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A Novel Formulation for Mebeverine Hydrochloride

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The antispasmodic drug mebeverine hydrochloride was formulated into a film-forming gel to be used as a topical local anesthetic. A mixture of cellulose derivatives was used as a base. Additives were used to enhance the release as well as the residence time. Formulations were characterized in terms of drug release, mucoadhesion and rheology. Clinically, the selected formula has shown faster onset ($p = 0.0156$), longer duration ($p = 0.0313$), better film residence ($p = 0.0313$), and no foreign body sensation ($p = 0.0313$) in comparison to Solcoseryl® dental paste. Histopathological examination showed no change in inflammatory cells count, concluding that this topical anesthetic is efficacious and safe orally.

Keywords mebeverine hydrochloride; local anesthetic; film-forming gel; mucoadhesion; clinical and histopathological evaluation

INTRODUCTION

The antispasmodic drug mebeverine hydrochloride (HCl) exerts a local anesthetic action by blocking voltage operated sodium channels, an action similar to lidocaine (Den Hertog & Van den Akker, 1987). Although, mebeverine HCl has been used per orally in the symptomatic treatment of bowel disturbances and intestinal discomfort related to irritable bowel syndrome, it has never been used before as a local anesthetic. On the contrary to other local anesthetics mebeverine HCl was reported to have nonsignificant central or peripheral side effects (Gilbody et al., 2000; Van Outryve et al., 1995). Moreover, it has shown rapid and facile hydrolysis on reaching circulation (Dickinson et al., 1991).

Gels usually have a limited residence time as they are quickly washed away by saliva from the treatment site. Thus, to overcome this drawback a novel invention was made by Tapolsky et al., 2000; which is a nonwater soluble mucoadhesive film-forming gel for application to mucosal surfaces. Typically, it is composed of at least one water-insoluble, edible alkyl cellulose e.g., ethyl cellulose (EC) and hydroxyalkyl cellulose, e.g., hydroxypropyl cellulose (HPC); a volatile or nonaqueous, pharmacologically approved solvent e.g., ethanol (95%) and the active drug. A bioadhesive may also be added such as polyvinylpyrrolidone (PVP).

Upon application and adherence to the mucosal surface; the volatile or nonaqueous solvent evaporates, diffuses, or penetrates the surrounding tissues and the gel forms an adhesive film. The film offers protection to the treatment site, while also providing effective drug delivery. Over time, the film erodes away. The gel provides an effective residence time and is easy to apply and use.

The characteristics of the film formed from the gel may be modified depending on the combination ratio of the water soluble polymer, e.g., HPC to water insoluble alkyl cellulose, e.g., EC. Typically, as the ratio of HPC to EC increases, the water erodability increases, i.e., the films are more readily washed away. Thus, the water soluble HPC is a component which acts to adjust the kinetics of erodability of the carrier gel. The residence time of the film formed upon dissipation of the solvent depends on several factors including the amount of the gel applied, as well as the components used to make the composition and their relative percentages.

The aim of work in this study will be directed towards the formulation of mebeverine HCl into a film-forming gel for the treatment of different oral painful conditions using a binary mixture of the cellulose derivatives HEC/HPC together with the film-forming polymer EC. Different additives such as surfactants and hydrophilizing agents would be also used to enhance drug release. A mucoadhesive polymer (PVP) would be used to further increase the residence time of the gelling system. Formula showing a compromise between a quite fast in vitro release and a good in vitro mucoadhesive performance would be rheologically examined. Finally, clinical evaluation as well as histopathological examination would be made for the selected formula.

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MATERIALS AND METHODS

Materials

Mebeverine hydrochloride, Hydroxypropylcellulose HPC (Klucel MF), Polyvinylpyrrolidone PVP (Kollidon K-25) were all kindly supplied by E.I.P.I.Co. (Egypt). Cetyltrimethylammonium bromide (Cetrimide) and Crude porcine gastric mucin were purchased from Sigma Chemical Co. (USA). Hydroxyethylcellulose HEC (Cello size WP-40') and Ethylcellulose (Ethocel) were purchased from Fluka (Switzerland). All other chemicals were of analytical grade, or equivalent quality. Male and female Sprague Dawley rats weighing 50–70 g (Animal house, Faculty of Pharmacy, Ain Shams University).

Preparation of the Film-Forming Gel

Preparation of Mebeverine HCl in the Binary Mixture (HEC/HPC)

Mebeverine HCl at concentration (20% w/w) was dissolved in the calculated amount of distilled water at room temperature. Hydroxyethyl cellulose (HEC; 3% w/w) was then dispersed in this amount of distilled water with continuous agitation using the magnetic stirring bar. Thereafter; amounts equivalent to concentrations 3, 5, and 7 (% w/w) of hydroxypropyl cellulose (HPC) were added each time with continuous stirring till a highly viscous mass is formed which is indicated by the difficulty in movement of the stirring bar. Gels were left overnight at ambient conditions. A formulation containing only hydroxypropyl cellulose (HPC; 5% w/w) was also prepared by the same procedure.

Preparation of Mebeverine HCl Film-Forming Gels Using (EC)

Mebeverine HCl (20% w/w), EC (1, 2% w/w), HEC (3% w/w) and HPC (3% w/w) were added consecutively into a vehicle formed of ethyl alcohol (95%) and distilled water at room temperature, such that the alcohol comprised about (60% w/w) and the water comprised (12–13% w/w) of the final formula composition. Gels were prepared as mentioned above and left overnight in tight closed containers at ambient conditions.

Preparation of Mebeverine HCl Film-Forming Gels Using Different Surfactants and Hydrophilizing Agents

Medicated gels based on HEC (3% w/w), HPC (3% w/w), and EC (1% w/w) were prepared with additional amounts of different surfactants; and hydrophilizing agents; Table 1. The gels were prepared by dissolving or dispersing each of these additives at the given concentrations with mebeverine HCl (20% w/w) in the calculated amount of hydro-alcoholic solution, then the required amounts of EC, HEC and HPC were added respectively with continuous agitation using the magnetic stirring bar. Gels were left overnight at ambient conditions.

Preparation of Mebeverine HCl Film-Forming Gels Using PVP as a Mucoadhesive Additive

Medicated gels based on HEC (3% w/w), HPC (3% w/w), and EC (1% w/w) with PG (10% w/w) were prepared with additional amounts of PVP as a mucoadhesive polymer at the concentrations of 1and 3 (% w/w). The gels were prepared as mentioned before in the calculated amount of hydro-alcoholic solution (ethyl alcohol (95%) comprised 55% w/w and water 5–7% w/w of the final omposition). Gels were left overnight at ambient conditions.

Preparation of the Selected Film-Forming Gel Formula (F) for Rheological, Clinical, and Histopathological Assessment

Medicated gels consisting of HEC (3% w/w), HPC (3% w/w), PVP (1% w/w), EC (1% w/w), and PG (10% w/w) were prepared with additional amounts of citric acid (2% w/w) as a taste enhancer, aspartame (3% w/w) as a sweetener and orange flavor (1% w/w). The gel was prepared by initially dissolving the soluble components in the calculated amount of the hydro alcoholic mixture at room temperature (ethyl alcohol (95%) formed 52% w/w while distilled water formed 4% w/w of the final composition of the preparation), followed by dispersing the aforementioned polymers. The gel was left in a tight closed container and kept at ambient conditions.

TABLE 1
Composition of Different Film-Forming Gels using Different Surfactants and Hydrophilizing Agents

	Cetrimide (0.005%)	Cetrimide (0.05%)	Tween80 (0.01%)	Tween80 (0.05%)	PEG400 (5%)	PEG400 (10%)	PG (5%)	PG (10%)
Mebeverine HCl	20	20	20	20	20	20	20	20
HEC	3	3	3	3	3	3	3	3
HPC	3	3	3	3	3	3	3	3
EC	1	1	1	1	1	1	1	1
Ethyl alcohol (95%)	63	63	63	63	63	55	60	55
Water	10	10	10	10	8	8	8	8

*All numbers are expressed as % w/w.

**PG: Propylene glycol; PEG: Polyethylene glycol.

In Vitro Release of Mebeverine HCl

Drug release from oral gels was monitored by USP paddle method (USP XXIV) but with some modifications (Jones et al., 1999, 2000) as this method appears to be more simulating to reality where there would be no barriers for swelling as well as for different conformational movements of the polymers nor a limiting membrane that may control drug transfer. Formulations were retained within glass cups anchored to the bottom of the dissolution vessels, thus ensuring drug release to occur principally from the top of the cups. A 2 g sample of the gel (equivalent to 400 mg mebeverine HCl) was weighed in the cup on an analytical balance and was gently lowered through the 750 mL of the dissolution medium (Phosphate buffer saline PBS; 8 g NaCl, 0.19 g KCl, 0.2 g KH^2PO^4, and 2.86 g Na^2PO^4 in 1 L distilled water; pH 6.8) (Le Brun et al., 1989), by means of a forceps. The paddle was centrally positioned 2.5 cm above the rim of the cup. The release study was carried out at 37 ± 0.5°C and the stirring paddles were rotated at a speed of 50 rpm. Aliquots of 2 mL were withdrawn from the dissolution medium at time intervals of 5, 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 min. All samples were replaced by fresh PBS. Samples were suitably diluted and measured spectrophotometrically at λ_{max} 263.5 nm. The concentration of drug was determined from the previously constructed calibration curve, which was linear over the concentration range 1.0–3.0 mg% (r = 0.9999, with zero intercept). The presence of different formulation excipients did not interfere with the analysis. The experiments were conducted in triplicates, the results were averaged and blank experiments were carried out at the same time using plain bases.

Statistical Analysis of Drug Release Data

Drug release data generated from the dissolution experiments were fitted to the following general release equation (Peppas, 1985) using logarithmic transformations and least squares regression analysis:

$$M_t/M_\infty = kt^n$$

Where M_t/M_∞: the fraction of released drug at time t

k: the release constant incorporating structural and geometrical characteristics of the delivery system.

n: the release exponent, a measure of the primary mechanism of drug release

Statistical analyses were performed on the times required for the release of 10, 30, and 50% ($t_{10\%}$, $t_{30\%}$, and $t_{50\%}$) of the original loading of mebeverine HCl from each formulation using one-way ANOVA (Analysis of Variance). Post-hoc statistical analyses were performed using Tukey-Kramer test for multiple comparisons. The software employed was Graph Pad Instat® V2.04 and the level of significance was set at 5%.

In-Vitro Evaluation of the Mucoadhesion for the Gels

The mucoadhesive force of the film-forming gels was determined using the mucoadhesive force measuring device which is a modified balance that was developed in our lab as shown in Figure 1. This was according to previously reported methods (Desai & Kumar, 2004; Yong et al., 2001). The mucoadhesive strength of the formulations under examination was determined by measuring the force required to detach the formulation from a mucin disc. Initially, mucin discs were prepared by compression of crude porcine mucin (250 mg) by a single punch tablet press (10 mm diameter die). These discs were horizontally attached to the upper stage of the modified balance by a cynoacrylate adhesive. Prior to mucoadhesion testing, the mucin disc was hydrated by submersion in a freshly prepared 5% w/w dispersion of mucin for 60 sec. Samples of each gel formulation (0.5 g) were placed on the lower vertically movable stage. The lower stage was then elevated till the surface of the sample became contacted to the mucin disc adhered to the upper stage. A constant (preload) downward force of 10 g weight was then applied for 30 sec and removed. The sample was left in contact for 5 min with the mucin disc to ensure intimate contact. To the pan on the other side of the used device, water was then added from a glass bottle through an infusion set into a plastic jar at a constant rate of 18–20 drops per min. The addition of water was stopped when mucin disc was detached from the sample. The minimal weight of water required to detach the sample from the mucin disc was noted as the mucoadhesive force, and these experiments were repeated with fresh mucin discs and gel samples in an identical manner (n = 4). Mucoadhesive force or the detachment stress (dyne/cm^2) was determined using the following equation stated by Ch'ng et al. (1985):

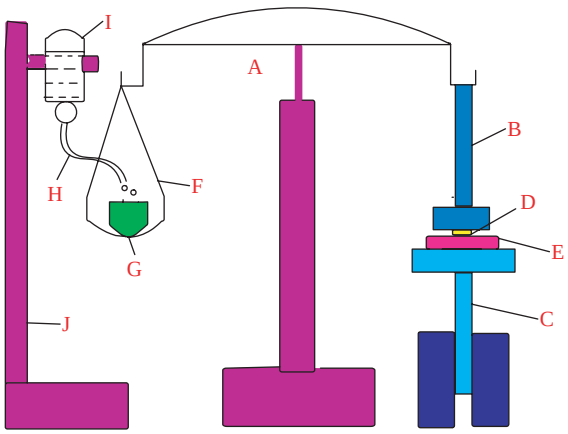


FIGURE 1. Diagrammatic representation of the mucoadhesive force-measuring device. (A) Modified balance; (B) Upper stage; (C) Lower stage moving on screw; (D) Mucin disc; (E) Gel preparation; (F) Balance pan; (G) Plastic jar; (H) IV Infusion set (I) Glass bottle containing water; (J) Stand-holder.

Detachment stress (dyne/cm^2)=m.g/A
where m: the weight of water (gm)
g: acceleration due to gravity taken as 981 cm/sec^2
A: area of the mucin disc (area of contact) and is equal to πr^2 (r is the radius of the mucin disc)

The mucoadhesive force was evaluated as previously mentioned in order to study:

Effect of (EC) on the Mucoadhesion of the Film-Forming Gel

Mucoadhesive force was determined for medicated film-forming gels consisting of HEC (3% w/w) and HPC (3% w/w) using ethylcellulose EC at the concentration (1% w/w).

Effect of (PVP) on the Mucoadhesion of the Film-Forming Gel

Mucoadhesive force was determined for medicated film-forming gel consisting of HEC (3% w/w), HPC (3% w/w) and EC (1% w/w) using PVP at concentration (1% w/w).

Statistical Analysis of Mucoadhesion Data

The results were statistically evaluated using one-way ANOVA. Post-hoc statistical analyses were performed using Tukey-Kramer test for multiple comparisons. The software employed was Graph Pad Instat® V2.04 and the level of significance was set at 5%.

Rheological Measurements

Steady shear measurement was conducted where the rheogram of the selected film-forming gel formula (*F*) was performed at 25 ± 0.1°C (to examine performance at room temperature) and at 37 ± 0.1°C (to examine performance at body temperature) using the spindle CP 52 of the Brookfield cone and plate viscometer in the controlled rate mode, with the shear rate ranging from 0.1 to 2 sec^{-1}, however the upper limit of the shear rate was extended to 6 sec^{-1} to examine the hysteresis of the rheogram as these higher ranges are more representative to spreading and chewing processes. Equilibration of the sample for 5 min was made following loading of the viscometer. Ramp time for each velocity stage was reading after 30 sec. Rheograms were performed in triplicate.

Statistical Analysis of Rheological Data

Rheological data for the selected gel formula (*F*) was fitted to different models (Bingham, Power law, Casson) to examine the pattern of flow.
Bingham:

$$\tau = \tau_0 + \eta\gamma$$

Power law:

$$\tau = \eta\gamma^n$$

Casson:

$$\tau^{1/2} = \tau_0^{1/2} + \eta^{1/2}\gamma^{1/2}$$

where (τ) is the shear stress, (τ_o) is the yield value, (η) is a constant called the apparent viscosity or the consistency index, (γ) is the shear rate and (n) is the flow index.

Clinical Evaluation of the Selected Film-Forming Gel Formula (*F*)

19 subjects; 10 males, and 9 females aged 18–65 years were randomly chosen from the flow of the outpatient Diagnosis Clinic, Department of Oral Medicine, Diagnosis and Periodontology, Faculty of Dentistry, Ain Shams University, Cairo, Egypt. The protocol of the study was approved by the Ethics Committee of the institute and each patient signed a written consent where the full details of the study were explained. The investigation was designed as a randomized, single blinded clinical trial (split-mouth design). The patients were stratified by a coin flip into one of the following treatment groups:

Group (1)

Included 7 patients with bilateral lesions treated with Mebeverine HCl film-forming gel (*F*) versus Solcoseryl® dental paste (*S*).

Group (2)

Included 12 patients with bilateral lesions treated with Mebeverine HCl film forming gel (*F*) versus a Placebo with the same taste.

Patients assessed pain by using a 10-points verbal rating scale, ranging from “no pain” to “unbearable pain” (Jacox et al., 1994). Patients were asked to choose a score (from 0 to 10) according to the degree of their pain sensation before drug application then they were instructed to apply the preparations 3–4 times daily for 2 days, where they were counseled not to drink or eat for 30 min after application. After 2 days of treatment the patients were asked again to score pain according to the same criteria and to judge the physical properties of the prepared formula through a scoring questionnaire form (Tapolsky et al., 2000; Ukai & Harada, 2003). Patients were asked about the handling, numbness, bitterness, foreign body sensation, onset and duration of action, film residence and their overall impression.

Statistical Analysis of Clinical Data

The results were evaluated statistically by Wilcoxson Matched Pairs Signed Test and Mann-Whitney-U test using Graph Pad Instat® software V2.04. The level of significance was set at 5%.

Histopathological Evaluation of the Selected Film-Forming Gel Formula (*F*)

Preparation of the Rats

Application was made only on the right side of the gingiva, leaving the left side as control. Formula (*F*) was applied three times daily with a 3 h interval between each application for 2 days. Rats were kept away from food and water for only half an hour after each application. On the third day, they were sacrificed where the head of each rat was separated. Dissection, separation, and fixation of the gingival tissues were carried out. Four-micron thick sections were cut sequentially from each section. Hematoxylin and eosin stain was made for histological examination. Slides were then observed under the microscope (using a colour video camera fitted to light microscope and attached to computer).

Inflammatory cells (plasma cells and lymphocytes) in the connective tissue were counted where a total of four adjacent medium power microscopic fields were analyzed at the power of 20X. Counting was made by image analysis software analySIS® version3.

Statistical Analysis of Histopathological Data

Statistical analysis was made using paired-*t*-test at $p < 0.05$ using Graph pad Instat®V2.04 software.

RESULTS AND DISCUSSION

Effect of Different Binary Gel Mixtures of (HEC/HPC) on the Release of Mebeverine HCl

It was decided to make a suitable combination of HEC and HPC in order to obtain a gel of acceptable consistency. It was designed to begin with HEC polymer kept at a constant concentration of (3% w/w) of the gel based on its relatively low molecular weight (123×10^3 Daltons) in comparison to the high molecular weight of HPC (850×10^3 Daltons) which was added in ascending concentrations (1, 2, and 3% w/w) to HEC (3% w/w) each time. Gels started to form only at the combination HEC (3% w/w) plus HPC (3% w/w). Binary mixtures containing HEC (3% w/w) plus HPC (5% w/w) and HEC (3% w/w) plus HPC (7% w/w) were then prepared. Figure 2 shows the percentage of mebeverine HCl released at different HEC/HPC combinations, where it is clear that by increasing HPC concentration the release rate of the drug is reduced. Moreover, Figure 2 shows that the single component HPC (5% w/w) gel has a slower release rate than the binary mixture HEC (3% w/w) plus HPC (3% w/w). Table 2 shows that the time required for the release of mebeverine HCl ($t_{10\%}$, $t_{30\%}$, and $t_{50\%}$) from the binary gel mixture HEC (3% w/w) plus HPC (3% w/w) was significantly shorter than that of any other combination or HPC(5% w/w) gel alone, ($p < 0.001$). Values of the release exponent (n) for different combinations ranged from 0.625 to 0.787 indicating anomalous diffusion.

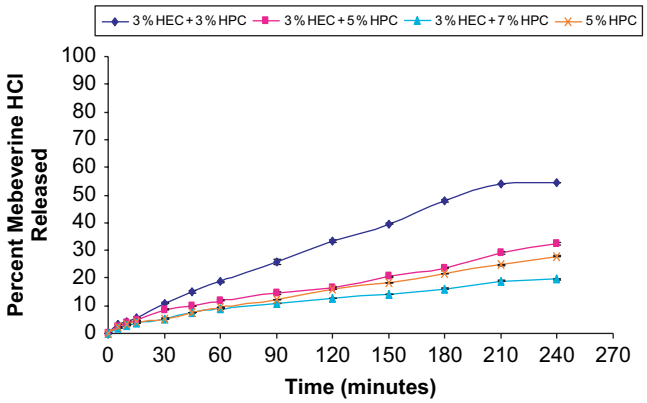


FIGURE 2. Release profiles of Mebeverine HCl at different HEC and HPC combinations.

The polymers HEC and HPC were selected as the base for the film-forming gel due to their good compatibility with the drug, ease of preparation and most importantly, the presence of HPC specifically with the water insoluble alkyl cellulose (EC) was highly required for the formation of the nonwater soluble film-forming gel without the need of an esterification agent or a chemical reaction (Tapolsky et al., 2000). The aim of using a multi-component gel formed of highly hydrophilic compatible polymers was to formulate a system that possesses unique mechanical and rheological properties that cannot be obtained using individual components, which in turn affects drug diffusion and hence drug release. The differences observed in the release of mebeverine HCl from various cellulose gels are likely due to the chemical factors, like molecular weight and nature of the polymers (Paavola et al., 1995). HPC probably forms harder polymer chain structures and networks due to its high molecular weight (850 000 Daltons) in comparison to HEC, thus by increasing its concentration drug release was reduced significantly due to the more entangled nature of the polymeric network and the extensive swelling of the gel matrix which creates a thick gel barrier for drug diffusion. These results were in accordance with what reported by Jones et al., 2000. Also, Mitchell et al., 1993 have reported that by increasing polymer chain entanglement in gels, this would result in a more concentrated gel and increased gel tortuosity which leads to a more convoluted diffusional path for the drug. The cellulose formulations examined in this study possessed release exponents indicating anomalous diffusion. Considering the swelling properties of these formulations following the ingress of water, drug release was therefore the result of the interaction of two apparently independent mechanisms, i.e., Fickian diffusion and dynamic swelling (Siepmann & Peppas, 2001). Erosion of the polymeric matrix was another predominant factor, beside diffusion, in the mechanism of drug release from these formulations.

TABLE 2
Effect of Hydroxypropyl Cellulose (HPC) on the Time Required for the Release of Mebeverine HCl (10, 30, and 50% of Original Drug Loading) from (3% w/w) Hydroxyethyl Cellulose (HEC) Gels

	Time (min) Required for Release of Mebeverine Hydrochloride (Mean ± *SE*)		
Formula (%w/w)	$t_{10\%}$	$t_{30\%}$	$t_{50\%}$
5%HPC	59.80 ± 0.78	324.19 ± 0.70	711.39 ± 2.84
3%HEC+3%HPC	26.56 ± 0.24*	107.5 ± 0.96*	205.93 ± 1.84*
3%HEC+5%HPC	47.21 ± 0.32	242.87 ± 0.87	520.10 ± 1.81
3%HEC+7%HPC	79.71 ± 0.63	461.73 ± 2.24	1044.90 ± 3.89

*Considered statistically significant versus the corresponding values of the other combinations at $p < 0.001$ using one way ANOVA followed by Tukey-Kramer test for multiple comparisons.

Effect of Ethyl Cellulose (EC) on the Release of Mebeverine HCl From the Film-Forming Gel

EC was incorporated into the binary gelling mixture of HEC (3% w/w) and HPC (3% w/w), which has shown the fastest release among other combinations, in order to form the water insoluble film on application of the gel. EC has markedly reduced the release in comparison to the base without EC. Moreover, by increasing the concentration of EC in the formulation, the release was significantly reduced furthermore. This effect is highly prominent as shown from the values of $t_{30\%}$ and $t_{50\%}$ in Table 3, where it appears that as time elapses a sustained effect is obtained by increasing the concentration of EC. At (2% w/w) EC has shown a more retarding effect on drug release rate in comparison to (1% w/w) EC. Kinetic release data has shown that the release mechanism was still anomalous diffusion after the addition of EC to the base as indicated by the values of the exponential constant (n = 0.787–0.838).

Ethyl cellulose (EC) is a hydrophobic polymer with low water permeability and moderate flexibility (Porter, 1989). However in this study the combination of the water soluble polymer HPC to the water insoluble ethylcellulose in a non-aqueous solvent has resulted in a film-forming gel. Typically, as the concentration of EC increased at constant HPC concentration, the water erodability of the film formed from the gel was reduced and the film was less readily washed away which had resulted in a more sustained release action for mebeverine HCl.

Effect of Different Surfactants and Hydrophilizing Agents on the Release of Mebeverine HCl from the Film-Forming Gel

The base selected for the film-forming gel was the binary mixture HEC/HPC at (3% w/w) for each polymer and EC (1% w/w) as this base has shown a relatively fast release among other combinations. Different surfactants and hydrophilizing agents were incorporated to this base for the aim of enhancing drug release. All the additives at different concentrations

TABLE 3
Effect of Ethylcellulose (EC) on the Time Required for the Release of Mebeverine HCl (10, 30, and 50% of Original Drug Loading) from the Binary Gel Mixture of Hydroxyethyl Cellulose (3% w/w) and Hydroxypropyl Cellulose (3% w/w)

	Time (min) Required for Release of Mebeverine Hydrochloride (Mean ± *SE*)		
Formula (%w/w)	$t_{10\%}$	$t_{30\%}$	$t_{50\%}$
3%HEC+3%HPC	26.56 ± 0.24	107.50 ± 0.96	205.93 ± 1.84
3%HEC+3%HPC+1%EC	35.12 ± 0.17	130.28 ± 0.55*	239.67 ± 0.97*
3%HEC+3%HPC+2%EC	36.20 ± 0.15	137.17 ± 0.85	254.98 ± 1.81

*Considered statistically significant versus the corresponding values of the control and the base containing 2%EC at $p < 0.001$ using one way ANOVA followed by Tukey-Kramer test for multiple comparisons.

significantly enhanced the release ($p < 0.001$), except for cetrimide (0.05% w/w). Nevertheless, the values of $t_{10\%}$, $t_{30\%}$, and $t_{50\%}$ were significantly the lowest for PG (10% w/w) appearing to have the best drug release enhancing effect in comparison to other additives and to the base without an additive, ($p < 0.001$), Table 4. Among all the additives, only cetrimide (0.05% w/w) has shown a retarding effect on the release rate which was indicated by the high values of $t_{30\%}$ and $t_{50\%}$ in comparison to those of the base without any additive as shown in Table 4. Release kinetics data for the formulae with different hydrophilizing agents has shown (n) values approaching zero order.

Incorporation of glycols such as PEG or PG into polymer bases like cellulose derivatives has significantly resulted in enhancing drug release rate due to their high hydrophilizing power (Szczesniak & Kubis, 1993). In this study, the high solubility of these additives resulted in decreasing the resistance to drug diffusion by increasing the formulation porosity following their dissolution. These results were in accordance to what reported by Jones et al., 1996. Addition of these polyhydoxy compounds to the bases is also required to act as humectants, to prevent drying and crusting of the vehicles (Miller & Drabik, 1984).

When an ionic surfactant like cetrimide binds to cellulose ethers, its electrically charged head group will effectively increase the solubility of the polymer due to electrostatic repulsion between the polymer-surfactant aggregates (Carlsson et al., 1986). Moreover, to maintain electro neutrality conditions, the bound surfactant is accompanied by its counter ion which increases the osmotic pressure inside the polymer microgel particles (Jeon et al., 1998). This could lead to increased ingress of water into the gel thus effectively increase the rates of both gel dissolution and/or erosion. This was true in case of cetrimide (0.005% w/w). On the other hand, at the higher concentration of cetrimide (0.05% w/w) the release was reduced which is attributed to increased hydrophobic interactions among the tails of bounded surfactant molecules to polymer. This induces a decrease in the hydrodynamic volume of polymer or an increase in the drug path length due to obstruction, thus restricting the diffusion movements of drug and leads finally to a reduced release rate. These results were reported by Barreiro-Iglesias et al., 2001. On the other hand, the addition of the nonionic surfactant Tween 80 to the cellulose based gels has enhanced the release rate which could be attributed to increasing the number and dimensions of the aqueous channels available for drug diffusion, thus increasing the effective porosity of the gel matrix.

Effect of the Mucoadhesive Additive (PVP) on the Release of Mebeverine HCl From the Film-Forming Gel

PVP was added to increase the mucoadhesion of the film-forming gel formula; (HEC [3% w/w], HPC [3% w/w], EC [1% w/w], and PG [10% w/w]) in order to increase its retention time on application. It is clear from the results that PVP has a retarding effect on drug release, which increases by increasing the concentration of PVP revealed by the values of $t_{10\%}$, $t_{30\%}$, and $t_{50\%}$ of the base without PVP versus those containing 1, 3 (% w/w) PVP, Table 5. Initially, at $t_{10\%}$ there was no significant difference between the formulae containing 1 and 3 (% w/w) PVP respectively, but later on, PVP especially at (3% w/w) had a significant retarding effect on drug release which was shown

TABLE 4
Effect of Different Surfactants and Hydrophilizing Agents on the Time Required for the Release of Mebeverine HCl (10, 30, and 50% of Original Drug Loading) from the Film-Forming Gel Consisting of Hydroxyethyl Cellulose (3% w/w), Hydroxypropyl Cellulose (3% w/w) and Ethylcellulose (1% w/w)

	Time (min) Required for Release of Mebeverine Hydrochloride (Mean ± *SE*)		
Formula (%w/w)	$t_{10\%}$	$t_{30\%}$	$t_{50\%}$
3%HEC+3%HPC+1%EC (A)	35.12 ± 0.17	130.28 ± 0.55	239.67 ± 0.97
A+5% PG	27.94 ± 0.73	83.81 ± 0.57	139.71 ± 0.71
A+10% PG	20.39 ± 0.20*	62.82 ± 0.35*	106.00 ± 0.38*
A+5% PEG 400	27.20 ± 0.24	100.31 ± 0.37	184.02 ± 0.28
A+10% PEG 400	24.93 ± 0.41	80.70 ± 1.53	139.33 ± 2.81
A+0.005% Cetrimide	27.32 ± 0.01	94.90 ± 0.06	169.34 ± 0.11
A+0.05% Cetrimide	35.27 ± 0.41	148.09 ± 0.83	288.56 ± 1.04
A+0.01% Tween80	30.89 ± 0.24	109.00 ± 0.53	195.91 ± 1.62
A+0.05% Tween80	31.34 ± 0.25	96.62 ± 0.47	163.07 ± 0.96

*Considered statistically significant versus the corresponding values of control and other additives at $p < 0.001$ using one way ANOVA followed by Tukey-Kramer test for multiple comparisons.

TABLE 5
Effect of Polyvinylpyrrolidone (PVP) on the Time Required for the Release of Mebeverine HCl (10, 30, and 50% of Original Drug Loading) from the Film-Forming Gel Consisting of Hydroxyethyl Cellulose (3% w/w), Hydroxypropyl Cellulose (3% w/w), Ethylcellulose (1% w/w) and Propylene glycol (10% w/w)

	Time (min) Required for Release of Mebeverine Hydrochloride (Mean ± *SE*)		
Formula (%w/w)	$t_{10\%}$	$t_{30\%}$	$t_{50\%}$
3%HEC+3%HPC +1%EC+10% PG (B)	20.39 ± 0.20	62.82 ± 0.35	106.00 ± 0.38
B+1% PVP	30.76 ± 0.06	90.02 ± 0.26*	148.29 ± 0.48*
B+3% PVP	31.85 ± 0.36	94.82 ± 1.10	157.49 ± 2.49

*Considered statistically significant versus the corresponding values of (B) and (B)+3%PVP at $p < 0.05$ using one way ANOVA followed by Tukey-Kramer test for multiple comparisons.

by the high values of $t_{30\%}$ and $t_{50\%}$ in comparison to those at (1% w/w) PVP. Therefore, PVP at (1% w/w) was selected to be added to the film-forming gel formula due to its relatively minimal retarding effect on drug release when compared to (3% w/w) PVP. Moreover, Release kinetic data has shown that the release pattern after the addition of PVP was following zero order. Addition of PVP to the formulation increased the concentration of polymeric components and hence gel consistency which has lead to extensive swelling of these formulations, which created a thick barrier against drug diffusion causing the aforementioned, retarded drug release.

Effect of Ethylcellulose (EC) on the Mucoadhesion of the Film-Forming Gel

The addition of ethyl cellulose EC at (1% w/w) to the binary mixture of HEC (3% w/w) and HPC (3% w/w) did not show any significant change for detachment force in comparison to the base without EC (*p*-value = 0.633), thus EC had no effect on mucoadhesion, Table 6. EC as mentioned above is a hydrophobic polymer and this explains why it did not affect mucoadhesion, as good mucoadhesives are hydrophilic polymers possessing hydrogen bond forming groups.

TABLE 6
Effect of Ethyl Cellulose (EC) on the Mucoadhesive Strength of the Binary Gel Mixture: HEC (3% w/w)+HPC (3% w/w)

EC Concentration (% w/w)	Detachment Force (dyne/cm^2×10^2) (Mean ± *SE*)
zero	45.41 ± 1.64
1	42.24 ± 5.92*

*Considered statistically nonsignificant versus the corresponding value of the formula without EC at $p < 0.05$ using two sided Student *t*-test.

Effect of the Mucoadhesive Additive (PVP) on the Mucoadhesion of the Film-Forming Gel

The film-forming gel formula: HEC (3% w/w), HPC (3% w/w), EC (1% w/w), and PG (10% w/w) seemed to have a very weak mucoadhesion. However, on close examination of the mucin disc, it appears that this gelling mixture has expressed a cohesive failure in its structure indicated by the amount of gel on the mucin disc. The addition of PVP (1% w/w) has significantly intensified the detachment force (*p*-value = 0.0017) for this mixture (about one fold increase) in comparison to the base without PVP as shown in Table 7. Polymers such as HEC and HPC as well as PVP were reported to be used in different buccal systems due to their adhesive properties (Jones et al., 2000; Peh & Wong, 1999). Chemically, cellulose derivatives are linear polymers possessing various degree of substitution (Lin et al., 1993). Their good bioadhesiveness may be related to their numerous hydrogen bonding sites. The low value of detachment force exhibited by the binary gel mixture of HEC (3% w/w) and HPC (3% w/w) used in this study was explained by cohesive failure of the gels where gel-gel (cohesive) fracture rather gel-mucin fracture occurred and this usually occurs

TABLE 7
Effect of Polyvinylpyrrolidone (PVP) on the Mucoadhesive Strength of the Film-Forming Gel Formula: HEC (3% w/w) +HPC (3% w/w)+EC (1% w/w)+PG (10%w/w)

PVP Concentration (% w/w)	Detachment Force (dyne/cm^2×10^2) (Mean ± *SE*)
zero	24.78 ± 2.23
1	45.41 ± 1.64*

*Considered statistically significant versus the corresponding value of the formula without PVP at $p < 0.01$ using two sided Student *t*-test.

at low polymer concentration. This was confirmed by the large gel layer adhered to the mucin disc on detachment. This result was in accordance with what reported by Jones et al., 1997. The addition of PVP, which is a highly water soluble polymer that carries a positive charge (Choi et al., 1998) makes it highly attracted to the negatively charged mucin and this may explain why the detachment force was doubled on the addition of PVP (1% w/w) to the binary cellulose gel mixture. Moreover, as PVP swells it increases the cohesion of gel leading to an enhancing effect on the gel viscosity due to the increase of active polymer concentration (Duchene et al., 1988).

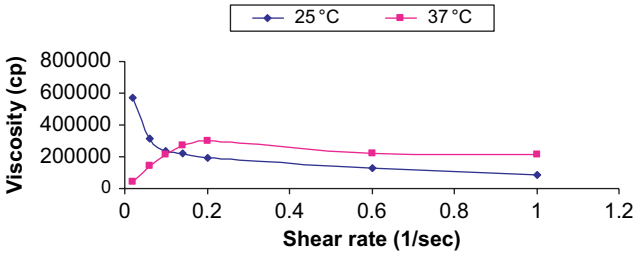


FIGURE 4. Rheogram of the film-forming gel (*F*) at room (25°C) and at body temperatures (37°C).

Rheological Flow Pattern Exerted by the Film-Forming Gel Formula (*F*) Selected for Clinical Evaluation

The additives for taste improvement were added before rheological assessment, as this step was the final before clinical evaluation. The film-forming gel formula (*F*): *HEC (3% w/w), HPC (3% w/w), EC (1% w/w), PVP (1% w/w), PG (10% w/w), citric acid (2%w/w), aspartame (3% w/w) and orange flavor (1% w/w),* which was selected to be tested clinically has shown no hysteresis where the up and down curves coincide as shown in Figure 3, which indicates a nonthixotropic behavior. The data was best fitted to Casson model, Table 8. Moreover, Figure 4 shows a shear thinning behavior for *F* at 25°C which was revealed by the decrease in viscosity at increasing shearing rates while shear thickening behavior at 37°C was noticed where viscosity increased by increasing the shear rate. The loss of consistency on application of shear, i.e., shear thinning, which was shown by the film-forming gel formula is an advantageous property for formulations intended to be applied to the oral mucosa (Pena et al., 1994). The dilatant (shear thickening) behavior shown by the film-forming gel formula at 37°C was due to the volatilization of alcohol which constitutes more than 50% w/w of the formula leading to an increase in its concentration exhibiting dilatancy as dilatant materials are defined as dispersions containing more than 50% of particles. Nonthixotropic behavior estimated by the absence of a hysteresis loop was another desired character for the film-forming gel that helps the retention of gels on the oral mucosa. Mathematical models provide a mean of representing a large quantity of rheological data in terms of a simple mathematical expression. They are useful to predict the flow behavior in complex systems in a certain shear rate range (Laba, 1993). The Bingham, Power law and Casson mathematical models describing viscoplastic systems were applied in this study. The best fitting model for (*F*) was Casson's revealing that this formula has shown a plastic flow but with negligible yield value, indicating the limited resistance to flow at low stress values.

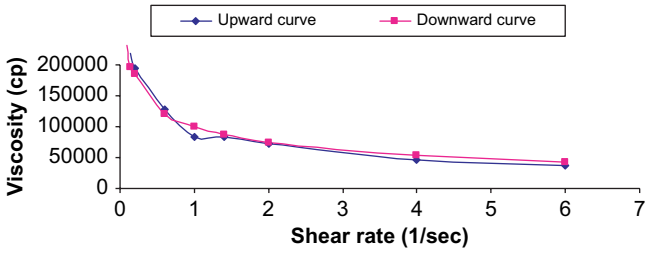


FIGURE 3. Rheogram of the film-forming gel (*F*) showing up and down curves.

TABLE 8
Fitting Data of the Selected Film-Forming Gel Formula (*F*) to Different Rheological Models

Model	Equation	Regression Coefficient (r^2)
Power Law	$y = 938.59\, x^{0.5577}$	0.980
Bingham	$y = 655.29\, x + 204.18$	0.968
Casson	$y = 20.976\, x + 9.144$	0.985

Clinical Evaluation of the Selected Film-Forming Gel Formula (*F*)

In case of pain reduction efficiency, anesthesia obtained by (*F*) was statistically significant than placebo, however there was no significant difference between (*F*) and (*S*) in pain reduction efficiency, Table 9. Interestingly, some patients had reported that (*F*) reduced the course of ulcer duration. In case of the physical parameters, Table 10, there was no significant difference in the ease of handling of (*F*) versus the market product (*S*). Despite of using flavor and a sweetener, (*F*) was slightly bitter than (*S*) ($p = 0.0313$). However, patients stated that this bitterness did not last long and did not affect their compliance. (*F*) has shown a higher degree of numbness when compared to (*S*) ($p = 0.0313$), which reflects its greater anesthetic efficiency. On the contrary to (*F*), (*S*) has significantly shown foreign body sensation, ($p = 0.0313$). This feeling caused the patient to peel off (*S*) either by tongue or fingers which affected its duration of action and needed them to reapply (*S*) many times. Furthermore, (*F*) has shown to provide a superiority in residence time

TABLE 9
Pain Scores of (*F*) versus that of Placebo and Market Product (*S*)

Formula	Mean ± *SE*	Median	Median Reduction in Pain Scores	*p*-value
(*n* = 12)				
F	2.50 ± 0.55	2	–	0.002*
Placebo	6.67 ± 0.56	6		
(*n* = 7)				
F	2.00 ± 0.75	2	75%	0.2969
S	3.71 ± 1.08	4	50%	

*Statistically significant at $p < 0.05$ using Wilcoxson-signed ranks test.

than (*S*) (9 h for F versus 2 h only for S), ($p = 0.0313$). This long residence for (*F*) has improved drug effect due to its long contact with the pain site; and provided a mechanical protection for the lesion as well specially during eating.

The median onset of action for (*F*) was quite significant from (*S*) (15 sec for F versus 2 min for S), ($p = 0.0156$). This could be simply explained by the faster onset of a gel (*F*) versus that of a paste (*S*) (Nairn, 2000). On the other hand, there was also a great significant difference between (*F*) and (*S*) in their duration of action in the favor of (*F*) (5 h for F versus 1.5 h only for S), ($p = 0.0313$). This was due to the long residence for the drug provided by the film formed on application while the film forming behavior and bioadhesion of (*S*) did not last long. Although patients were counseled to apply (*F*) for 4 times daily, some have reported that two applications were only sufficient to cover the day.

Pain assessment should be determined by patient in his own words as pain perception is subjective. The Numeric Rating Scale (NRS) used in this study to assess pain is easy to administer and demonstrates high compliance rates. Moreover, the assessment of physical characters for preparations intended to be applied locally in the oral cavity has been performed before (Ceschel et al., 2001; Desai and Kumar, 2004) to investigate the extent of patient acceptance and comfortability to the formula and hence compliance.

Histopathological Assessment of the Selected Film-Forming Gel Formula (*F*)

Comparison of the photomicrographs of control gingival tissues against the photomicrographs of gingival tissues, which have received treatment with formula (*F*), Figure 5, has shown no detectable tissue damage resulting from the exposure to (*F*). Moreover, the count of inflammatory cells infiltration in connective tissue, e.g., plasma cells and lymphocytes, Table 11 has shown nonsignificant difference in the inflammatory cells count between (*F*) versus its control, ($p = 0.1513$). On the contrary to inflammatory cells counting technique applied in this study, methods previously used for histopathological examinations of the oral cavity has been always subjective, depending on observations for the application site only by naked eye or by photomicrographs using light and electron microscopes (Ikinci et al., 2000; Şenel et al., 1998). This makes the counting technique applied in this study a more reliable and reproducible tool for histopathological evaluation.

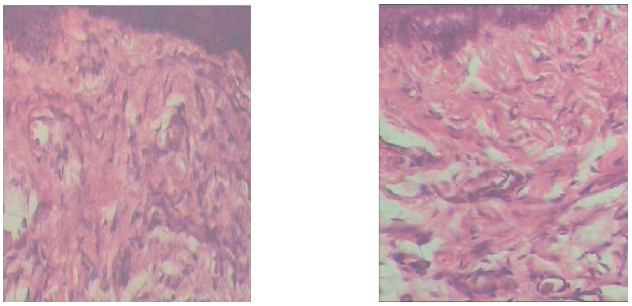
CONCLUSION

Mebeverine HCl used for the first time as a local anesthetic in this study, has shown to be highly effective for the treatment of different oral painful conditions when used in the film-forming gel formula (*F*): (HEC [3% w/w], HPC [3% w/w], EC [1% w/w], PVP [1% w/w], PG [10% w/w], citric acid [2% w/w], aspartame [3% w/w], and orange flavor [1% w/w]). This formula has shown a compromise between quite high mucoadhesive strength and an acceptable drug release profile. Moreover, it

TABLE 10
Scores for Physical Parameters of (*F*) versus that of Market Product (*S*)

Physical Parameter	Formula		Mean ± *SE*	Median	*p*-Value
1) Handling	F	(*n* = 7)	2.85 ± 0.14	3	0.375
	S		2.28 ± 0.42	3	
2) Bitterness	F	(*n* = 7)	2.57 ± 0.61	3	0.0313*
	S		4.85 ± 0.14	5	
3) Numbness	F	(*n* = 7)	2.42 ± 0.42	3	0.0313*
	S		4.42 ± 0.29	5	
4) Foreign body sensation	F	(*n* = 7)	0.28 ± 0.18	0	0.0313*
	S		1.57 ± 0.20	2	
5) Film residence (h)	F	(*n* = 7)	9.83 ± 2.04	9	0.0313*
	S		1.92 ± 0.49	2	

*Statistically significant at $p < 0.05$ using Wilcoxson-signed ranks test.
**Bitterness (Numbness) increases by the decrease of the median value.



(a) **(b)**

FIGURE 5. Photomicrographs of rat gingiva stained with hematoxylin and eosin showing connective tissue infiltrated with few inflammatory cells (20×) for (a) Control; (b) Formula F.

TABLE 11
Mean Number of Inflammatory Cells Count

Formula	Mean ± *SE*	*p*-Value
F	37.67 ± 1.28*	0.1513
Control	35.00 ± 1.55	

*Considered nonsignificant versus control at $p < 0.05$ using Paired Student-*t*-test.

has exhibited a shear thinning, nonthixotropic behavior with a negligible yield value, which made it suitable to be examined clinically. Mebeverine HCl film forming gel (*F*) was quite as effective as Solcoseryl® dental paste but with better residence, faster onset, longer duration of action and no foreign body sensation. Moreover, (*F*) did not show any tissue damage or inflammatory response for oral mucosa after continuous application for 2 days, which indicates its safety as a topical preparation.

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