Bull. Pharm. Sci., Assiut University
Vol. 13, Part 2, pp 247-254

RELEASE CHARACTERISTICS OF CAFFEINE AND MEBEVERINE HYDROCHLORIDE FROM ISOPROPYL MYRISTATE MULTIPLE EMULSIONS

M.S.Mohamed, F.S.Ghazy, M.A.Mahdy and M.A.Gad

Department of Pharmaceutics, Faculty of Pharmacy

Zagazig University, Zagazig, Egypt

ABSTRACT

Double emulsions (w/o/w) were prepared by two steps emulsification procedure using isopropyl myristate as the oily phase. The influence of the inner aqueous phase volume and emulsifier concentration on the release characteristics of either caffeine or mebeverine hydrochloride from the prepared emulsions was studied. For the purpose of comparison, the release of each drug from either o/w or w/o emulsion was investigated. The results showed that the release of both drugs from w/o/w emulsions was independent on the inner aqueous phase volume. The release of mebeverine hydrochloride was sustained from either w/o/w or w/o emulsions while that of caffeine was not significantly retarded as indicated by the amount released after 24 hours. Increasing the concentration of the hydrophilic emulsifier (Tween 20) had a little effect on the release of both drugs from w/o/w emulsions. On the other hand, the release of mebeverine hydrochloride was more prolonged on increasing the concentration of the lipophilic emulsifier (Span 80), while the release of caffeine was not significantly retarded.

INTRODUCTION

The preparation of w/o/w emulsion was previously described by Matsumoto et al[1,2]. The ability of w/o/w emulsions to entrap materials is one of their most useful assets. In medicine, w/o/w emulsions have been investigated to prolong drug release[3]. W/o/w emulsions possess many of the advantages of w/o emulsions but, in addition, have a low viscosity, due to the lower viscosity of the aqueous external phase, which makes them more convenient to handle and use, especially to inject[4]. Davis[5] pointed out a large number of factors that affect the stability and drug release characteristics of emulsions. The release of drugs from w/o/w emulsions is controlled by all the factors controlling the release of drugs from simple emulsions such as the nature and concentration of the oil and surfactants, internal phase volume, droplet size and also by a number of factors specific to w/o/w systems[6].

In the present work, caffeine and mebeverine hydrochloride were used as model drugs. They were entrapped separately in the inner aqueous phase of w/o/w emulsions. Then, the effect of different factors on the release of these drugs was investigated.

In addition, the release of the above mentioned drugs from w/o and o/w emulsions was also conducted in order to determine the effectiveness of w/o/w emulsion in sustaining the release of drug.

EXPERIMENTAL

Materials :

Tween 20 and Span 80 (Atlas Chem. Ind. USA). Isopropyl myristate (Aldrich Chem. Co., 940 West Saint Paul Avenue, Milwakee, Wisconsin 53233 USA). Mebeverine hydrochloride (Duphar, B.V. Weesp, Holland). Caffeine, Merck, West Germany). Double distilled water.

Equipment :

Atomic absorption flame emission spectrophotometer (A.A. 640-130, Shimadzu, Japan). Homogenizer, type MPW 302 and power supply unit, type ST-2 (Mechanika Precyzina, Warszawa, Poland). Magnetic stirrer, type MM5 (Poland). Cellulose dialyzer tubings, molecular weight cutoff 10000, flat width 25 mm, diameter 15.9 mm (Arthur H. Thomas Co., Philadelphia, USA)

Preparation of emulsions :

W/O/W emulsions were prepared by a two-step emulsification procedure according to Matsumoto et al[1]. In the first step a w/o emulsion was prepared by the homogenization method. The aqueous phase was mixed with isopropyl myristate containing a specified concentration of Span 80 and the phases were homogenized for 5 minutes at 7000 rpm. In the second emulsification step, specified amount of the freshly prepared w/o emulsion was dispersed into specified amount of an aqueous solution of Tween 20. Then, the mixture was emulsified using magnetic stirrer for 15 minutes fol-

lowed by homogenization at 7000 rpm for 30 seconds at 25°C. Simple o/w and w/o emulsions were prepared by homogenization at 7000 rpm for 5 minutes.

Release Studies :

Caffeine and mebeverine hydrochloride were separately incorporated into the inner aqueous phase of w/o/w emulsion during the preparation of w/o emulsion in definite concentrations. In case of w/o or o/w emulsions, the drugs were incorporated into the aqueous phase of the emulsion. Cellophane dialysis tubing was washed several times and left soaking in distilled water overnight before use. After preparation of the bag, 5ml of emulsion was pipetted to the bag which is double tied at each end. The bag was placed in 100 ml of water at 25°C. The dialysis solution was agitated with a magnetic stirrer bar. A 5 ml of the dialysis solution was withdrawn at appropriate intervals and replaced by 5 ml of fresh water to maintain the volume constant. The amount and percentage of caffeine and mebeverine hydrochloride released was determined spectrophotometrically at 273 and 262 nm, respectively[7,8].

RESULTS AND DISCUSSION

The influence of the inner aqueous phase volume ratio (0 w/o) on the release of drugs was studied. Table 1 and Figure 1 show the release patterns of caffeine and mebeverine hydrochloride from w/o/w emulsions as a function of the inner aqueous phase volume. It was found that higher release rates of caffeine, after 4 hours, were obtained when 0 w/o was at 0.4 followed by that at 0 w/o 0.3 and 0 w/o 0.5. While after 24 hours the difference in the released amounts was insignificant. In the case of mebeverine hydrochloride there was no significant difference in the released amounts during the first 4 hours of dialysis, a higher amount of the drug was released at 0 w/o 0.3 after 24 hours (Table 1). These results indicate that the release of either caffeine or mebeverine hydrochloride from w/o/w emulsion is independent on the inner aqueous phase volume. This assumption is in agreement with those results obtained by Fukushima et al[9] who found that the release of cytarabine from w/o/w emulsions prepared with oily lymphographic agent was independent on the inner aqueous phase volume.

Then, the influence of the concentration of lipophilic emulsifier (Span 80) on the release of caffeine and mebeverine hydrochloride from w/o/w emulsion was investigated (Table 2 and Figure 2). In case of caffeine, there was no significant effect on the release of the drug when the concentration of the lipophilic emulsifier (Span 80) was increased from 5 to 15% (w/v). On the other hand, the release of mebeverine hydrochloride was significantly reduced as the concentration of Span 80 was increased. The percentage amount released of mebeverine hydrochloride after 24 hours was reduced from 55 to 37.5 on increasing the concentration of Span 80 from 5 to 15% (w/v) (Table 2). This finding is in agreement with that reported by Whitehill[6] who pointed out that increasing the viscosity of the oil phase retards the diffusion of the entrapped drug molecules. In the present investigation, increasing the concentration of Span 80 increased the viscosity of the oil phase and hence the release is diminished. In addition, increasing the concentration of

the lipophilic emulsifier was found to give higher yield of w/o/w drops and consequently the amount of drug already entrapped in the inner aqueous phase was increased.

Moreover, the release of caffeine and mebeverine hydrochloride from w/o/w emulsions as a function of the concentration of hydrophilic emulsifier (Tween 20) was studied (Table 3 and Figure 3). No significant increase in the released amount of either caffeine or mebeverine hydrochloride could be demonstrated on increasing the concentration of Tween 20 from 2 to 4% w/v, after 4 hours. These results are in agreement with that pointed out by Fukushima et al[10]. who reported that the concentration of the hydrophilic emulsifier (HCo - 60) had a little effect on the release of cytarabine from w/o/w emulsion.

On the other hand, the release of either caffeine or mebeverine hydrochloride from simple o/w and w/o emulsions in comparison with that from multiple w/o/w emulsion was investigated (Table 4 and Figure 4). Higher rates of release after 4 hours were noted for both drugs from o/w emulsions in comparison to that from w/o/w and w/o emulsions where a comparatively slow release was obtained. But no significant difference in the released amount of caffeine from o/w, w/o/w and w/o emulsions after 24 hours (Table 4). On the other hand, the amount released of mebeverine hydrochloride after 24 hours were 71.5, 55 and 33.3% from o/w, w/o/w and w/o emulsions, respectively. These results indicate that the second step of emulsification enhanced, to some extent, the release of drug from w/o/w emulsions.

All the above mentioned results showed that mebeverine hydrochloride release at slower rates in comparison to caffeine (Figure 1-4). The difference in the released amounts of mebeverine hydrochloride and caffeine from simple w/o emulsions (Table 4) indicates that mebeverine hydrochloride molecules diffuse at slower rate through the oil phase than that of caffeine. This finding can account for the difference in the released amounts of the two drugs from w/o/w emulsions. These results are in accordance with that pointed out by Fukushima et al[9]. Who reported that the permeability through the oil phase of w/o/w emulsions was different among drugs. 5-fluorouracil, which has both hydrophilicity and lipophilicity and small molecular weight, permeated so fast that the release was completed within one hour. Permeation of cytarabine and glucose, which have high hydrophilicity was sustained for a long time. Peplomycin, which has high hydrophilicity and much higher molecular weight, hardly permeated through the oil phase of w/o/w emulsion. In the present investigation and on the above basis, caffeine molecules which are nonionizable, have the lower molecular weight (M.W. 194.2) and lower hydrophilicity are expected to diffuse at faster rate than that of mebeverine hydrochloride which are ionizable, more hydrophilic and have the higher molecular weight (M.W. 466.0).

Finally it can be concluded that retardation of the release of any drug entrapped in an w/o/w emulsion is mainly dependent on its physicochemical characteristics.

TABLE (1)

Effect of the internal phase volume ratio (ϕ w/o) on the release of drugs from w/o/w emulsions.

Drug	ϕ w/o	% Drug released after the following time intervals in hours				
		1	2	3	4	24
Caffeine	0.3	44.2	58.9	69.2	69.9	86.9
	0.4	47.7	64.8	70.2	75.8	83.5
	0.5	38.4	52.5	62.9	65.7	84.8
Mebe-verine HCL	0.3	17.1	24.1	27.2	35.7	64.4
	0.4	14.7	21.9	28.7	32.1	53.2
	0.5	16.6	25.1	31.1	34.4	55.5

ϕ w/o/w 0.5, Span 80 5% and Tween 20 2%.

TABLE (2)

Effect of the concentration of lipophilic emulsifier (Span 80) on the release of drugs from w/o/w emulsions.

Drug	Span 80 Conc. g %	% Drug released after the following time intervals in hours				
		1	2	3	4	24
Caffeine	0.5	38.4	52.5	62.9	65.7	84.8
	10.0	41.2	56.3	63.2	64.5	82.1
	15.0	38.7	52.0	58.5	61.0	80.3
Mebe-verine HCL	5.0	16.6	25.1	31.1	34.4	55.5
	10.0	12.1	16.9	20.5	23.5	45.9
	15.0	9.1	12.7	16.0	17.5	37.4

ϕ w/o 0.5, ϕ w/o/w 0.5 and Tween 20 2%.

TABLE (3)

Effect of the concentration of hydrophilic emulsifier (Tween 20) on the release of drugs from w/o/w emulsions.

Drug	Tween 20 conc. %	% Drug released after the following time intervals in hours				
		1	2	3	4	24
Caffeine	2.0	38.4	52.5	62.9	65.7	84.8
	4.0	48.0	62.2	68.1	69.2	88.9
Mebe-verine HCL	2.0	16.6	25.1	31.1	34.4	55.5
	4.0	17.8	25.3	31.4	36.5	69.7

ϕ w/o 0.5 , ϕ w/o/w 0.5 and Span 80 5%.

TABLE (4)

Effect of the emulsion type on the release of drugs.

Drug	Emulsion type	% Drug released after the following time intervals in hours				
		1	2	3	4	24
Caffeine	o/w*	45.3	62.9	70.4	74.2	83.1
	w/o/w**	38.4	52.5	62.9	65.7	84.8
	w/o***	25.2	33.2	38.6	44.6	80.0
Mebe-verine HCL	o/w*	22.9	40.2	47.7	50.4	71.5
	w/o/w**	16.6	25.1	31.1	34.4	55.5
	w/o***	17.4	18.9	19.6	24.6	33.3

* ϕ o/w 0.5 and Tween 20 2%

** ϕ w/o 0.5, ϕ w/o/w 0.5, Span 80 5% and Tween 20 2%

*** ϕ w/o 0.5 and Span 80 5%

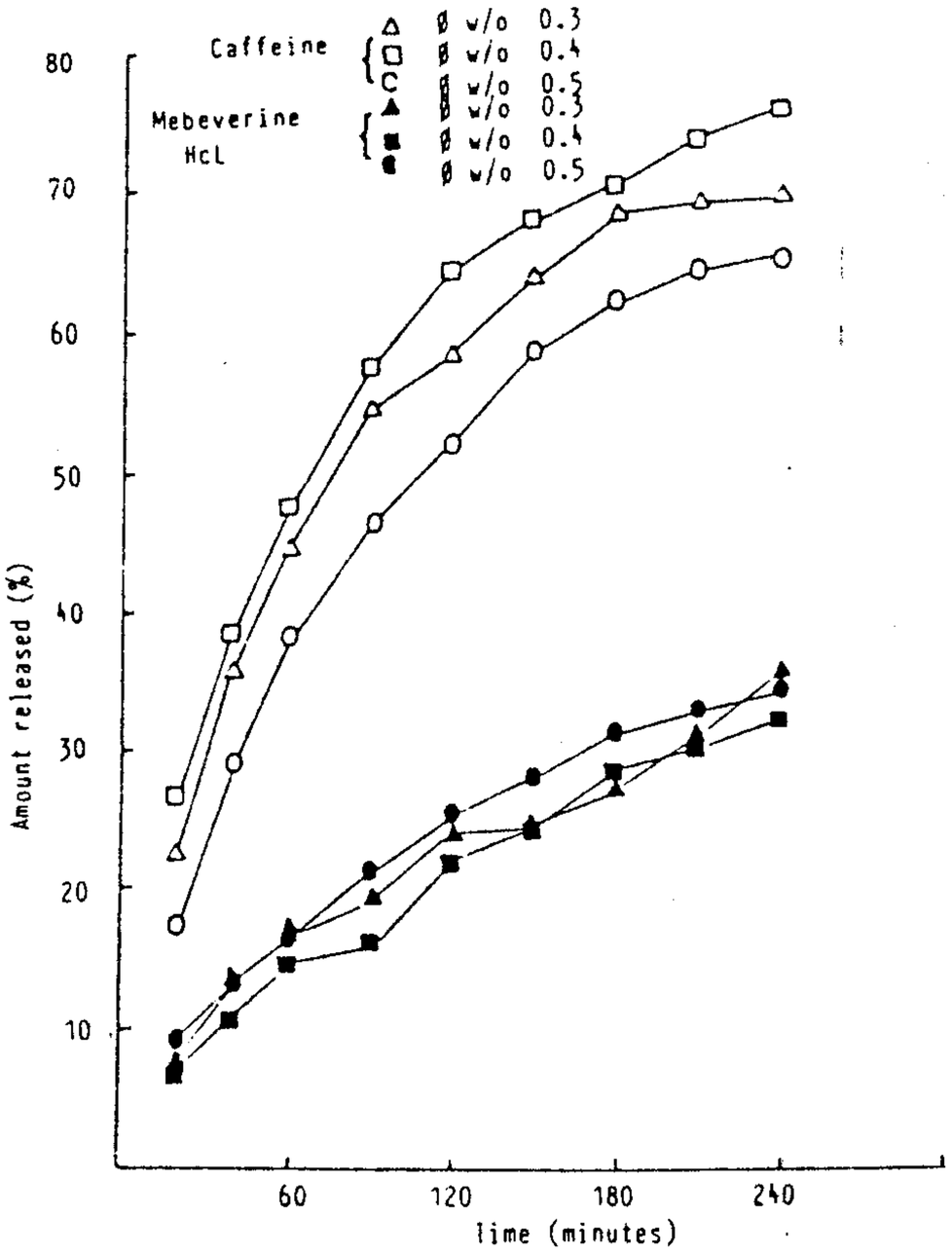

Fig. (1): Effect of the internal phase volume ratio (Ø w/o) on the release of drugs from w/o/w emulsions. (Ø w/o 0.5, Span 80 5% and Tween 20 2%).

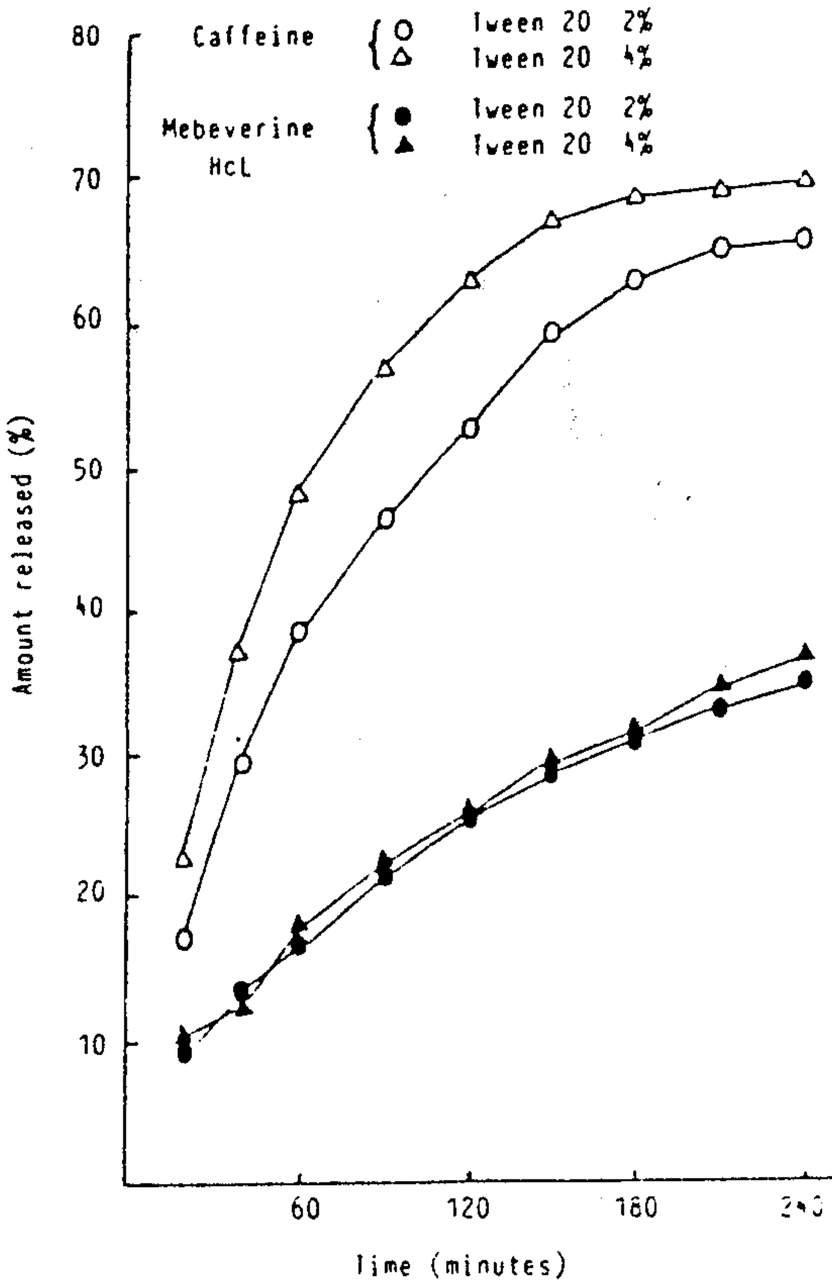

Fig. (3): Effect of the concentration of the hydrophilic emulsifier (Tween 20) on the release of drugs from w/o/w emulsions (Ø w/o 0.5, Ø w/o/w 0.5 and Span 80, 5%).

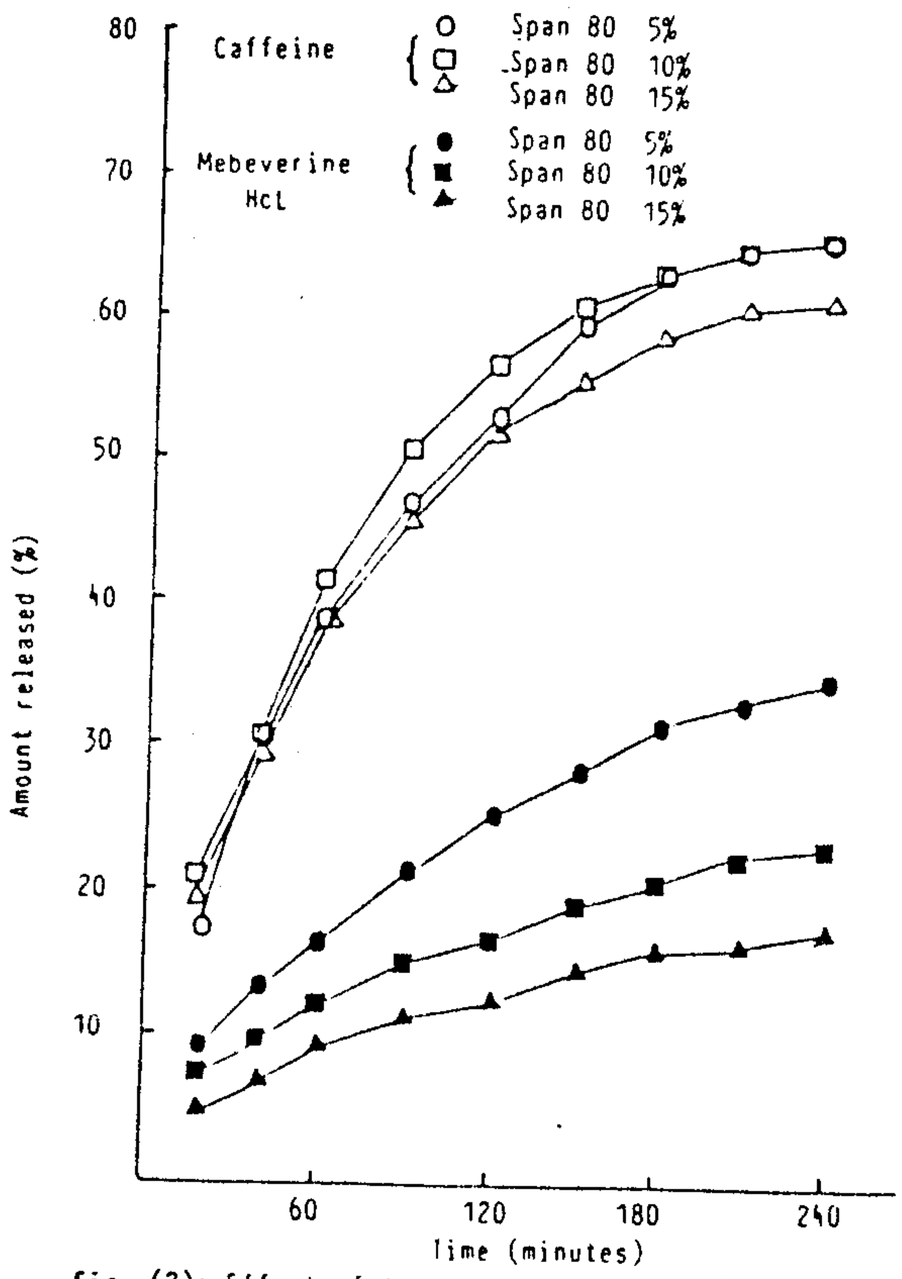

Fig. (2): Effect of the concentration of lipophilic emulsifier (Span 80) on the release of drugs from w/o/w emulsions. (Ø w/o 0.5, Ø w/o/w 0.5 and Tween 20 2%).

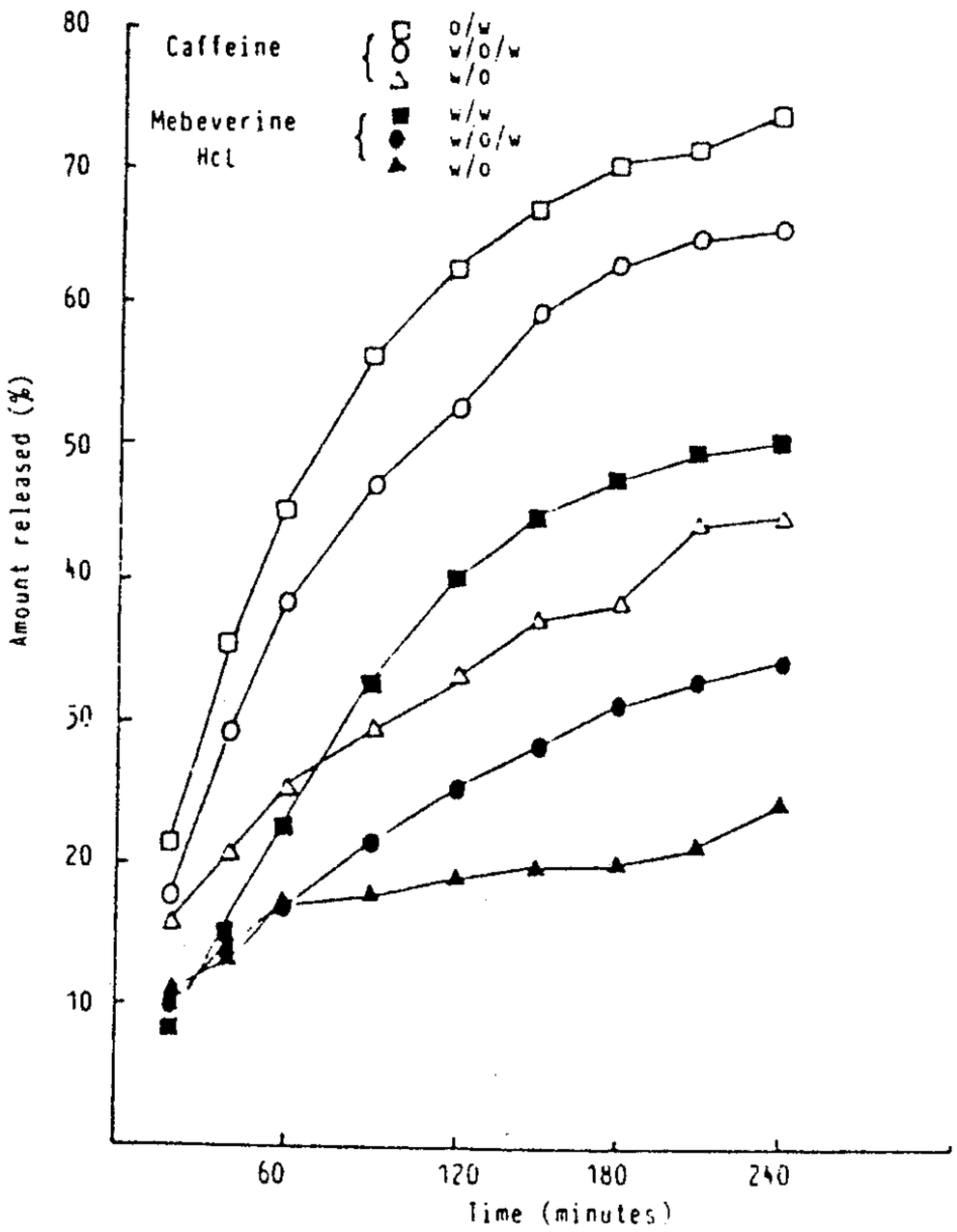

Fig. (4): Effect of the emulsion type on the release of drugs. o/w (Ø o/w 0.5 and Tween 20 2%), w/o/w (Ø w/o 0.5, Ø w/o/w 0.5, Span 80 5% and Tween 20 2%) and w/o (Ø w/o, 0.5 and Span 80 5%).

REFERENCES

1-S.Matsumoto, Y.Kita and D.Yonezawa, J. Colloid Interface Sci., 57, 353 (1976).

2-S.Matsumoto, M.Kohda and S.Murata, J. Colloid Interface Sci., 62, 149 (1977).

3-A.Brodin, D.R.Kavaliunas and S.C.Frank, Acta Pharm. Suec., 15, 1 (1978).

4-A.T.Florence and D.Whitehill, Intl. J. of Pharm., 11, 277 (1982).

5-S.S.Davis, J. Clin. Pharm., 1,11 (1976).

6-D.Whitehill, Chemist & Druggist 213, 130 (1980).

7-E.G.C.Clarke, "Isolation and Identification of Drugs. In Pharmaceuticals, Body Fluids and Postmortem Materials." The Pharmaceutical Press. London, 3rd Ed., (1974) p. 234.

8-The Pharmaceutical Codex. 11th Ed., The Pharmaceutical Press, London, (1979), p. 517.

9-S.Fukushima, M.Nishida and M.Nakano, Chem. Pharm. Bull., 35, 3375 (1987).

10-S.Fukushima, K.Juni and M.Nakano, Chem. Pharm Bull., 31, 4048 (1983).

انطلاق عقارى الكافيين و ايدركلوريد الميبفرين من مستحلبات عديدة الوسط

محمد سلامة محمد ـ فخر الدين سليمان غازى ـ محمود عبد الغنى مهـــــــــدى ـ محمـد عبد النعيم جـــاد

قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة الزقازيـــق

تم تحضير مستحلبات عديدة الوسط (ماء فى زيت فى ماء) وذلك على خطوتين فى الخطوة الاولى تم تحضير مستحلب ماء فى زيت باستخدام مادة سبان ٨٠ كعامل للاستحلاب وفى الخطوة الثانية تم اعادة استحلاب المستحلب السابق باستخدام مـــادة توين ٢٠ كعامل للاستحلاب ليتكون مستحلب ماء فى زيت فى ماء . وقد استخدمـــت مادة ميرستات الايزوبروبيل كوسط زيتى . ثم تمت دراسة بعض العوامل التـــى تؤثر على انطلاق المواد المتحوصلة فى الوسط المائى الداخلى للمستحلبات مثـــل نسبة حجم وسط الماء الداخلى للمستحلب وتركيز المواد التى تساعد على عمليـــة الاستحلاب للماء فى الزيت ثم للزيت فى الماء . كذلك تم تحضير مستحلبـــات بسيطة وهى ماء فى زيت او زيت فى ماء للمقارنة .

وقد اوضحت النتائج ان انطلاق العقارين المستخدمين لايعتمد على نسبة حجـــم وسط الماء الداخلى . كذلك ثبت بطء انطلاق عقار ايدركلوريد الميبفرين مـــن المستحلبات عديدة الوسط وكذلك من المستحلب البسيط للماء فى الزيت بينما لم يظهر ذلك فى حالة عقار الكافيين وذلك بعد تعيين كمية العقار المنطلقة بعد ٢٤ ساعة وثبت ايضا ان زيادة تركيز توين ٢٠ كان لها تأثير طفيف على انطلاق العقارين من المستحلبات عديدة الوسط وعلى الوجه الاخر لوحظ بطء انطلاق ايدركلوريـــد الميبفرين من المستحلبات عديدة الوسط بزيادة تركيز سبان ٨٠ بينما لم يتأثر انطلاق عقار الكافيين .

---

received in 18/12/1990 - accepted in 28/2/1990