variations of petrolatum, found changes in the Newtonian viscosities by a factor of ten.

Since the microcrystalline structure in petrolatum is a mixture of n and iso paraffines, it is possible that their amount may change,hence, the crystal distribution may differ within the gross structure of petrolatum. Since there are no differences between the X-ray and DTA data, the only possible explanation seems to be the variation in the distribution of the crystal agregation of both petrolatums and this may cause a difference in the release properties of the incorporated drug.

The difference of the data presented with both petrolatums indicates an important fact which might be of use for furher studies. There are several official preparations using petrolatum as an ointment base. Bacitracin and polymixin B sulphate ointments in USP, penicilline and calamine ointments in BPC and zinc oxide, niaouli oil and sulphur ointments in National Formulary of France can be mentioned among a few. If a significant variation in release as it is seen from the present data can be expected, depending on the type of petrolatum, the release properties of those officially accepted ointments must be examined further, for the structural variations of petrolatums used. Or else, the structural properties of petrolatums given in the pharmacopeia must be defined more precisely. Barry and Grace (20) recommended rheological testing of these vehicles. We also recommend the inclusion of definite range of physical caharacterictics in pharmacopeial monograph, such as continuous shear rheometry.

Effect of Sodium Benzoate on Release

In Figure 4,release of caffeine from petrolatum B ointments containing Complexes I and II are presented.

Both sodium benzoate complexes were found to increase the release of caffeine significantly. But no significant difference in release could be found between the release from ointments containing the complexes. A similar data was also obtained using the PEG bases. In this set of results (Fig.5), an increased release from both complexes were also found. As in petrolatum ointment, there were no

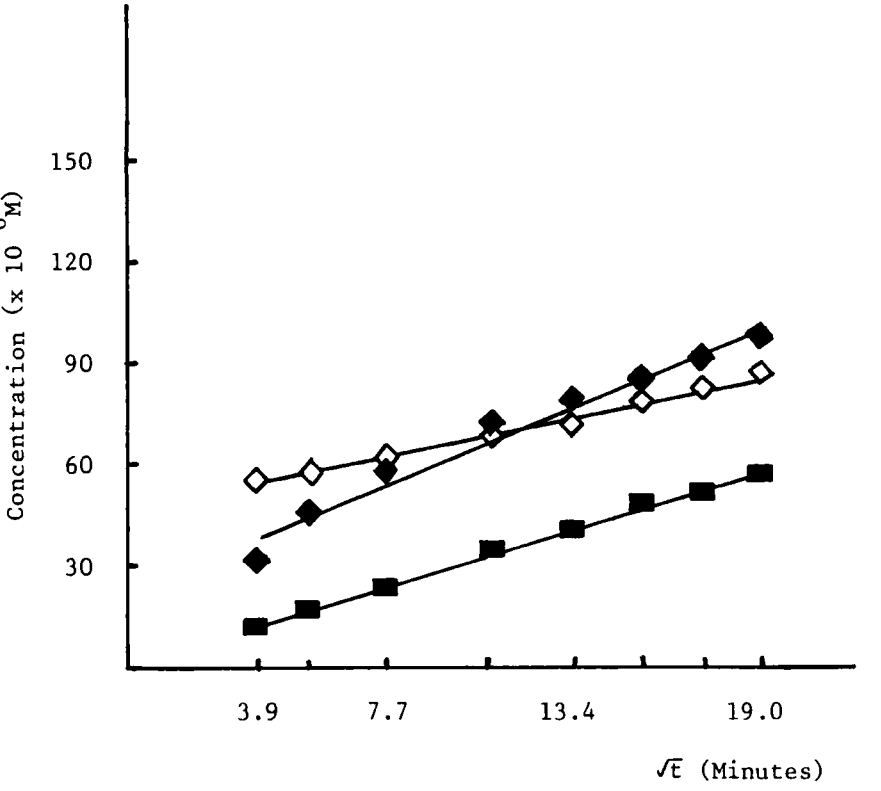

FIGURE 4

Release of Complex I and Complex II From Petrolatum B.
Key : ■ , 10 % Caffeine; ● , 20 % Complex I; ◇ , 20 % Complex II.

differences in release from two complexes, but both complexes increased the release of caffeine significantly.

Release data from PEG ointment showed a linear relationship when plotted released amounts versus $\sqrt{t}$ and logarithm of released amounts against logarithm of time. As seen in Figure 5, the log-log presentation of this particular data was preferred, because it gave higher correlation coefficients between the variables. Thus, a better fit could be obtained.

The variation observed with PEG ointments may be due to the interaction of this base with sodium benzoate and the solubility of

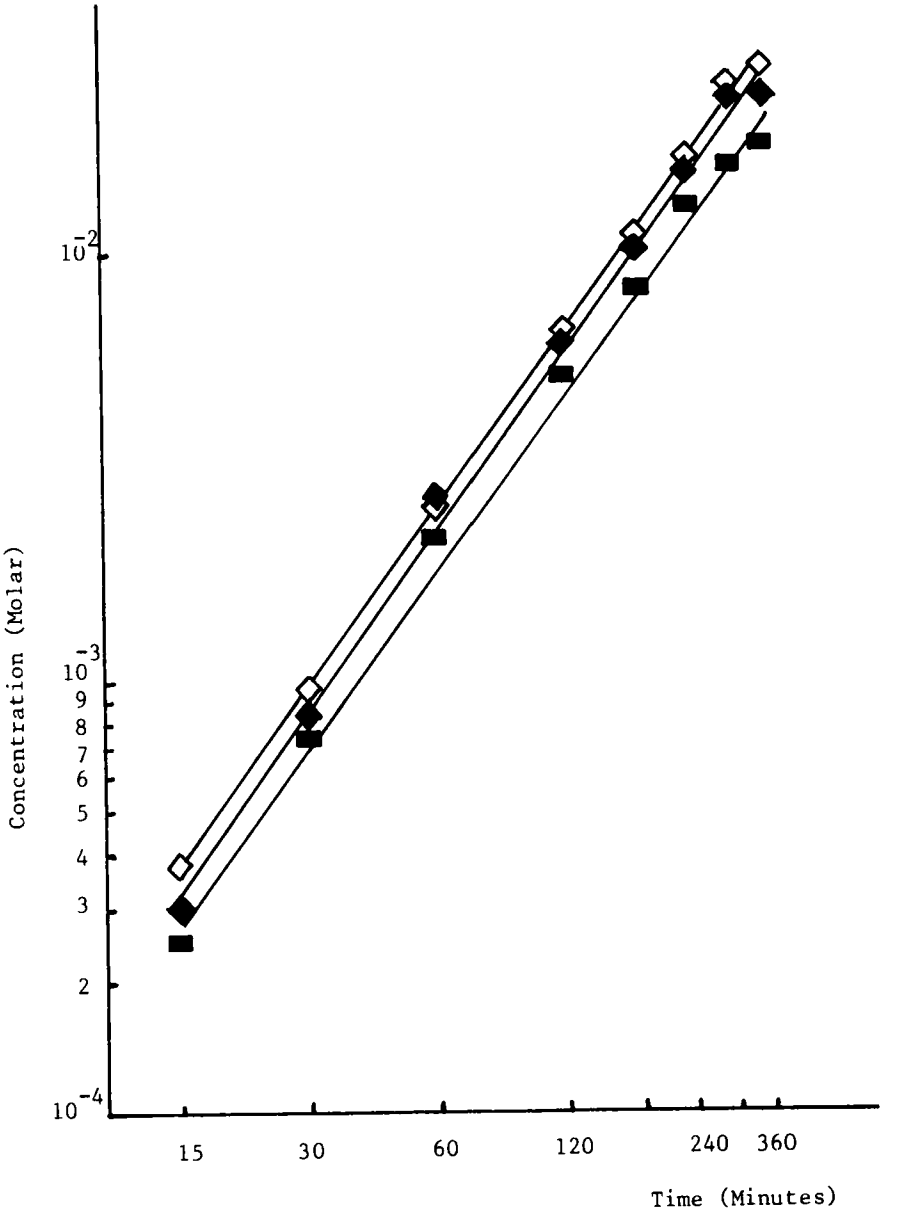

FIGURE 5

Release of Complex I and Complex II From PEG Ointment.
Key : ■ , 10 % Caffeine ; ● , 20 % Complex I; ◇ , 20 % Complex II.

caffeine in it. Therefore, release from this ointment is both diffusion and solubility dependent. Thus, it is reasonable to expect that, the mutual interaction will be reflected on the results. Petrolatum, on the other hand can be accepted as a most suitable base to determine the effect of a single variant.Figure 4 and 5 indicate that the methods of preparation did not significantly effect the properties of both complexes as there was no difference in released amounts nor the release patterns between them. But in each case, use of sodium benzoate increased the realed amounts of caffeine. This effect will be further investigated to find out how much of this is reflected on in vivo stduies.

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FOOTNOTES

1) Merck, Germany
2) Bausch and Lomb-Spectronic 700, U.S.A.
3) Rheotest 2, East Germany

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