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Formulation and in vitro evaluation of verapamil HCl suppositories

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Summary

19 formulations of verapamil HCl in different water-soluble and fatty bases were prepared. Fatty bases included Witepsol H15, Witepsol E75, Suppocire AM and their mixtures. PEGs of different molecular weights and mixtures thereof represented the water-soluble bases. Urea and lysine HCl were included as additives in some formulations to investigate their role in enhancement of drug release and diffusion through the membrane barrier. All the formulations proved to be satisfactory as regards content uniformity and other physical tests; appearance, melting range, breaking test and disintegration. Release experiments from the different suppository bases, with or without the use of membrane barriers, were conducted using the USP XXII dissolution tester. Cellophane bags containing 10 ml of the dissolution medium were used to represent the rectal compartment. The data obtained from these experiments proved the superiority of the PEG formulation (PEG 1500 : PEG 6000 : water; 65 : 28 : 7): $T_{90\%}$, 180 min using the bag. However, it appears that increasing the proportion of high molecular weight fraction of PEG in the formulation has an adverse effect on the rate and extent of diffusion of the drug through the membrane. Good results were also obtained with the mixtures of Witepsol E75 : Witepsol H15 (1 : 3) and Witepsol E75 : Suppocire AM (1 : 1); $T_{70\%}$, 120 and 210 min, respectively, using the bag. Lysine HCl and urea improved the release of the drug from Witepsol-E75 probably by decreasing the melting point and increasing the spreading coefficient of the base. An optimum concentration of each additive was found to exert the desired enhancement of release.

Introduction

Verapamil HCl (Vp-HCl) is a calcium channel blocker used as anti-anginal, anti-arrhythmic, and antihypertensive. The drug is well known to suffer to a great extent from the first-pass effect, leading to the formation of norverapamil as the major metabolite together with minor products (Reynolds and Prasad, 1982). The observed bioavailability ranged between 20 and 30% of the oral dose. In addition, by virtue of its high lipid solubility and high partition coefficient, it represents an excellent model for rectal administration. This route of administration was utilized successfully for administration of different drug groups, e.g., aspirin (Gibaldi and Grundhofer

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TABLE 1

Formulation of verapamil HCl (40 mg) suppositories in PEG-bases

Formula	PEG 1500 (%)	PEG 6000 (%)	Water (%)	Additives	k [a]
1	33	47	20	-	0.0089
2	33	47	20	urea (5%)	0.011
3	93	–	7	–	0.01
4	65	28	7	–	0.013

[a] First-order release rate constant (m^{-1}).

1975), paracetamol (Feldman 1975), anti-inflammatory drugs (e.g., El-Massik (1987) and Ali et al. (1982)) and CNS depressants (e.g., Habib et al. (1990)). The release of drugs from different suppositories depends mainly on the physicochemical properties of the drug and the nature of the base employed (e.g., Habib et al. (1987) and El-Massik (1987)). A literature survey of Vp-HCl pointed out a lack of rectal formulations of this drug. This work describes the formulation, preparation and in vitro evaluation of Vp-HCl suppositories using water-soluble and fatty bases. Furthermore, the effect of certain additives, namely, urea and the amino acid lysine HCl, on the drug release was investigated in different concentration ranges.

Materials and Methods

Materials

Vp-HCl and urea (E. Merck, Darmstadt, Germany), PEG (Fluka AG, Chemische Fabrik, Buchs, SG Switzerland), DL-lysine hydrochloride (BDH Chemicals Ltd, Poole, U.K.), Witepsols (Dynamit Nobel, Germany) and Suppocire AM (Gattefossé Etablissements, France) were obtained from the indicated sources. Dialyzer tubing (diameter, 5/8 inch; wall thickness, 0.0008 inch; Mol. Wt cutoff, 12000; Cat. No. 3787-D22 (Arthur Thomas Co., Philadelphia, PA, U.S.A.)) was used. All other chemicals were either analytical or reagent type grades.

Methods

Preparation of suppositories

Suppository formulations were prepared from either fat or water-soluble bases by the melting technique so as to contain 40 mg of Vp-HCl per

TABLE 2

Formulations of verapamil HCl (40 mg) suppositories in fatty bases

Formula	E75 (%)	H15 (%)	AM (%)	Water (%)	Additives (mg)	k [a]
5	80			20		0.0007
6	80	-		20	lys., [b] 7.5	0.0013
7	80	–	-	20	lys., 15	0.0015
8	80	–		20	lys., 30	0.0008
9	80	–	-	20	urea, 5	0.0009
10	80	-	-	20	urea, 10	
11	80	–	–	20	urea, 20	0.0011
12	80		-	20	urea, 40	0.0034
13	80	–	–	20	urea, 100	
14	80	–	–	20	urea, 200	0.0037
15	24	72	-	4	-	0.0064
16	24	72		4	lys., 7.5	0.0066
17	46	–	46	8		0.0057
18	46	–	46	8	lys., 7.5	
19	46	-	46	8	urea, 100	0.0053

[a] First-order release rate constant (m^{-1}).
[b] Lysine HCl.

suppository. The fatty bases investigated were Witepsol E75 (W-E75), Witepsol H15 (W-H15) mixed with W-E75 (3:1) and Suppocire AM (S-AM) in combination with W-E75 (1:1). The water-soluble bases investigated were PEG 1500, PEG 6000 and mixtures thereof. The drug and the different additives were included in the formulae by dissolving them in a calculated amount of water followed by addition to the molten base. The composition of all formulations including PEGs and fatty bases is summarized in Tables 1 and 2, respectively.

Weight variation

The average weight was calculated by weighing 20 suppositories individually. The percent deviation from the mean was subsequently determined.

Content uniformity

Individual suppositories, in eight-replicate, were placed in 250 ml Erlenmeyer conical flasks containing 25 ml of 0.1 N hydrochloric acid and maintained at 37 °C. After complete melting of the suppositories, the volume was completed with the same medium to 100 ml and the containers were allowed to rotate in a constant temperature water bath at 37 °C and at 120 rpm for 15 min. Aliquots were withdrawn from the aqueous phase and suitably diluted and assayed spectrophotometrically at 278 nm. For water-soluble bases, the formulation was allowed to dissolve in 100 ml water at 37 °C and assayed as mentioned earlier. In both cases, blank suppositories without drug were prepared and subjected to the same analytical procedure to serve as the blank for spectrophotometric determination.

Disintegration

The test was performed using the USP tablet disintegration tester (Erweka Type ZT4, Erweka GmbH, Germany) at 37 °C.

Fracture point

For evaluation of the resistance of the formulations to deformation under the effect of increasing weight, the Erweka apparatus, Model SBT was utilized.

Melting point determination

The ascending melting point method was used for this purpose. Capillary tubes, 10 cm in length, open at both ends, were filled with the formula to about 1 cm height and dipped in gradually heated water along with a thermometer.

Partition coefficient

The partition coefficient of Vp-HCl between water and chloroform was evaluated by dissolving 20 mg of Vp-HCl in 100 ml of phosphate buffer in the pH range from 2.2 to 7.4 against 16.7 ml chloroform. The mixture was then shaken for 15 min at 20 °C and allowed to stand for some time for complete phase separation. The aqueous phase was assayed for drug content by spectrophotometry at 278 nm.

In vitro release study

The USP XXII dissolution tester, apparatus 1 (Hanson Research Corp., Northridge, CA, U.S.A.) was used for this purpose, employing 500 ml of the different dissolution media. The temperature was maintained at 37 °C and the stirring rate was kept constant at 50 rpm. The release of the drug from different bases was determined by placing the suppositories either directly in the dissolution medium or contained, with 10 ml of the dissolution medium, in dialysis tubes. The tubes were fixed around the paddle before starting the release experiment with the help of sewing threads to ensure regular movements of the bag through the dissolution medium.

Effect of additives on drug release

Urea and DL-lysine HCl were tested as possible enhancers for in vitro drug release. The effect of these additives at different concentrations was also investigated with regards to their influence on drug release and diffusion through the artificial barrier employed.

Results and Discussion

Physical examination

Appearance

The prepared suppositories were well-formed, white or creamy white in colour, with a smooth

shining surface. After slicing them longitudinally they did not show any fissures or cracks, nor did they display contraction holes or entrapped air bubbles.

Weight variation and content uniformity

Suppositories assessed for these two parameters were found to be quite satisfactory and conformed with the requirements of the B.P. 1988. The observed good content uniformity may be due to incorporation of the drug into the different formulations as a solution completely mixed with the hydrophilic bases or emulsified within the fatty bases, rather than as dispersed drug particles.

Disintegration, fracture point and melting range

The data determined for these tests are summarized in Table 3. The different formulations exhibited different disintegration times. They either dissolved or softened and melted within the range of 7–15 min. Rapid disintegration would enable fast and easy spreading of the formula which would in turn affect largely the drug release. The prepared suppositories exhibited a reasonable degree of hardness ranging between 1.8 and above 5.8 kg. Melting point determination revealed considerable variability between the tested formulations (34–48 °C). PEG bases showed a higher and wider melting range.

TABLE 3

Physical parameters of some formulations

Formula	Disintegration time (min)	Fracture point (kg)	Melting range (°C)
F1	15	1.8	38 –47.5
F3	13	> 5.8	38 –44.5
F4	15	25	39 –48
F5	13	> 5.8	36.5–38
F7	13	4.7	36 –37.5
F8	13	4.8	36 –37.5
F11	12	4.8	35 –37.5
F13	9	4.4	35 –37.5
F15	7	3.2	34 –36.5
F17	8	5.4	34.5–37

The implications of the above factors on drug release and diffusion will be discussed later.

Release study

The effect of different factors on drug release from the different formulations was studied by plotting the percent of drug released vs time. Moreover, for easier and more quantitative comparison, the kinetics of drug release was investigated to enable the calculation of release rate constants, k (Tables 1 and 2). The drug release from the different formulations followed a first-order pattern.

Effect of base type

The release of VP-HCl from the different PEGs (F1, F3 and F4) and fatty bases (F5, F15 and F17) is illustrated in Figs 1 and 2, respectively. The results indicated that drug release from PEG bases was superior to that from fatty bases. All formulations showed essentially a more or less identical release pattern. Release of Vp-HCl from fatty bases showed different behaviour, since release from F15 and F17 was distinctly greater than that from F5. It could be concluded, therefore, that decreasing the proportion of W-

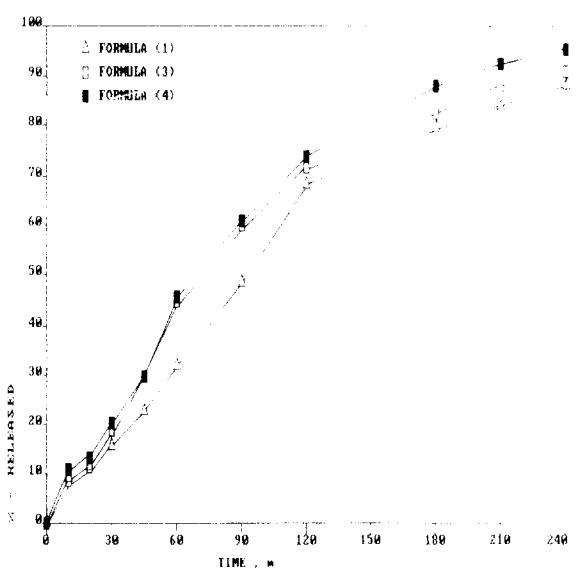

Fig. 1. Release of verapamil HCl from different PEG-based formulations.

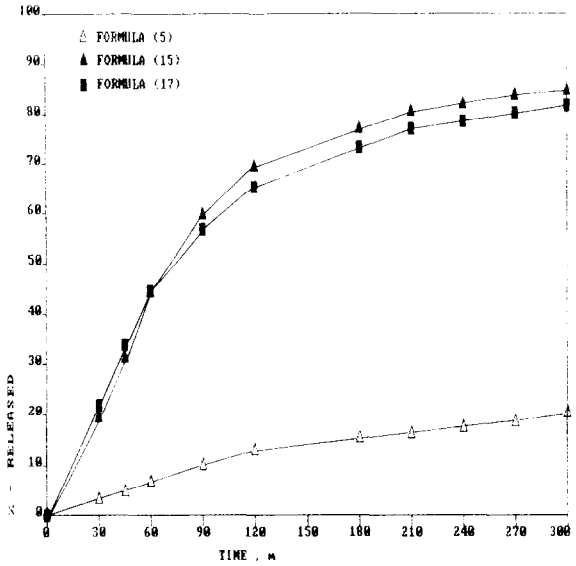

Fig. 2. Release of verapamil HCl from different fatty bases.

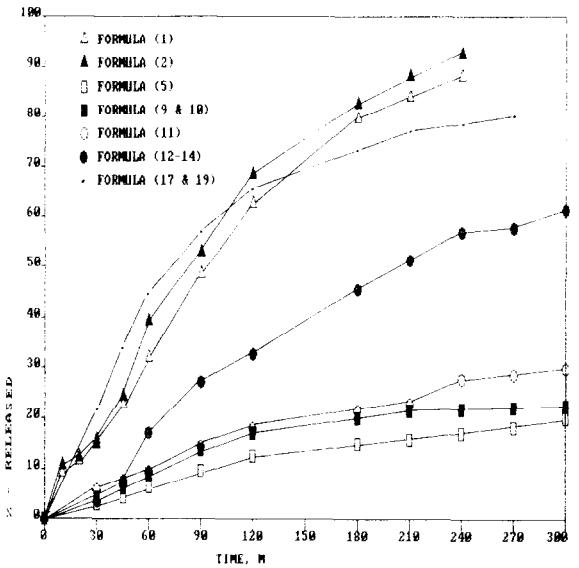

Fig. 3. Effect of different concentrations of urea on release of verapamil HCl from different formulations.

E75 improves the release characteristics. This could be explained by the observed higher m.p. of F5 in comparison with F15 and F17 (Table 3) which enabled faster softening and easier spreading of the mass during the release study of the last two formulations.

Influence of additives on release

Inclusion of either urea or DL-lysine HCl in some formulations was carried out to study their effects on drug release. The results are shown in Figs 3 and 4, respectively, and in Table 2. These two substances were selected on the basis of the osmotic effect of urea and ion-pair initiation by lysine HCl, in addition to their compatibility with body fluids, being normal components of the human body. Basic amino acids have been used successfully to improve rectal absorption of ampicillin sodium in the form of salts with diclofenac (Yaginuma et al., 1982), and as enamine derivatives (Murakami et al., 1981) to enhance the rectal absorption of different β-lactam antibiotics.

The effect of urea (5%) on release from PEG bases, e.g., F2, was demonstrated by a slight increase in the rate and extent of drug release. In the case of fatty bases, the effect was more pronounced with bases which did not show initially good drug release, e.g., F5. The drug release was slightly increased in the presence of 5–20 mg of urea/suppository. Higher concentrations of urea (40 mg) produced a distinctly further improve-

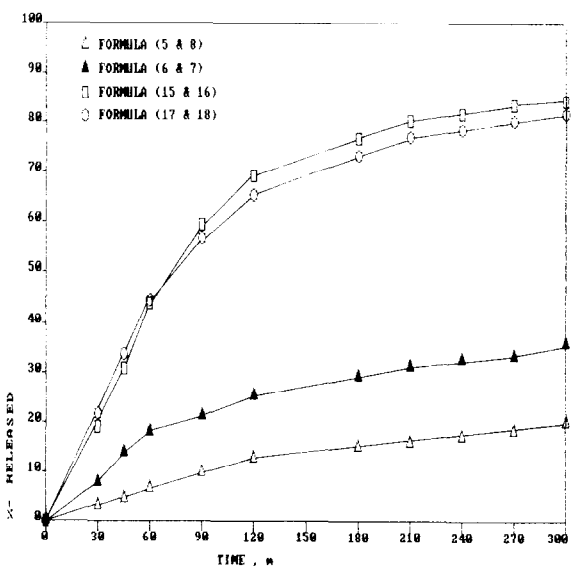

Fig. 4. Effect of different concentrations of lysine HCl on release of verapamil HCl from fatty bases.

ment in drug release, where the observed release rate constant from F12 was 5-fold that of F5 (Table 2). However, higher concentrations of urea showed no further improvement in drug release as indicated from F13 and F14 (Fig. 3). On the other hand, formulation containing a mixture of W-75 and S-AM (F17) which exhibited good drug release, 80% after 3 h, did not show better release on addition of urea (F19) (Table 2). Further, the effect of lysine HCl was investigated in an attempt to increase release from fatty bases (Fig. 4). Inclusion of either 7.5 or 15 mg with W-E75 (F6 and F7) doubled the release rate constant in comparison with the parent formula (F5) (Table 2). However, increasing lysine concentration to 30 mg (F8) reversed the drug release profile to the parent formula (F5). This effect may be explained by the possible formation of a verapamil-lysinate complex exhibiting less water solubility than Vp-HCl. This suggestion is substantiated by the observed separation of an oily liquid during mixing of Vp-HCl with the amino acid solution. The molar ratio of drug:amino acid was found to be 1:2 which could further support the above explanation. Lysine HCl did not affect the drug release from bases already showing good release characteristics, e.g., those containing W-H15 (F15) and S-AM (F17) in mixtures with W-E75. The observed effect of additives on drug release could be explained by their abilities to reduce the melting range and disintegration time of such bases with relatively higher initial values (F5) (Table 3). This will be reflected in better spreading and improved drug release. Lysine HCl did not change the pH of the dissolution medium, while urea only raised the pH of water from 6.2 to 6.4. Therefore, an effect on pH would be excluded.

Effect of the cellophane bag on diffusion

The release experiments were carried out directly in the dissolution media to investigate the role of the cellophane membrane on drug release. The results obtained and those determined using the bag are illustrated in Fig. 5. A distinct increase in release behaviour was observed on excluding the cellophane barrier in the three formulations studied. The largest difference was observed with F5, where the release rate constant and the extent of release without membrane was 10- and 3-fold, respectively, in comparison with the corresponding values employing the bag. Regarding the other two formulations studied (F15 and F17), the rate of drug release in the initial stage was greatly reduced in the presence of the membrane to about one-third the values without the bag. However, the extent of drug released from the bag after 3 h from both formulations was only 10–15% less than without the bag. The above results show that the initial drug release from the base determines to a great extent the amount diffusing through the membrane. Therefore, the observed release from F5 without the membrane was less than the release from F15 and F17 with the membrane. This is explained by the better spreading, and hence greater surface contact with the medium, due to the shorter disintegration time and lower melting range such as in the case of F15 and F17 relative to F5.

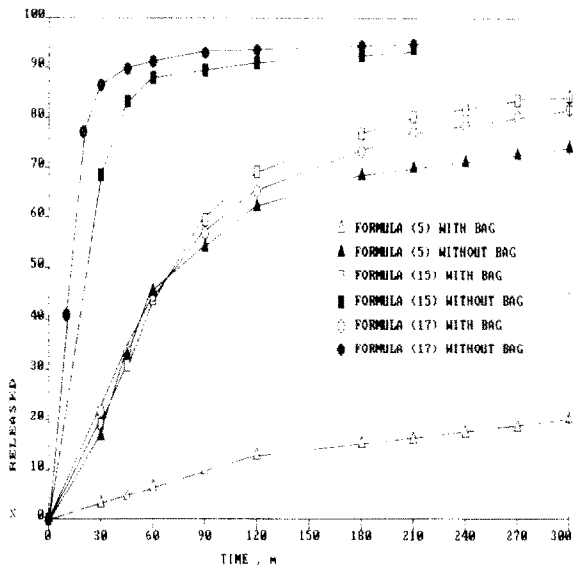

Fig. 5. Influence of the cellophane bag on release of verapamil HCl from fatty bases.

Mechanism of additive effect

In order to specify the role of additives in drug release, whether they act on drug release from the formulation and/or modify the diffusibility of

the drug through the membrane, the following experiments were undertaken. Either lysine HCl or urea were mixed with Vp-HCl solution solely (without base) in the cellophane bag and the amount released of the drug was measured over 4 h. The release patterns obtained (Fig. 6) in the presence and absence of these additives were principally the same. The results indicate that the primary effects of such additives is confined to improving drug release from the formulation rather than facilitating drug diffusion through the barrier.

Effect of buffer on release

In order to investigate the possible effects of buffer components on drug release, phosphate buffer (pH 6.2) was applied as the release medium and compared with the results observed with distilled water. The results shown in Fig. 7 demonstrate a negligible effect of buffer on drug release from fatty bases as exemplified by W-E75 (F5). On the other hand, buffer components reduced drug release from PEG bases to variable degrees according to the presence or absence of PEG 6000 in the formula. The amount of drug released from F3 after 210 min using water and

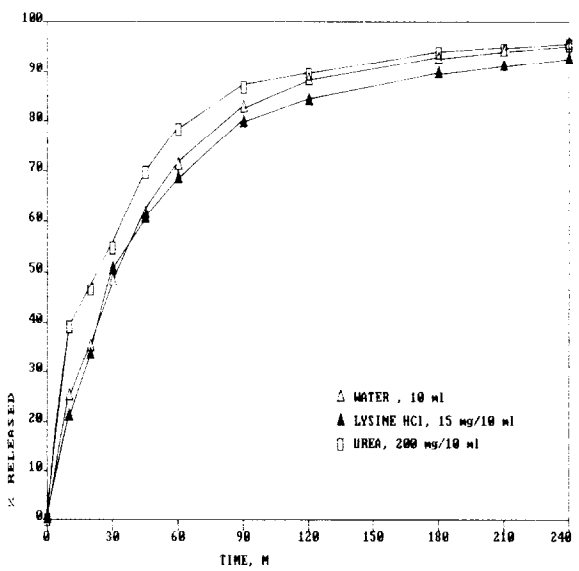

Fig. 6. Role of urea and lysine HCl on diffusion of verapamil HCl from aqueous solutions through the cellophane membrane.

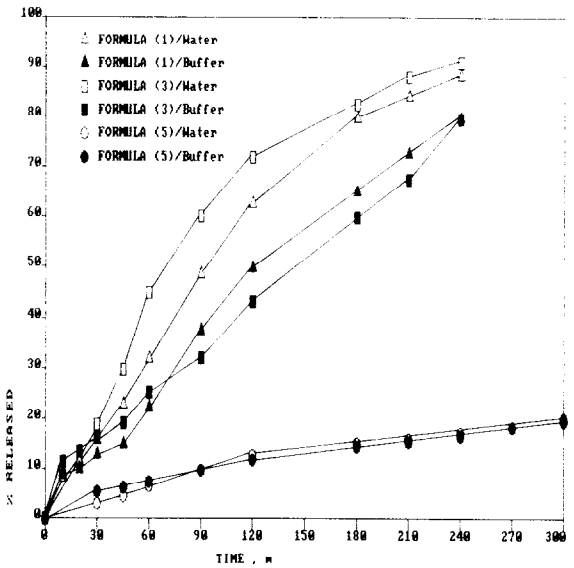

Fig. 7. Comparative release profile of verapamil HCl from PEGs and Witepsol E75 in water and phosphate buffer at the same pH (6.2).

buffer was found to be 85 and 65%, respectively. The amount released after the same period by F1 in water and buffer was 80 and 70%, respectively. According to the above findings, one could conclude that the buffer species may cause some type of salting out of Vp-HCl leading to reduced water solubility. The relatively smaller decrease in drug release from F1, containing PEG 6000 in buffer may be due to better solubility of Vp-HCl in the bag solution containing the polymer mixture. On the other hand, such an effect was not observed with the fatty bases (F5), since Vp-HCl is more soluble in lipid than in water and hence might be retained preferentially in the fatty base away from the effect of the buffer components. This suggestion could be substantiated by the observed poor release of drug from this base whether in water or buffer.

This work has been planned as a preliminary part essential for the in vivo work currently being undertaken in our laboratory, which is necessary to verify the idea and to achieve the goal of bypassing the first-pass effect of liver enzymes on Vp-HCl.

References

Ali, A., Kazmi, S., Deutsch, T. and Plakogiannis, F.M., Medicament release from suppository bases: III. Ibuprofen – Physicochemical characteristics and bioavailability in rabbits. *Drug. Dev. Ind. Pharm.*, 8 (1982) 411–428.

El-Massik, M.A., Optimization of certain drug delivery systems. Ph.D. Thesis. Department of Pharmaceutics, Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt (1987).

Feldman, S., Bioavailability of acetaminophen suppositories. *Am. J. Hosp. Pharm.*, 32 (1975) 1173–1175.

Gibaldi, M. and Grundhofer, B., Bioavailability of aspirin from commercial suppositories. *J. Pharm. Sci.*, 64 (1975) 1064–1066.

Habib, F.S., Sayed, H.A., Ismail, S., Gomea, A.A. and Shaker, A., Preparation and evaluation of hydroxyzine suppositories. *Bull. Pharm. Sci., Assiut Univ.*, 13 (1990) 265–280.

Habib, F.S., Sayed, S.A., Ismail, S., Shaker, S. and Shaker, A., Formulation and evaluation of different chlordiazepoxide HCl suppositories. *Bull. Pharm. Sci., Assiut Univ.*, 10 (1987) 123–145.

Murakami, T., Yata, N., Tamauchi, H., Nakai, J., Yamazaki, M. and Kamada, A., Studies on absorption promoters for rectal delivery preparations. I. Promoting efficacy of enamine derivatives of amino acids for the rectal absorption of β-lactam antibiotics in rabbits. *Chem. Pharm. Bull.*, 29 (1981) 1998–2004.

Reynolds, J.E.F. and Prasad, A.B., *Martindale, The Extra Pharmacopoeia*, 28th Edn, The Pharmaceutical Press, London, 1982, pp. 1097–1100.

Yaginuma, H., Isoda, Y., Wada, Y., Itoh, S., Yamazaki, M., Kamada, A., Shimazu, H. and Makita, I., Rectal delivery of antiinflammatory drugs. III. Effect of basic amino acid salts of diclofenac sodium on the rectal absorption of ampicillin sodium. *Chem. Pharm. Bull.*, 30 (1982) 1073–1076.