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A NEW APPLICATION OF MEBEVERINE-HYDROCHLORIDE AS A LOCAL ANAESTHETIC DRUG

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ABSTRACT

The efficiency of the well known antispasmodic drug mebeverine-hydrochloride, as a local anaesthetic was evaluated. The drug was formulated into different ointment and gel bases. The prepared topical applications were evaluated for the in vitro release of the drug and for the local anaesthetic effect on the rabbit's eye. The release profile agreed with the first order kinetics, the release rate and the duration of action of the drug was found to be a function of type of base. Carbopol 934 gel gave the longest duration of action (113 minutes), the polyethylen glycol base gave a moderate duration (50 minutes), while the shortest duration of action (15 minutes) was achieved in case of hydrophilic petrolatum.

INTRODUCTION

Mebeverine hydrochloride (MB-HCl) is a musculotropic spasmolytic drug with a strong and selective action on the smooth muscle of the gastrointestinal tract particularly of the colon[1].

Czechowicz et al.[2] recognized that, a non-specific depressant action of MB-HCl in addition to a local anaesthetic activity and potentiation of the sympathetic inhibitory influence resulting into a decrease in intestinal motility.

Linder et al.[3] suggested that, the local anaestehtic action of MB-HCl may contribute to relaxation of intestinal tract by acting presynaptically and accordingly limit transmitter release from nerve endings. On the other hand, Hertog et al.[4] reported tht MB-HcL exerts a local anaesthetic action by blocking voltage operated sodium channels.

In general, hypersensitivity to local anaesthetics seems to occur most prominently with compounds of the ester type, whil amide types are essentially free from this problem[2]. Having amide group in its structure, MB-HCl was thought to be a good candidate as a local anaesthetic drug. The absence of marked dosage forms of MB-HCl encouraged the author to formulate this drug in different topical preparations.

EXPERIMENTAL

Materials:

Mebeverine Hydrochloride powder was a kind gift from EPICO (Tenth of Ramadan, Egypt), carbopol 934, 940, 941 (B.F. Goodrich, chemical Co., USA) white wax, white petrolatum (winlab, a division of wilfried smth limited, UK), cholesterol, stearyl alcohol, polyethylene glycol 6000, 3350, 600 and 400, Tween 20 (B.D.H. Chemicals Ltd. poole, England). Tragacanth, Triethanol amine, Propylene glycol (pharmaceutical grades).

Cellophane membrane (spectropor, M.W. cut off point 10,000 spectrum medical industries, U.SA.

Magnetic stirrer (W. Germany), spectrophotometer (pye unicam sp. 8800, Cambridge, UK).

Mature olbino rabbits, body weight ranged from 1.9 to 2.3 kg.

Methods:

I. Preparation of Mebeverine Hydrochloride in Topical Formulation:

MB-HCl was formulated into topical formulations using several bases polyethylene glycol ointment bases (usp), oleaginous base (usp), Bassorine paste (usp) and hydrophilic petrolatum (usp) were used.

The composition and method of preparation given in US pharmacopoeia were followed with no modifications. Carbopol gels with the following formula were also used:

	% by weight
Carbopol (940, 941 or 934)	3.5
Water	7.7
Carbowax 6000	2.5
Tween 20	2.5
Tiethanol amine x 10%	10
Propylene glycol	6

The gels were prepared by dispersing the carbopol resin in sufficient amount of water with rapid agitation using a magnetic stirrer. Propylene glycol, Carbowax 6000 and Tween 20 were dissolved in the remaining water. The homogeneous solutions were combined with slow stirring. Triethanolamine was then added and stirring was effected until uniform.

2% Topical preparations of MB-HCl were prepared by dispersing the drug in the previously prepared bases.

II- In Vitro Release, Studies:

Accurately weighted 2 g of the medicated bases (containing 2% of MB-HCl) were placed on a piece of standard cellophane membrane, which was previously soaked in distilled water over night. The loaded membrane was stretched over the end of an open glass cylinder (diameter 2.5 cm) and tied firmly with rubber band, the surface of the dialyzing chamber was rolled gently to smooth it and remove all air formed between the medicated bases and membrane. The dialyzing chamber was immersed in a 400 ml beaker containing 300 ml of isotonic phosphate buffer (pH-6-8) being careful to keep the solution level below rubber ring. The beaker was placed in thermostatically controlled water both maintained at 37.5 ± 0.5°C. The solution in the beaker was constantly strirred at 70 rpm with magnetic stirrer. At intervals, samples (1 ml each) were withdrawn from the dialysis medium. The withdrawn samples were replaced by equal volumes of phosphate buffer maintained at the same temperature. The amount of drug released in each sample was specterophotometrically determined at 270 nm.

The release data were analyzed according to zero, first, second order kinetics and diffusion controlled release mechanisms. Curve fitting was done by linear regression analysis and the c.v% was calculated in each case[6].

Evaluation of Local Anaesthetic Activity:

The rabbits were randomly divided into 7 groups, four rabbits each. For each rabbit the left eye used for the test preparation, while the right one served as a control.

Accurately weighted 25 mg of the tested preparation was transferred to a microspatula and placed inside the center of the lower eye lid with care being exercised not to irritate the eye or touch the corneal surface. The lower lid was gently moved across the cornea to spread the preparation uniformly. The right eye was similarly treated with the respective plain base. 2% aqueous solution of MB-HCl was used as a reference preparation.

The anaesthetic activity was evaluated through the effect on the corneal reflex. The rabbit's eye ball was touched from the side by a fin glass rod ended with a small cotton plug. This act was repeated at one minute intervals. The time from application of the preparation until the corneal reflex is last was taken as the onset time. Duration of action, which is the time elapsed between the loss of the corneal relex and its return, was also determined.

RESULTS AND DISCUSSION

The release behavior of MB-HCl from the formulated topical applications was evaluated. Table 1 shows the results of the kinetic and statistical treatment of in vitro release data. The gel and ointment bases were containing the same concentration (2% w/w) of MB-HCl. The coefficient of variation (c.v%) as well as the $t_{1/2}$ and k for all formulae were calculated. From this table, it is clear that the drug release profile follows first order kinetics (the lowest c.v%).

The in vitro release profile from different bases at 37°C is illustrated in Fig. 1. From this figure, it is evident that, the cumulative amount of drug released is directly but not linearly proportional to the time. The release behavior was found to be a function of the type of the base. From Figure 1 and Table 1, it is apparent that, the release rate of MB-HCl from carbopol 934, oleaginous and PEG bases are faster than the other bases. On the other hand the hydrophilic petrolatum bases showed that lowest drug release rate.

The drug release through PEG base exhibited a fast initial phase up to 30 minutes followed by a slow release up to 6 hours. This may be due to the fact that, in the initial phase the drug molecules adjacent to the membrane were ready for diffusion. In the second phase, a slower process of drug release from the base proceeds its diffusion through the membrane. Furthermore, an equilibrium between MB-HCl in the base and in the dissolution medium might has been established resulting into the slower release in the second phase. Also, the water miscibility of PEG may be a contributing factor in achieving improved release, compared to the other vehicles, up to 6 hours. These results are in agreement with James et al[7].

In case of hydrophilic petrolatum base, the release rate of MB-HCl is very slow (k = 0.005) in comparison with the other bases Table 1. Hydrophilic petrolatum might absorb water from the dissolution medium forming w/o emulsion, MB/HCl was held firmly in the internal phase of emulsion because of its water solubility.

The results of local anaesthetic behavior of the drug in rabbit's eye are given in Table 2. Both onset and duration times were found to depend on the type of base. The onset time varied from 3 to 9 minutes, while the duration time was in the range of 15 to 113 minutes. Carbopol 934 base gave a short onset time of 3 minutes and the longest duration time of about 113 minutes while hydrophilic petrolum gave the longest onset time of 9 minutes and the shortest duration time of 15 minutes. It is worthy noting that 2% solutions of MB-HCl gave an onset time of 3 minutes and a duration time of 21 minutes. The prolongation of drug action caused by the use of carbopol 934 gel base was also

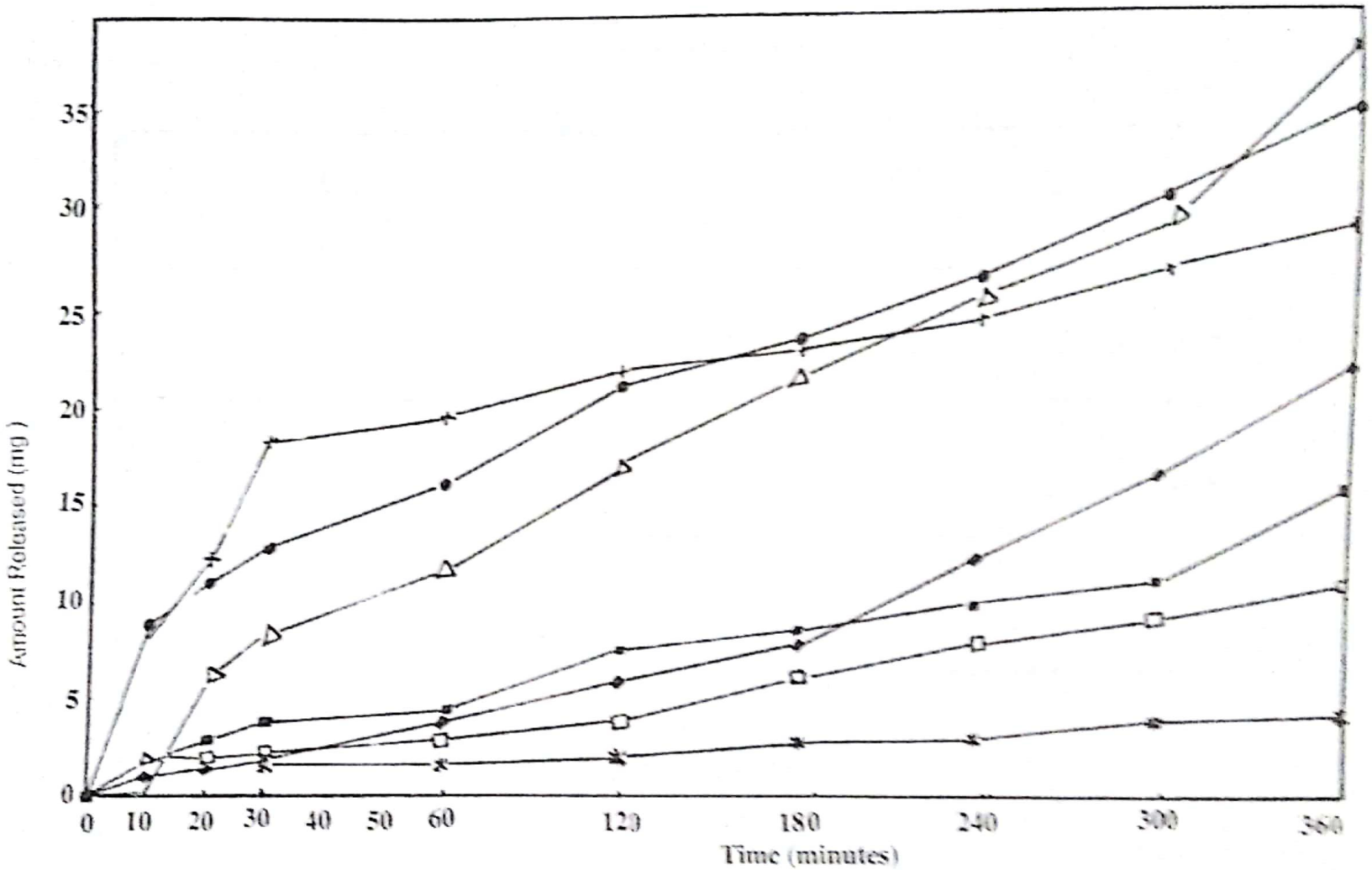

Figure (1): In Vitro release profile of mebeverine hydrochloride from different bases.

Key:

♦ Oleaginous base
■ Carbopol 941 gel
* Hydrophilic petrolatum base
♦ Carbopol 940 gel
x Polyethyien glycol base
Δ Carbopol 934 gel
□ Bassorin base

Table (1): Kinetic and statistical treatment of in vitro release data of mebeverine-hydrochloride from different bases.

Type of bases	Order	C.V.%	$t_{1/2}$ (minutes)	K
Carbopol 940	Zero	13.439	14.880	3.359
	First	0.322	18.410	0.037
	Second	1.750	23.640	0.000
	Diffusion	26.575	29.040	9.279
Carbopol 941	Zero	11.103	24.411	2.040
	First	0.203	31.072	0.022
	Second	0.970	40.991	0.000
	Diffusion	13.240	74.112	5.808
Carbopol 934	Zero	7.299	9.470	5.283
	First	0.407	10.341	0.0673
	Second	2.421	11.623	0.000
	Diffusion	9.343	11.013	15.071
Bassorine	Zero	4.499	32.441	1.541
	First	0.059	42.232	0.016
	Second	0.293	57.220	0.00
	Diffusion	14.055	134.550	4.310
Hydrophilic petrolatum	Zero	6.611	98.000	0.511
	First	0.036	132.160	0.005
	Second	0.171	185.610	0.00
	Diffusion	10.668	1213.610	1.435
Oleagenous	Zero	6.466	12.020	4.160
	First	0.314	12.920	0.0536
	Second	1.201	14.370	0.0011
	Diffusion	3.724	17.270	12.030
Polyethylene glycol	Zero	14.041	17.850	2.800
	First	0.751	19.720	0.035
	Second	2.961	22.580	0.000
	Diffusion	10.472	34.860	8.460

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Table (2): Effect of base type on the onset time and duration of local anaesthetic action of mebeverine hydrocholoride.

Bases	Onset time in minutes (Mean ± SD)	Duration of action in minutes (Mean ± SD)
Carbopol 940 Gel	3.0 ± 2.45	34.5 ± 6.18
Carbopol 941 Gel	4.0 ± 1.10	25.5 ± 1.50
Carbopol 934 Gel	3.0 ± 0.00	113.3 ± 1.22
Bassorine Base	4.5 ± 1.15	30.0 ± 3.00
Hydrophilic petrolatum, usp	9.0 ± 1.01	15.0 ± 0.00
Oleaginous Base	0.0 ± 2.01	35.5 ± 1.30
PEG Base	0.0 ± 0.99	50.3 ± 1.85
2% Aqueous solution	3.0 ± 1.08	21.0 ± 0.00

Table (3): Analysis of variance (ANOVA) for the duration of action obtained from different topical formulations using rabbits eye.

Sources of variation	Degrees of freedom (DF)	Sum of squares (SS)	Mean squares (MS)	Variance ratio (F)	Least significant (L.S.D.)
Treatment	7	29488.2	4212.6	619.5	3.7
Error	24	163	6.8	--	--
Total	31	27048.5	--	--	--

($\alpha = 0.05$)

Table (4): Correlation coefficient (r) between duration of action and some In vitro release parameter.

Parameter	r	t*	Significance
Amount released after one hour	0.7467	3.765	Sig.
Amount released after six hours	0.7106	3.210	Sig.
t_{50} first order	-0.7630	4.081	Sig.
First order Release constant (k)	0.6060	2.141	Non Sig.

* Calculated from the relation $t = \frac{r \quad n-2}{1-1^2}$ (DF = n-2 , $\alpha = 0.05$).

reported by other investigators working on indomethacin[7].

The data obtained for the duration of action of the local anaesthetic drug from its topical formulations were statistically analzed using one-way analysis of variance (one-way ANOVA)[6]. No statistically significant differences were observed between carbopol 940, Bassorine and oleaginous bases at $\alpha = 0.05$. The data of the other bases were found to differe significantly. All bases showed significant differences from the aqueous solutions containing 2% MB-HCl. The ANOVA calculations are given in (Table 3).

Correlation of the in vitro release of the drug from its bases (except carbopol 934 gel) with its duration of action in rabbit's eye was tested. The correlation coefficients "r" between the duration of action and various release parameters were calculated (Table 4) and used as a measure of association. Testing the significance of the correlation coefficient values[6] revealed a significant positive correlation between the duration of action and both the amount released after one and 6 hours. A significant negative correlation awas existing between the $t_{1/2}$ of the first order release and the duration of time. On the other hand no association between the first order release rate constant and the duration of action was existing as indicated by the non significant correlation coefficient (Table 4).

To recapitulate, MB-HCl is suitable for use as a local anaesthetic. The drug is non irritant and non toxic[8], the onset time of anesthetia produced by all the tested formulated bases ranged from 3-9 minutes. Carbopol 934 gel was proved to be the best base.

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تطبيق جديد لأيدروكلوريد الميفرين كمخدر موضعى

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قسم الصيدلانيات - كلية الصيدلة - جامعة حلوان - مصر

تم تقييم كفاءة عقار ايدروكلوريد الميفرين المعروف كمضاد للتقلص من ناحية تأثيره المخدر الموضعى. وقد تم صياغة العقار فى مراهم وهلاميات مختلفة. وقد تم تقييم المستحضرات معملياً لبيان التأثير المخدر الموضعى على عيون الأرانب.

وقد ثبت أن إتاحة العقار يتبع ميكانيكية الرتبة الأولى كما أن سرعة الإتاحة ومدة المفعول للعقار تعتمد على نوع القاعدة المستخدمة. وقد أعطى الكاربوبول ٩٣٤ كقاعدة للامام اطول فترة فاعلية ١١٣ دقيقة، بينما أعطى عديد إيثلين الجليكول فترة فاعلية متوسطة (٥٠ دقيقة) فى حين أعطى البترولاتم المحب للماء أقل فترة فاعلية ١٥ (دقيقة).