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FORMULATION OF INFANTILE EPHEDRINE HYDROCHLORIDE SUPPOSITORIES

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ABSTRACT

Ephedrine hydrocloride suppositories were prepared with non-ionic surfactants, and using Witepsol H15, Witepsol W35 and Witepsol E75. Mixtures of H15 + W35 and H15 + E75 in 1:1 ratio were also used. The prepared suppositories were evaluated for physical properties and release characteristics and were found to be base and surfactant dependant. Amount of drug released from the base mixture was found to be higher than those obtained with the individual base. Addition of non-ionic surfactants variably affects the amount of drug released depending on the nature and concentration of the surfactant used. Brij 72 and Myrj 45 were found to decrease the amount of drug released, however Tween 80 increased the release rate. The surfactant composition was found to affect the drug release. In conculsion, it was found that formulation of ephedrine hydrocloride in suppository form, suitable for infantile administration was possible.

INTRODUCTION

Ephedrine hydrochloride is of value in preventing bronchial spasm in asthma[1]. The medicament is formulated in form of tablets and injections. Great attention has been

paid to searching for another route for ephedrine hydrochloride administration,especially in case of young children suffering from difficulties in respiration. Formulation of this drug in form of suppository, may be the proper way for its administeration in infantile dose. The literature contains numerous reports on the different suppository bases. It was reported, that the base composition has long recognised as having an influence on the therapeutic activity of the drug-base combination[2-4], as the release of drug from the base depends on the relative affinities of the drug for the vehicle and the rectal fluid[5]. Not only the type of the base is affecting in-vitro and in-vivo availabilities of drugs[6-9] but also the type and concentration of surfactants incorporated in the bases during formulations[8-12].

The aim of this study was to formulate infantile ephedrine hydrochloride suppositories with acceptable physical standards. In order to establish a suitable suppository formulation, some studies were proceeded in direction of enhancement of the drug release. This was acheived by using different types of non-ionic surfactants in different concentrations and incorporated with some selected types of adeps solidus bases.

EXPERIMENTAL

Materials:

Ephedrine Hcl (Knoll A.G., Ludwigshafen, W. Germany); Witepsols H‡5, W35 and E75 (Dynamit Noble, W. Germany); Tween 80, Brij 72 and Myrj 45 (Atlas Chem. Indust., U.S.A.) and Cellophane membrane, Spectrapor, MW. Cutoff: 12,000 - 14,000 (Fisher Sci. Co. U.S.A.).

Formulation of Infantile Ephedrine Hydrocloride Suppositories.

Methods:

1- Preparation of suppositories:

The fusion method of Anschel and Lieberman[13] was adopted to prepare the different batches of ephedrine HCl suppositories, each weighed 1 gm ± 5% and containing 10 mg of the medicament using Witepsol H 15, W 35 and E 75. The bases were used alone and in combination with the selected non-ionic surfactants, namly Tween 80, Myrj 45 Brij 72 in concentrations 1,3 and 5%. Other batches using mixtures of H 15 and W35 and E 75 each in 1:1 ratio were prepared.

2- Evaluation of prepared suppositories:

Weight variation and drug content uniformity:

Twenty suppositories were weighed from each batch and the average weight and percent deviation for each suppository were determined according to the B.P. 1980[14]. Drug content was carried out according to the B.P. C. 1973[15].

Hardness teat:

Erweka apparatus model SBT was used to determine the fracture point at 37°C.

Melting point and deformation time:

These were determined using the capillary method and Erweka apparatus model SSP (West Germany).

Solidification point:

The solidification temperature was determined using a small double-walled Dewar-type vacuum vessel[16]. The vessel is 10 cm in high, 5 cm external diameter and 3 cm internal diameter. The molten base without the drug was poured into the flask and gently agit-

ated firstly to reach a uniform temperature. The thermometer is then immersed in the mass and the temperature readings were plotted against time. The solidification temperature was that at which the falling cooling curve was temporarily arrested owing to the liberation of the latent heat of fusion, when the liquid began to crystallise out.

Measurement of the partition coefficient of ephedrine Hcl:

For this study, all the bases with and without surfactants used for for the preparation of the suppositories were tested. For each base, 10 mg of ephedrine hydrochloride was dissolved in 30 ml of a distilled water and then added to the suppository base in a glass bottle. The latter was then tightly closed and allowed to revolve at 40 r.p.m. in a thermostatically controlled water bath adjusted at 37 $\pm$ 0.2^{o} over three hours. At each time interval, the bottle was removed and left at 37$\pm$ 0.2^{o} in a vertical position. One-ml samples were withdrawn and replaced with the same volume of distilled water, diluted then cooled to room temperature, and frozen to solidify the oily phase. Filtration using filter paper was acheived to separate the oily phase and the amount of ephedrine hydrochloride in the aqueous phase was determined spectrophotometrically at 256.5 nm[17] using Unicam SP 1600 spectrophotometer. A control experiment was done under the same conditions using plain bases and distilled water without the drug. The concentration in the aqueous phase, C_w, µg / 30 ml, was calculated from the determined absorbance values and the concentration in the suppository base, C_b, from the equation $C_b = 10 - C_w$ and the partitioning of the drug between the base and the aqueous medium at each time interval was calcuated according to the equation: $K = \frac{C_b}{C_w}$.

Determination of the released amount of ephedrine hydrochloride:

Kruwczinski method[18] was used. One suppository was placed in a glass tube with an open end 3.8 cm in diameter and covered with cell-

ophane membrane stretched firmly by the aid of rubber band to be water-tight. Into 200-ml beaker containing 30 ml distilled water at 37 ± 0.2 C the inverted tube was suspended so that the suppository in the tube was just below the surface of the water. The beaker was placed in a thermostatically controlled water bath to keep the temperature constant throughout the dissolution time. At certain time intervals, one - ml aliquot was taken from the dialysate and analysed for ephedrine HCl released at 256.5 nm[17]. The withdrawn amount was replaced by fresh distilled water. The concentration of the medicament was calculated from a previously constructed calibration curve. Average of six determinations was calculated.

RESULTS AND DISCUSSION

At shown in Table 1., partitioning of ephedrine HCl was a function of the type and concentration of the tested surfactants. The effect of the nature of the base was found to be insignificant. All tested Witepsols contain an emulsifying agents making them more hydrophilic and so the affinity of the medicament to the base would be similar. On other hand, non-ionic surfactants were found to affect the rate of partitioning depending on the type and concentration of the surfactant used. Witepsols incorporated with Tween 80 were found to have a lower affinity to the ephedrine HCl than that observed in case of Witepsols mixed with Brij 72 and Myrj 45.

All the suppositories prepared met the acceptable limlimits of the B.P 1980[14] towards the weight variation which was varied only by ± 5% from the average wight. The content uniformity was determined and found to be within

the stated limits according to B.P.C. 1973[15]. Witepsol E 75 compared with Witepsol H 15 and W 35 showed low hardness value which may be attributed to the higher melting range (37 - 39°C). It is worthy to mention, that the hardness values being lower in case of Witepsols mixture (H15+ W 35) despite its lower melting point (33.8°C) as shown in Table 2. The deformation times of the prepared batches were in correlation with their melting point values. Irrespective of the type of surfactants used, the physical parameters were greatly affected as the surfactant concentration is accompanied with concomitant decrease of hardness. Melting points for all tested Witepsols were decreased as a result of adding Tween 80 and was proved to be concentration dependent. Brij 72 and Myrj 45 were found to increase the melting point of Witepsol H 15 and E 75 depending on the surfactant concentrations. The same results were noticed in case of the solidifying point and deformation time.

From the data illustrated in Figure 1, it can be concluded that the amount of drug released was greatly affected by the nature of the drug, its physical properties and the chemical composition of the base. The release of ephedrine HCl was higher from fatty suppository base of low melting point than of higher melting ones. Thus, with respect to the triglyceride esters, Witepsol H 15 with the lowest value of both melting point and deformation time (D.T) (34.3°C and 4.51 min.) afforded the highest amount released followed by Witepsol W 35 (m.p and D.T were 34.9°C and 5.42 min. respectively) and finally Witepsol E 75 (37.4°C and 8.5 min). As the melting point and deformation time of the base increased,, the rate of release of the drug decreased. As reported by Anschel and Lieberman[13], this might be referred to

the fact that, until the suppository was liquified, the release was limited to the surface of the suppository in contact with the aqueous medium. After liquification the contact between the melted base and the diffusion membrane increased allowing rapid diffusion of the water soluble drug from the oleaginous base. These findings are in agreement with those obtained by Eckert and Muhlemann[19], where the release of drug depended upon the melting state and the interval between the moment when the suppository began to expand and when the melted mass was clear. The release of drug from Witepsols mixtures (H 15 + W35) and (H 15 + E75) was found to be higher than that of individual members of Witepsols. As seen in Table 2, the m.p. of the two mixtures were 33.8 and 35.6^{o}C respectively and this could explain the high release rate obtained with those mixtures. From these findings it was possible to enhance the release of ephedrine HCl from either Witepsol W 35 or E 75 by blending with H 15 in 1:1 ratio. The suppository bases can be arranged according to their release of ephedrine HCl as follows Witepsol (H 15 + W 35)> Witepsol (H 15 + E 75)> Witepsol - H15 > Witepsol W 35 > Witepsol E75.

Incorporation of non-ionic surfactants variably affected the release of ephedrine HCl from the different Witepsols used (Figure 2: A, B and C). This effect varies with the nature and concentration of surfactants. Either Brij 72 or Myrj 45 was found to decrease the drug release from the tested bases. This is in agreement with the work of Fincher et al[20] where incorporation of non-ionic surfactants might result in retardation of the amount medicament released. A slow release rate was obtained with a concentration of 5% then it relatively increased as the concentration decreased,

but it was still below the control. The greatest increase in ephedrine HCl release from Witepsol H 15, W 35 and E75 was obtained in case of using polysorbate 80 incorporated with the bases. The surfactant must have been increasing the rate of diffusion of drug through the cellophane membrane as proved by increasing diffusion with increased concentrations. Ward[12] has found that Tween 61 as a self-emulsifiable surfactant might aid dispersion of the medicament to the surrounding medium. From Figure 2., it is clear that Tween 80 in concentration of 5% produced the highest amount of medicament released. The HLB of the tested surfactants seems to have no effect on the release. This is in contrast to the findings of some investigators[11,12] who found a relation between HLB of surfactants and their efficiency to release the medicament. In spite of the fact that Tween 80 and Myrj 45 have a high HLB (15 and 11 respectively), the former was found to increase the release than the latter. However, Brij 72 which has HLB value of 4.9 is better than Myrj 45.

From the previous findings, it is obvious that HLB is not the sole factor affecting the medicament release but also the chemical composition of the surfactants has a great role. Tween 80 which is characterised by the presence of ester-ether linkage was superior in enhancing the ephedrine HCl release from tested bases than Myrj 45 (ester linkage) and Brij 72 (ether linkage) indicating that the ester-ether linkage type of surfactants is more efficient than the ester and ether types. On the basis of the previous results, it is clear that various factors could affect the medicament release and no single parameter would be designated to produce the desirable effect.

Table 1. Rate of Partitioning of Ephedrine HCl between the tested Suppository Bases and the Release Medium.

Types of Base	Partitioning at Different Times (min.)				
	15	30	60	120	180
Witepsol H 15	1.105	0.786	0.613	0.408	0.399
" + 1% Tween 80	0.961	0.724	0.563	0.379	0.316
" + 3% Tween 80	0.695	0.563	0.282	0.227	0.176
" + 5% Tween 80	0.613	0.449	0.212	0.163	0.087
" + 1% Myrj 45	10.111	4.263	1.174	0.538	0.429
" + 3% Myrj 45	17.182	6.143	1.532	0.653	0.471
" + 5% Myrj 45		15.667	3.082	1.041	0.724
" + 1% Brij 72	1.469	0.923	0.754	0.538	0.504
" + 3% Brij 72		1.941	1.041	0.852	0.653
" + 5% Brij 72		3.167	1.380	1.128	0.786
Witepsol W 35	1.174	0.887	0.639	0.449	0.418
" + 1% Tween 80	1.041	0.786	0.587	0.418	0.370
" + 3% Tween 80	0.786	0.639	0.408	0.316	0.242
" + 5% Tween 80	0.695	0.538	0.333	0.235	0.163
" + 1% Myrj 45	3.762	1.778	1.247	0.786	0.639
" + 3% Myrj 45	4.556	2.279	1.439	0.961	0.724
" + 5% Myrj 45	9.526	3.762	2.030	1.381	0.923
" + 1% Brij 72	1.941	1.326	0.818	0.613	0.538
" + 3% Brij 72	3.545	2.226	1.174	0.887	0.786
" + 5% Brij 72	4.263	3.762	1.597	1.174	1.041
Witepsol E 75	1.222	0.980	0.724	0.481	0.439
" + 1% Tween 80	1.105	0.887	0.538	0.379	0.205
" + 3% Tween 80	0.961	0.695	0.379	0.220	0.124
" + 5% Tween 80	0.802	0.538	0.290	0.163	0.087
" + 1% Myrj 45	1.564	1.273	0.852	0.681	0.563
" + 3% Myrj 45	2.279	1.564	1.105	0.852	0.739
" + 5% Myrj 45	3.762	2.263	1.564	1.222	0.905
" + 1% Brij 72	1.500	1.174	0.818	0.563	0.482
" + 3% Brij 72	2.448	1.439	0.980	0.786	0.575
" + 5% Brij 72	3.000	2.390	1.105	0.923	0.709
Witepsol H 15 + W 35 (1:1)	0.818	0.449	0.418	0.379	0.333
Witepsol H 15 + E 75 (1:1)	1.174	0.695	0.539	0.409	0.370

Table 2. Physical Parameters of the Prepared Ephedrine HCl Suppositories.

Test Applied	Hardness, Kg				Melting point, C°				Solidifying point, C°				Deformation time, min.			
Base + SAA (% w/w)	0	1	3	5	0	1	3	5	0	1	3	5	0	1	3	5
H_{15} + Tween 80	2.10	2.0	1.9	1.8	34.3	34.1	33.9	33.8	32.2	32.15	32.1	31.9	4.51	4.46	4.09	3.45
+ Brij 72		2.1	1.8	1.5		34.8	35.1	35.8		32.3	32.37	32.6		5.20	5.45	6.40
+ Myrj 45		2.0	1.8	1.5		34.7	34.9	35.2		32.25	32.4	32.56		5.55	6.25	7.15
W_{35} + Tween 80	2.4	2.35	2.2	2.1	34.9	34.75	34.5	34.35	30.4	30.1	29.8	28.9	5.42	5.29	5.0	4.45
+ Brij 72		2.35	2.3	2.2		35.0	35.1	35.2		30.45	30.6	30.8		6.30	7.1	8.30
+ Myrj 45		2.3	2.2	2.1		34.95	35.0	35.1		30.4	30.5	30.7		6.0	6.30	7.15
E_{75} + Tween 80	1.5	1.3	1.1	0.9	37.4	37.25	37.05	36.45	32.3	31.9	31.65	31.25	8.5	8.15	7.55	7.4
+ Brij 72		1.5	1.4	1.3		37.5	37.7	37.85		32.4	32.55	32.8		9.0	10.05	11.3
+ Myrj 45		1.45	1.3	1.2		37.45	37.6	37.75		32.3	32.36	32.7		8.55	9.25	10.35
H_{15} + W_{35} (1:1)	1.9				33.8				32.6				4.30			
H_{15} + E_{75} (1:1)	2.2				35.6				33.9				6.27			

Formulation of Infantile Ephedrine Hydrochloride Suppositrories.

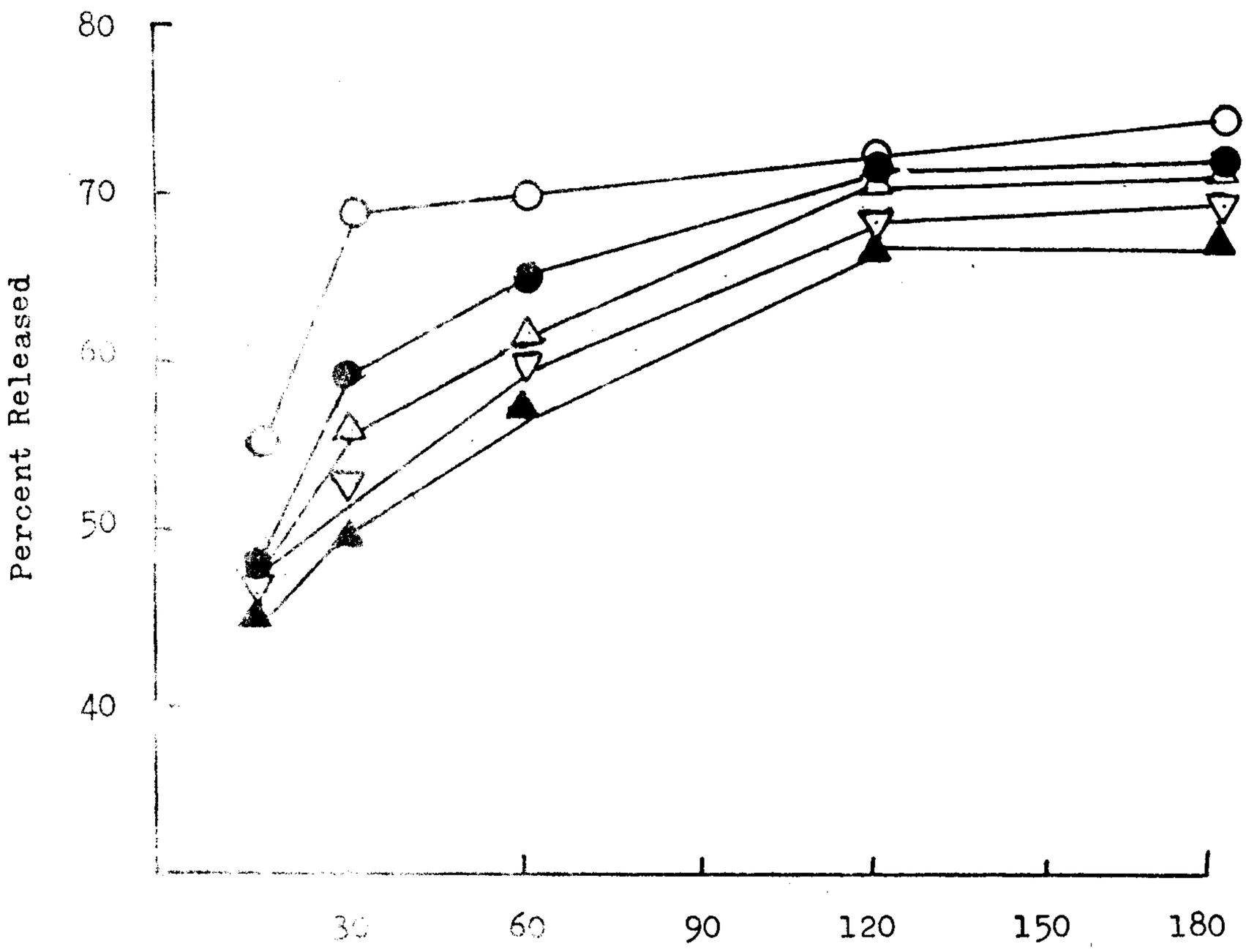

Figure 1: Effect of type of the bases on the amount of ephedrine HCl released from prepared suppositories.
○ Witepsol H 15 + W 35; ● Witepsol H 15 + E 75;
△ Witepsol H 15; ▽ Witepsol W 35 and ▲ Witepsol E 75.

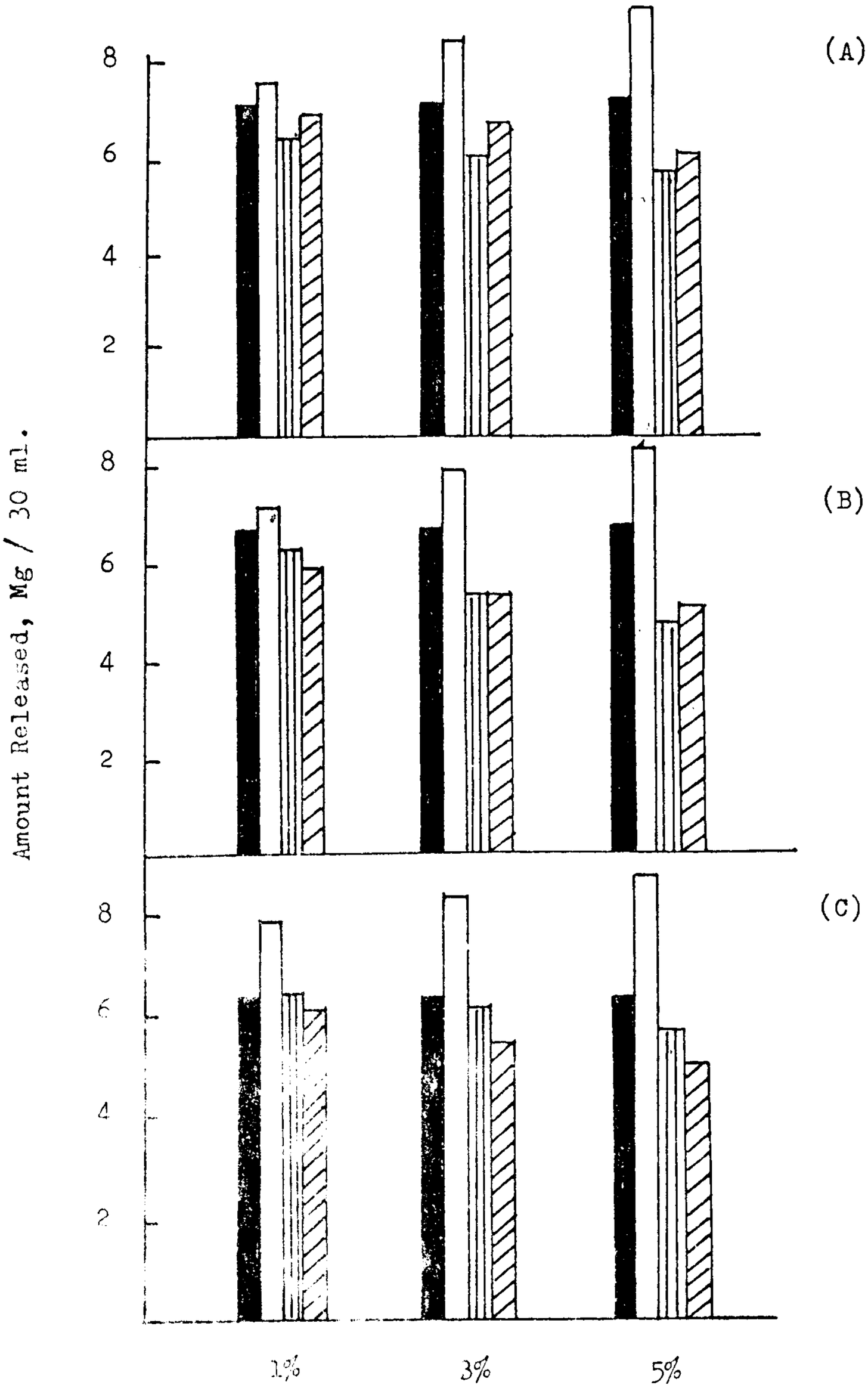

Figure 2. Effect of type and concentration of surfactants on the amount of ephedrine HCl released from different suppository bases after 3 hrs.
(A) Witepsol H 15; (B) Witepsol W 35 and (C) Witepsol E 75
■ Plain base; ▯ Base + Tween 80; ▯ Base + Brij 72; and
▨ Base + Myrj 45.

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صياغة ايدروكلوريد الافدرين فى اقماع الاطفال

عبد الجواد حلمى ـ احمد طلعت نوح ـ محمد الشابورى

قسم الصيدلانيات ـ كلية الصيدلة ـ جامعة المنصورة

تم فى هذا البحث صياغة ايدروكلوريد الافدرين فى لبوسات للاطفال باستخدام قواعد اللبوسات الاتية : ويتبسول هـ ١٥ ، ى ٣٥ ، و٧٥ ومخلوط من هـ ١٥ ، ى ٣٥ (١ : ١) وهـ ١٥ ، و ٧٥ (١ : ١) . كما اضيفت الى هذة القواعد ١ ،٣ ، ٥ / من المواد المنشطة سطحيا وهى تويين ٨٠ وبرج ٧٢ ومرج ٤٥ .

وقد قيمت الاقماع المحضرة من حيث الخواص الطبيعية وانطلاق الدواء ووجد ان اضافة المواد النشطة سطحيا يقلل درجة الانصهار والصلابة لهذه اللبوسات كما وجد ان اعلى معدل لانطلاق الدواء يأتى من مخاليط القواعد المختلفة يليها ويتبسول هـ ١٥ ثم ى ٣٥ ثم ٧٥ . كما وجد ايضا ان تويين ٨٠ يزيد من انطلاق الدواء ولكن برج ٧٢ ومرج ٤٥ يقللان من انطلاقه .

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