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Formulation, in-vitro release and ex-vivo spasmolytic effects of mebeverine hydrochloride suppositories containing polycarbophil or polysorbate 80

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Abstract

The release of mebeverine hydrochloride, in two different strengths 100 and 200 mg, from different suppository bases was studied in-vitro to choose the best base to be used in-vivo. The results showed that the fastest release of the drug was from polyethylene glycol 4000 suppository base. On studying the effects of the suppositories on some spasmogens on the isolated guinea-pig ileum the polyethylene glycol suppository containing 100 mg drug gave zero antagonism to acetyl choline (ACh), histamine and barium chloride ($BaCl_2$). Addition of 1% Tween 80 or 5% polycarbophil to the suppository formulation resulted in 33.3, 29.5, 12.1 and 25.3, 32.7 and 25.7% antagonism to ACh, histamine and $BaCl_2$, respectively. The suppository formulation containing 200 mg drug produced 60, 33.3 and 60% antagonism to the three agonists arranged in the same order previously mentioned. The addition of 1% Tween 80 or 5% polycarbophil to the formulation resulted in a significant increase in the drug antagonism to the three agonists producing 86, 65, 62 and 90, 66 and 90% antagonism, respectively. Weighing the suppository remaining after 2 h of administration revealed that addition of 1% Tween 80 to the formulation increased significantly ($P < 0.05$) the dissolution of the suppository by 52–58% indicating the wetting effect of that additive. While, addition of 5% polycarbophil although improved the availability of the drug it did not affect the dissolution of the suppository indicating the adhesive effect that the polycarbophil exerts between the particles.

Keywords: Mebeverine hydrochloride; In-vitro release; Suppository; Polysorbate 80; Polycarbophil; Ex-vivo spasmolytic effects

1. Introduction

Mebeverine hydrochloride is a musculotropic antispasmodic drug with direct action on smooth

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muscles of gastrointestinal tract, especially the colon (Connell, 1965). It is not a specific anticholinergic therefore it does not cause the unwanted effects such as dry mouth, blurred vision and difficulty with micturition typical of many other anticholinergic spasmolytic compounds (Eisenburg et al., 1978). Mebeverine hydrochloride is also the most prescribed product currently available for the treatment of irritable bowel syndrome.

The mechanism of drug absorption from the rectum is probably not different from that in the upper part of GIT, despite substantial differences in the physiological conditions (pH, fluid content, surface area) between the two regions. Absorption from suppositories is dependent on the nature of the suppository base, the use of surfactants or other additives and the solubility of the drug in the suppository base (Schmitt and Guentert, 1990).

Surfactants are one of the most important classes of adjuvants in pharmaceutical preparations. They could affect the rate and/or extent of absorption of drugs (Levy and Reuning, 1964; Swarbrick, 1965). Surfactants possess a high potential to promote absorption across rectal mucosa (Ichikawa et al., 1980; Nishihata et al., 1980). Polysorbates have been shown to increase the release of mebeverine hydrochloride from suppository bases (Al-Gohary and Foda, 1993).

Polycarbophil (Markus, 1965), a bioadhesive polymer, has been shown to be effective in rectal drug delivery of drugs (Hosny, 1988; Hosny and Robinson, 1991; Hosny and Al-Angary, 1995; Hosny et al., 1995, 1996). The objective of this study was to investigate the release of mebeverine hydrochloride from different suppository bases and study the influence of polysorbate 80 and polycarbophil on the ex-vivo spasmolytic effects of the drug on some spasomogens on the isolated guinea pig ileum from the best formulation.

2. Materials and methods

2.1. Materials

Mebeverine hydrochloride powder was a kind gift from EPICO (10th of Ramadan, Egypt). Bulk polycarbophil was kindly provided by Lee Laboratories (Petersburg, VA, USA). Polysorbate 80 was purchased from Atlas Industries (Wilmington, DE, USA). Polyethylene glycol 4000, histamine, barium chloride and acetyl choline were from BDH Chemicals (Poole, England). Witepsol H15 and Witepsol W45 were from Novel Dynamite (Witten Werke, Germany). Cocoa butter (B.P. grade) was purchased from the local market. Suppocire MC was obtained from Gattefosse (St. Priest, France).

2.2. Methods

2.2.1. Preparation of mebeverine hydrochloride suppositories

Suppositories of 1 g, each containing 100 or 200 mg of mebeverine hydrochloride, were prepared using PEG 4000, Witepsol H15, Witepsol W45, Suppocire MC and Cocoa butter suppository bases adopting the cream melting technique. Where, the used bases were melted over a water bath, the drug and any other additives were then added subsequently with stirring after each addition until a homogenous mass was produced and poured into 1 g metal mould and cooled. The drug, polycarbophil and Tween 80 displacement values in the used bases were first determined (Vidras et al., 1982).

2.2.2. In-vitro release studies

The release of mebeverine hydrochloride from the prepared suppositories was studied using an automated PU 8605 dissolution monitoring system consisting of USP dissolution apparatus II with 50 rpm paddle rotational speed. The dissolution medium was 900 ml of distilled water maintained at 37 ± 0.5°C. The mebeverine hydrochloride concentration was recorded every 10 min for 3 h at 263 nm using Philips PU 8620 spectrophotometer (England), connected to an IBM computer model PS 30, using TDS software from Philips (England). Each determination was carried out in triplicate.

2.2.3. Animal studies

Albino guinea-pigs (500 g) were fasted from food for 18 h before the experiment but were provided with water ad libitum. On the days of the experiments, the animals were divided into various groups ($n = 2-5$). One group acted as a control and the other groups were rectally administered 1 g suppositories containing 100 or 200 mg mebeverine hydrochloride each alone (plain) or plain suppositories containing 1% Tween 80 or 5% polycarbophil or just non medicated (placebo) suppositories. After insertion of each suppository, the anus of each animal was mechanically closed using a stainless-steel blunt clipper on a broad bull-dog. Animals within each group were then killed 1, 2 or 4 h after the administration of the suppositories.

2.2.4. Study of the spasmolytic activity of mebeverine hydrochloride in isolated guinea-pigs ileum

To investigate the spasmolytic effects of the various treatments, the following procedure was followed. Initially, control animals were killed. The abdominal cavity of each animal was opened and pieces of ileum (2 cm long) were cut and each suspended in an isolated organ bath containing oxygenated Tyrode's solution kept at 37°C. Each tissue was then attached to an isometric transducer fitted to a Narco-physiograph recorder. To each tissue tension of 0.5 g was applied. The sensitivity of the recorder was kept constant throughout the various experiments. A dose-response curve was then constructed for each of the agonists (spasmogens): acetylcholine, histamine and barium chloride. Contact time for each agonist with the tissue was 45 s and the intervals between doses and agonists were 4 min. The submaximal dose for each agonist was then selected ($\approx$ 75% of the maximal).

Ileal pieces from the treated animals (drug or placebo) were obtained and suspended in Tyrode's solution as described above. Each tissue was then challenged with the submaximal doses of the above agonists keeping the intervals between the agonists at 4 min. The mean amplitudes (in mg tensions) of each agonist in the non-treated (control) and the treated tissues were calculated. The percentage antagonisms induced by each treatment on the submaximal effects of the different agonists were then calculated. Significant differences were calculated using ANOVA. Results were reported as mean $\pm$ S.E.M. with n being the number of experiments performed.

Each suppository was weighed before insertion into the animal and after killing the animal. The mean percentage dissolution of each suppository was then calculated.

3. Results and discussion

Figs. 1 and 2 show the release of mebeverine hydrochloride from five suppository bases containing 100 or 200 mg of the drug, respectively. The two figures show the same pattern and order of release of the drug from the suppository bases indicating that the loading of the bases with 100 or 200 mg of the drug did not affect the mechanism of release. The fastest release was from the polyethylene glycol 4000 base where all the drug was released in the first 30 min. This may be due to the water solubility of both the drug and the base, where the drug can be released by both

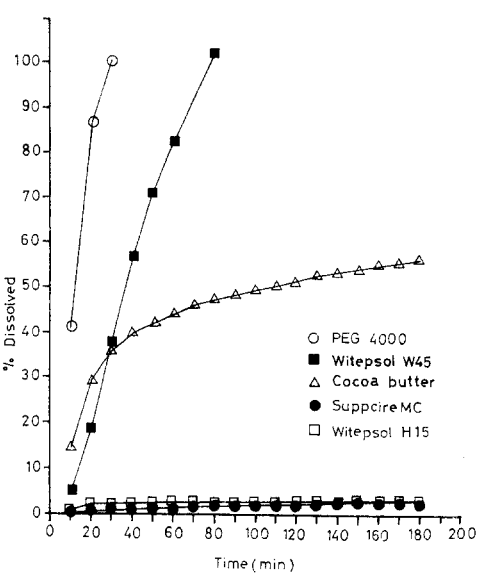

Fig. 1. In-vitro release of mebeverine hydrochloride (100 mg) from different suppository bases.

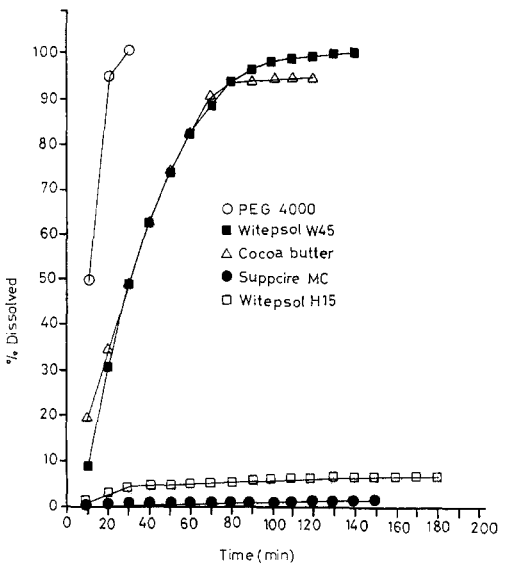

Fig. 2. In-vitro release of mebeverine hydrochloride (200 mg) from different suppository bases.

diffusion and erosion mechanisms. The release from Witepsol W45 and Cocoa butter was significantly faster than the release from Witepsol H15 and suppocire MC. This could be attributed to the presence of monoglyceride esters in the latter bases which act as emulsifying agent, that retard the dispersion of the water soluble drug to the surrounding medium. Also the higher release of the drug from Witepsol W45 and cocoa butter than that from Suppocire MC could be due to the difference in the melting points of these bases as the first two bases have melting ranges of 33.5–35.5°C and 30–34°C, respectively compared with 38–41°C for Suppocire MC.

As a result of these in-vitro release experiments, the formulations that contained the drug in polyethylene glycol base were chosen for evaluation of their ex-vivo spasmolytic effects on some spasmogens on the isolated guinea-pig ileum. The results of this evaluation are shown in Tables 1 and 2. The PEG placebo suppositories and those containing 100 mg mebeverine hydrochloride did not affect the agonists-induced contractions after treatment of the animals for 1, 2 or 4 h. However, clear antagonisms were observed following treatment with 200 mg suppositories producing 60 ± 5.7, 33.3 ± 2.9 and 60 ± 6.3% antagonism for ACh, histamine and $BaCl_2$, respectively ($P < 0.05$, $n = 4–5$). In all cases maximum inhibitions were observed 2 h after rectal administration of the suppositories. Trying to increase the absorption of mebeverine hydrochloride, some additives were used. The incorporation of 1% Tween 80 in the suppository formulation containing 100 mg drug resulted in 33.3 ± 4.6, 29.5 ± 3.9 and 12.1 ± 6.8% antagonism against the three agonists tested, respectively. This could be attributed to the actions of this surfactant in facilitating the absorption of the drug across the rectal mucosa through its direct effects on the permeability of the rectal epithelium. It could also be due to its effect in increasing the contact between the drug particles

Table 1
Ex-vivo spasmolytic effects of mebeverine hydrochloride (100 mg) suppository formulations on some spasmogens on the isolated guinea-pig ileum (mean ± S.E.M.)

Agonist (dose/ml)	Antagonism (%) Type of suppository		
	Plain	1% Tween 80	5% PC
Acetylcholine (10 ng)	0	33.3 ± 4.6*	25.3 ± 7.8
Histamine (25 ng)	0	29.5 ± 3.9*	32.7 ± 4.1*
Barium chloride (125 μg)	0	12.1 ± 6.8	25.7 ± 6.9
% dissolution	30 ± 5.1	88.0 ± 7.1	36 ± 6.3

* $P < 0.05$, $n = 4$, compared with plain suppositories.

Table 2
Ex-vivo spasmolytic effects of mebeverine hydrochloride (200 mg) suppository formulations on some spasmogens on the isolated guinea-pig ileum (mean ± S.E.M.)

Agonist (dose/ml)	Antagonism (%) Type of suppsitory		
	Plain	1% Tween 80	5% PC
Acetylcholine (10 ng)	60 ± 5.7	86 ± 7.1*	90 ± 6.3*
Histamine (25 ng)	33.3 ± 2.9	65 ± 4.6*	66 ± 4.6*
Barium chloride (125 μg)	60 ± 6.3	62 ± 5.3	90 ± 7.2*
% dissolution	34 ± 3.8	86 ± 6.7	32 ± 4.9

* $P < 0.05$, $n = 4–5$, compared with plain suppositories.

and the surrounding fluid, thus increasing its rate of dissolution. These effects were also clear with suppositories containing 200 mg drug (Table 2) where addition of 1% Tween 80 to the polyethylene glycol suppositories increased the antagonism from 60 ± 5.7, 33.3 ± 2.9 and $60 \pm 6.3\%$ to 86 ± 7.1, 65 ± 4.6 and $62 \pm 5.3\%$, respectively to the three agonists used namely ACh, histamine and $BaCl_2$. The placebo suppositories containing no mebeverine did not affect the spasmogens-induced contractions to any significant level. The magnitude of the induced contractions was similar to that from non-treated animals. The effect of 1% Tween 80 in increasing dissolution of polyethylene glycol suppositories was verified through weighing the suppositories after 2 h of rectal administration. The results as shown in Tables 1 and 2 indicate that the percentage dissolution increased from 30 ± 5.1 and $34 \pm 3.8\%$ to 88 ± 7.1 and $86 \pm 6.7\%$ by the addition of 1% Tween 80 to the suppositories containing 100 and 200 mg drug, respectively.

The addition of 5% polycarbophil (30/40 mesh particles) to the suppositories increased the antagonism from 0 to 25.3 ± 7.8, 32.7 ± 4.1 and $25.7 \pm 6.9\%$ for the 100 mg mebeverine hydrochloride containing suppositories and from 60 ± 5.7, 33.3 ± 2.9 and $60 \pm 6.3\%$ to 90 ± 6.3, 66 ± 4.6 and $90 \pm 7.2\%$ antagonism for the 200 mg drug containing suppositories with respect to the three agonists used respectively ($P < 0.05$, $n = 4-5$). The effect of polycarbophil on increasing the antagonism was not due to increasing dissolution of the suppository as the addition of polycarbophil did not result in any significant change in the weight of the suppositories remaining after 2 h of rectal administration as was the case for the Tween 80 in comparison to that of plain suppositories. As it is known polycarbophil produces its enhancing effect on absorption due to its adhesive effect (Gurney et al., 1984; Ch'ng et al., 1985, Longer et al., 1985; Nagai and Machida, 1985) that increases the intimacy of contact of the suppository with the rectal mucosa thus localizes the drug in a particular region, thereby improving and enhancing the bioavailability. Also, it could be due to the effect of polycarbophil on increasing the permeability of the epithelial tissues (Lue Ben et al., 1994).

As a conclusion the addition of 1% Tween 80 or 5% polycarbophil to the polyethylene glycol suppositories containing mebeverine hydrochloride is essential to improve the release and absorption of the drug as the magnitudes of inhibitions induced by the formulations containing these two additives were comparable at both dose levels. However, the 5% polycarbophil addition seems to be more inhibitory than the corresponding 1% Tween 80 especially for the barium chloride induced contractions ($P < 0.05$).

References

Al-Gohary, O.M.N. and Foda, N.H., Availability of mebeverine hydrochloride from suppositories. *Pharm. Ind.*, 55 (1993) 396–400.

Ch'ng, H.S., Park, H., Kelly, P. and Robinson, J.R., Bioadhesive polymers as platforms for oral controlled drug delivery: II Synthesis and evaluation of some swelling water insoluble bioadhesive polymers. *J. Pharm. Sci.*, 74 (1985) 399–405.

Connell, A.M., Physiological and clinical assessment of the effect of the musculotropic agent mebeverine on the human colon. *Br. Med. J.*, 2 (1965) 848–851.

Eisenburg, J., Kruis, W., Schusler, P. and Weinzierl, M., The irritable colon syndrome. New therapeutic possibilities in the treatment of a frequent syndrome. *Fortschr. Med.*, 96 (1978) 2064–2070.

Gurney, R., Meyer, J.M. and Peppas, N.A., Bioadhesive intraoral release systems: design, testing and analysis. *Biomaterials*, 5 (1984) 334–340.

Hosny, E.A., Rectal drug delivery using a bioadhesive containing dosage form. *PhD Thesis*, School of Pharmacy, University of Wisconsin, Madison, 1988.

Hosny, E.A. and Al-Angary, A.A., Bioavailability of sustained release indomethacin suppositories containing polycarbophil. *Int. J. Pharm.*, 113 (1995) 209–213.

Hosny, E.A., Niazy, E.M. and El-Gorashi, A.S., Effect of polycarbophil concentration on in-vitro and in-vivo availability in beagle dogs of dihydroergotamine mesylate suppositories. *Int. J. Pharm.*, 117 (1995) 147–150.

Hosny, E.A., Niazy, E.M. and El-Dardiri, M.M., Effect of polycarbophil concentration on diclofenac sodium bioavailability from suppositories in beagle dogs. *Int. J. Pharm.*, 136 (1996) 37–41.

Hosny, E.A. and Robinson, J.R., Rectal drug delivery of ketoprofen using a bioadhesive containing suppository, *2nd Anglo-Egyptian Conference of Pharmaceutical Scientists*, Abstract book, 18, Alexandria, Egypt, Nov. 9–12, 1991.

Ichikawa, K., Ohata, I., Mitomi, M., Kawamura, S., Maeno, H. and Kawata, H., Rectal absorption of insulin suppositories in rabbits. *J. Pharm. Pharmacol.*, 32 (1980) 314–318.

Levy, G. and Reuning, R.H., Effect of complex formation on drug absorption I. Complexes of salicylic acid with absorbable and non-absorbable compounds. *J. Pharm. Sci.*, 53 (1964) 1471–1475.

Longer, M.A., Ch'ng, H.S. and Robinson, J.R., Bioadhesive polymers as platforms for oral controlled drug delivery: III Oral delivery of chlorthiazide using a bioadhesive polymer. *J. Pharm. Sci.*, 74 (1985) 406–411.

Lue Ben, H.L., Lehr, C.M., Rentel, C.O., Naoch, A.B.J., de-Boer, A.G., Verhoef, J.C. and Junginger, H.E., Bioadhesive polymers for peroral delivery of peptide drugs. *J. Controlled Release*, 29 (1994) 329–338.

Markus, R.L., *U.S. Patent 3*, 202 (1965) 577.

Nagai, T. and Machida, Y., Mucosal adhesive dosage forms. *Pharm. Int.*, 6 (1985) 196–200.

Nishihata, T., Rytiting, J.H. and Higuchi, T., Enhancement of rectal absorption of drugs by adjuvants. *J. Pharm. Sci.*, 69 (1980) 744–745.

Schmitt, M. and Guentert, T.W., Influence of hydrophilicity of suppository bases on rectal absorption of carprofen, a lipophilic non-steroidal anti-inflammatory drug. *J. Pharm. Sci.*, 79 (1990) 357–363.

Swarbrick, J., Solubilized systems in pharmacy. *J. Pharm. Sci.*, 54 (1965) 1229–1237.

Vidras, N.J., Reid, V.E., Bohider, N.R. and Plakogiannis, E.M., Medicament release from suppsitory bases: I. Physicochemical characteristics and bioavailability of indomethacin in rabbits. *J. Pharm. Sci.*, 71 (1982) 8–10.