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Clinical evaluation of novel buccoadhesive film containing ketorolac in dental and post-oral surgery pain management

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Ketorolac tromethamine (KT), a non-steroidal anti-inflammatory drug, was formulated in buccoadhesive film to overcome the limitations in the currently available routes of administration which in sequence will increase patients' compliance. The film was formulated using aqueous solvents by means of two bioadhesive polymers namely: hydroxylpropyl methyl cellulose (HPMC) and Carbopol 934. The prepared film was subjected to investigations for its physical and mechanical properties, swelling behavior, *in vitro* bioadhesion, and *in vitro*, *in situ* and *in vivo* release. Anti-inflammatory efficacy and analgesic activity of the prepared buccoadhesive film were investigated in rats using the hind-paw oedema test and the hot plate method. The analgesic efficacy and tolerability of a single 30 mg dose of KT formulated into the buccoadhesive film was clinically evaluated using a standard, widely accepted post-oral surgery pain model. In this study, the prepared film has been administrated to dental post-operative patients for relieving pain in dental hospital clinic. Results indicate that the concentration of KT in the oral cavity was maintained above 4.0 μg/ml for a period of at least 6 h. The buccal KT film was excellently tolerated in all patients and no complains of GI side effects were reported. It is concluded from this clinical evaluation that KT formulated into a buccoadhesive film is effective as a potent analgesic in dental and postoperative oral surgery in a single dose of 30 mg with minimal GI side effects.

1. Introduction

Ketorolac (KT) is currently administered in multiple divided doses for short term management of post-operative pain (Buckley and Brogden 1990; Morszczak et al. 1990). Intramuscular injection is the preferable route of administration (30 mg four times a day). It is administered for moderate to severe pain management, even though patient compliance is rather low for this route. The drug is also administered orally as a conventional tablet (10 mg four times a day) for management of mild to moderate pain. However, the risk of serious gastrointestinal (GI) toxicity and inhibition of platelet function has limited its use (Olmedo et al. 2001).

The major adverse reactions of KT are the damaging effects on gastric mucosa resulting in erosions, ulcers and gastrointestinal bleeding.

KT induces gastric damage by a dual insult mechanism. It is an acidic substance that can damage the GIT even in the absence of hydrochloric acid by changing the permeability of cell membranes allowing a back diffusion of hydrogen ions. This weak acid remains unionized in the stomach, but the resulting lipophilic nature of KT allows an accumulation in gastric mucosal cells. Once inside these cells, the higher pH of the intracellular environment causes KT to dissociate and become trapped in the cells. The permeability of the mucosal cell membrane is thus altered, and the accumulation of hydrogen ions causes mucosal cell damage. This gastric damage is a result of the primary insult of acidic substances. The inhibition of prostaglandin biosynthesis in the GIT prevents the prostaglandins from exerting their protective mechanism on gastric mucosa and thus KT induces gastric damage through this secondary insult mechanism (Maliekal et al. 1995). Moreover, KT is a nonspecific inhibitor of the cyclooxygenase (COX) isozymes 1 and 2, and as such is associated with COX-1-mediated adverse effects such as the GI, platelet, and renal effects described earlier. COX-2 is predominantly expressed at sites of inflammation and is the COX isozyme involved in pain and inflammation. Thus it is hypothesized that delivery of KT to the site of pain and inflammation may be associated with lower incidences of hematologic and GI adverse effects (Cordero et al. 2001; Mulshine et al. 2004). Therefore, it seems appropriate to deliver the drug directly to the site of localized pain or inflammation via buccoadhesive films.

In a previous work, KT was formulated in different buccoadhesive films. The films were evaluated physically and mechanically as well as the release behaviors *in vitro* to determine the optimal film with the desirable choice (Alanazi et al. 2006). Experiments have indicated that film number K10 has given the best results as a buccoadhesive film. It has shown a good adhesion, an acceptable pH, and a reasonable KT release (about 85–90% in 6 h). Therefore, this film has shown promising results for administra-

tion KT via the buccoadhesive route and needed to be evaluated clinically in experimental animals and humans.
The aims of this study were: (a) to characterize the anti-inflammatory efficacy and the analgesic activity of the prepared buccoadhesive film (K10) in rats using the hind-paw oedema test and the hot plate method and (b) to evaluate the analgesic efficacy and tolerability of a single 30 mg dose of KT formulated into a buccoadhesive film using a standard, widely accepted post-operative oral surgery pain model in a dental hospital.

2. Investigations results and discussion

2.1. Pharmaceutical evaluation of the prepared buccoadhesive film

A ketorolac-polymeric buccoadhesive film was prepared and the two polymers (HPMC and carbopol 934) used were found to be compatible with KT using UV, IR and DSC techniques which is the prerequisite for the successful preparation of the buccal films.
The prepared film (K10), which was found optimal in all properties from the previous study (Alanazi et al. 2006), was soft and tough which is characterized by moderate tensile strength (TS), low elastic modular (EM) and high elongation at break (EIB) (Fig. 1-A). The tensile testing gives an indication of the strength and elasticity of the film. The prepared film was considered an ideal buccal film: flexible, elastic, and soft to get adequately strong to withstand breakage due to stress from mouth activities.
The results show that the prepared buccal film possesses good swelling and bioadhesive strength so that it can be retained in the mouth for a desired duration (Fig. 1-B). The adhesion occurs shortly after the beginning of the swelling. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer tissue interface. Also, it is worth mentioning that swelling of the film should not be too extensive to prevent discomfort.
The detachment stress reflects the film-mucoadhesion. Results of this film (K10) show good detachment stress and hence good mucoadhesion (Fig. 1-C). The film surface pH is considered in the acceptable pH range for buccal mucoadhesive film (Fig. 1-C). *In-vitro* KT from the prepared buccal film was reasonably released (about 85–90%) within 6 h (Fig. 1-D) which is considered to be a quick, adequate and sustaining release of the drug. This is also supported by the data calculated from the time required to release 50% of the drug ($T_{50}\% = 98.3 \pm 1.9$) which are less than 2 h.
The results of *in vitro* permeability experiments show that the prepared KT-film possesses good oral mucosal permeation and the buccal absorption could provide means for ketorolac administration (Table 1). This is represented by good values of the steady state flux (J) and permeability coefficient (P). Also, the inverse relationship between the value of steady state flux (J), and partition coefficient (K) obtained in the study (Table 1) suggests that the drug appears to be stored in the buccal mucosa, which would be beneficial in increasing the local concentration and hence the local therapeutic effect of the drug.
The results of the *in situ* release study are presented in Table 1. The concentration of KT released was maintained well above a concentration of 4 μg/ml for a period of 6 h using the (K10) film containing 10 mg of ketorolac. In a previous study (Kelm et al. 1996), the authors reported that topically used ketorolac as oral rinse (0.1%) was clinically effective in treatment of periodontitis. The authors measured the ketorolac concentration in the oral cavity, namely in the gingival crevicular fluid and reported a maximum concentration of about 4.2 μg/ml for the drug after application of 0.1% KT oral rinse for 30 s. In the present study, the *in situ* release results indicate that the prepared film could maintain a concentration of KT in the oral cavity above the clinically effective concentration.

A The physico-mechanical properties of the prepared film

TS Nmn^{-2}	EM $N\ mm^{-2}$	E/B % mm^{-2}	Mechanical observations
0.96	0.369	260	Soft & Tough

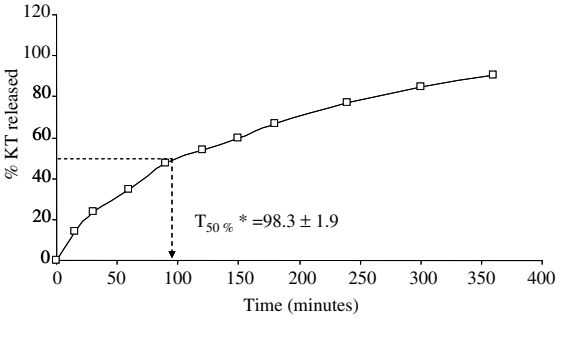
B % Hydration at time (minute) of the prepared film

5	10	15	30	60
15 ± 2.5	34 ± 2.6	48.0 ± 3.4	61.0 ± 6.1	70.2 ± .5

C Detachment force and surface pH of the prepared film

Detachment force $dync/cm^2 \times 10^{-3}$	Surface pH
22.0 + 2.3	6.0

D In vitro release profile of the prepared film



*$T_{50\%}$ = Time that required for 50% of KT to be released

Fig. 1: Pharmaceutical evaluation of the prepared KT buccoadhesive film

Table 1: Kinetics parameters of the prepared film

A Diffusion parameters

J	T_L	$D \times 10^6$	$P \times 10^{10}$	K	% cumulative
1.6	39.9	10.4	1.6	0.76	15

B In situ release parameters

C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-6\ h}$ (μg/ml·h)	Adhesion time (h)
20.4 ± 1.2	2.5	80.02 ± 9.1	6

C Pharmacokinetic parameters

C_{max} (μg/ml)	T_{max} (h)	$AUC_{0-6\ h}$ (μg/ml·h)
130.6 ±22.2	1.5	205.9 ± 44.5

Permeation parameters of KT 10 mg delivered from the prepared film through bovine buccal mucosa (A). J = flux ($mg \cdot cm^{-2} \cdot min^{-1}$), D = diffusion coefficient, TL = lag time (min.), P = permeability coefficient (cm^2/min), K = portion coefficient, * % cumulative permeated after 6 h. In situ diffusion parameters (B). C_{max} = maximum drug concentration, T_{max} = time of occurrence for peak drug concentration, AUC_{0-6} h = area under the plasma level-time curve between time interval of 0 to 6 h. Pharmacokinetic parameters of KT after buccal application of 10 mg dose using the prepared buccoadhesive film (C).

2.2. In vivo release evaluation of the prepared buccoadhesive film using human volunteers

The pharmacokinetics parameters of KT after (K10) buccal film application of 10 mg dose are presented in Table 1. Maximum drug concentration (C_{max}) is 130.6 ± 22.2 μg/ml and time of occurrence for peak drug concentration (T_{max}) is 1.5 h. These data indicate that the prepared film can attain reasonable KT concentration in the buccal cavity to treat oral painful stimulations or stop post-operative dental or gingival pain.

2.3. Investigation of the anti-inflammatory efficacy of the prepared buccoadhesive film using hind-paw induced oedema method

Several methods of induction of inflammation in animals including UV erythema, yeast pyresis, injection of carragenan or kaolin-induced paw oedema were used as an *in vivo* assay for the potency of the anti-inflammatory drugs. The injection of kaolin induced rat hind paw oedema model was selected as a model of acute inflammation due to the delayed inflammatory events produced by kaolin suspension injection (Winter 1964). KT preparations were administered 1 h after induction of oedema. The effects of the prepared film on the anti-inflammatory activity of KT administered buccally (via sticking the film to rats' buccal cavities) or applied locally on the site of oedema (via adhesion to inflammation area) were studied. The percent inhibition of kaolin-induced oedema by KT films administered buccally, or applied topically as well as by a marketed KT tablet (used for comparison) administered orally is shown in Fig. 2 and Table 2.

Fig. 2 shows that buccal and topical application of the prepared film showed a higher percentage of inhibition than the control film and the tablets. Table 1 shows the significance level of difference in percent swelling after buccal, topical administration of the investigated K10 film (containing 5 mg KT) and oral administration of KT tablet (1/2 tab. containing 5 mg KT), compared with placebo film as control as well as with each other. It is obvious that the differences are significant between the placebo and KT buccal film or commercial tablet. Statistical analysis of the differences is shown in Table 1.

It is clear from the obtained results that the reduction of oedema by the investigated KT film when applied buccally was significantly higher ($P < 0.05$) than that of the commercial KT tablet 30 min after application. The percent swelling inhibition by the prepared film given by the buccal route is significantly ($P < 0.05$) lower (i.e. higher anti-inflammatory activity) than that of the oral tablet.

When the prepared film was applied topically at the oedema site, this statistically significant difference appeared one hour after application. This could be explained on the basis of the difference of the drug absorption from each of the two routes. At an early stage after drug application the absorption from the buccal route is more rapid than that from skin. Buccal applications of the investigated film gave higher initial anti-inflammatory effect than the local application. However, difference in effect is non-significant between the buccal administration and topical application in time period from 0 up to 4 h.

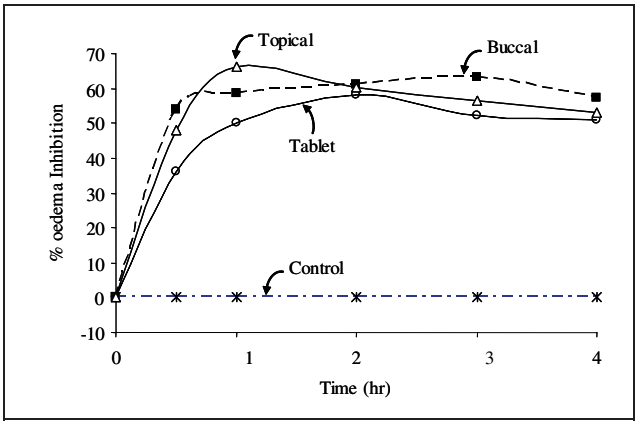


Fig. 2: Percent inhibition of oedema by buccoadhesive film containing s.o. mg ketrolac given one hour after induction of edema

Table 2: Percent inhibition of swelling of oedema by buccoadhesive film containing 5.0 mg KT given one hour after induction of edema

Time	Percent swelling (%)			
	Control	Marketed tablet[R]	Buccal film	Topical application
0	133.3 ± 6.6	133.3 ± 3.4	133.3± 16.7	133.4 ± 6.7
0.5	167.0 ± 6.7	106.7 ± 6.7	77.0 ± 6.6	86.7 ± 15.6
1	175.0 ± 10.0	87.3 ± 8.3	72.6 ± 3.4	58.4 ± 9.2
2	180.0 ± 16.6	75.0 ± 9.6	70.0 ± 9.3	70.6 ± 10.0
3	183.4 ± 17.0	87.7 ± 9.6	67.4 ± 8.3	80.0 ± 14.0
4	187.0 ± 16.2	91.7 ± 9.5	80.3 ± 9.3	87.8 ± 9.4

Level differences in the percent swelling after buccal application in comparison to other routes

	Control	Tablet	Topical application
Comparison	**	*	–

** donates a statistically significant difference ($p < 0.05$) at all time points
* donates a statistically significant difference ($p < 0.05$) at 0.5 hr
– no significant difference
R Ketolac tablet (10 mg) Amriya Pharm. Ind., Alexandrya, Egypt.

2.4. Investigation of the analgesic activity of the prepared KT buccoadhesive film adopting the hot-plate method in mice

Table 3 shows the latency in hot plate test. Both oral solution and buccal film of KT used in the study increased the latency in hot plate test, in the dose of KT used. The analgesic activity for oral treatment lasts for about 12 h, while in the case of film treatment, the analgesic effect was still observed after 24 h. The results also show significant differences in latency time between the investigated

Table 3: Latency in seconds of albino mice on the hot plate (56 ± 0.5 °C) after treatment with KT formulations

Time	Latency (s)			Statistical comparison	
	Control	Oral solution	Buccal film	Film: oral	Film: control
0	9.8 ± 0.8	9.3 ± 0.8	9.2 ± 0.7	–	*
0.5	9.4 ± 0.8	13.2 ± 2.3	13.7 ± 2.4	–	*
1	9.8 ± 0.6	17.1 ± 2.5	17.6 ± 4.2	–	*
2	10.0 ± 1.1	17.4 ± 3.0	16.6 ± 3.6	–	*
3	10.6 ± 1.2	16.4 ± 2.9	19.8 ± 2.9	*	*
4	10.4 ± 0.8	16.8 ± 3.6	20.2 ± 4.0	*	*
6	10.0 ± 0.9	14.9 ± 2.9	19.7 ± 3.8	*	*
9	9.8 ± 0.7	14.0 ± 4.3	18.0 ± 3.6	*	*
12	10.2 ± 0.8	12.2 ± 2.9	18.0 ± 2.9	*	*
24	9.8 ±1.0	10.0 ± 1.2	17.0 ± 3.2	*	*

* donates a statistically significant difference ($p < 0.05$)
– no significant difference

treatments. It is clear from the Table that there is a significant difference in latency between the oral treatment and the control group up to 9 h, while in the case of film treatment, the significant difference between control and film group was observed up to 24 h. There is no significant difference between film and oral treated groups in the first 3 h, however, the film showed significant increase in latency (i.e. more analgesic effect) over the oral treatment in the following 21 h.

2.5. Clinical evaluation of the prepared buccoadhesive films in dental post-operative patients

Previous studies have shown the analgesic effect of ketorolac administered orally as 10 mg tablets q.i.d. (Olmedo et al. 2001) or as 60 mg i.m. injection (Walton et al. 1993; Abbas et al. 2004) to patients with postoperative dental pain. The authors have reported that KT has been shown to be efficacious in the treatment of post-operative oral pain. However, gastrointestinal (GI) side effects have been claimed some of the patients. No previous studies have been made to use KT directly as buccoadhesive film on the site of pain that has been tried in this study.

Statistical analysis was undertaken to determine the efficacy and safety of the analgesic activity of KT formulated into the prepared film (K10) among patients with post-operative pain following clinical oral surgery procedure. A double-blind, randomized, parallel-group, placebo (33 patients) and active drug (35 patients), single-dose, trail was performed (Table 4). Unpaired t-test was performed to compare the results of the two groups and paired t-test was performed to compare the results within each group. Efficacy analysis was performed on the intent-to-treat population. So patients who required rescue medication within 1 h after receiving placebo were given the active study medication to alleviate their post-operative pain. Actually all patients of the placebo group claimed moderate to severe pain 1 h after receiving placebo and were given the active study medication (KT film) at that time. After that they completed the study, pain intensity (PI) was assessed for the following 24 h.

Table 5 shows the results of statistical comparison between the two groups and within each group. It is clear from the results that the for both of the KT film and the placebo film group was high before the application of the treatment. The PI values were 6.857 and 7.122, respectively, with no significant difference between the two groups. One hour after the application of films (contains drug or placebo), the drug treated group has experienced a low mean value of PI (1.14) which reflects efficient and highly significant ($p < 0.001$) pain relief compared with zero time, while the placebo group has shown a high mean value of PI (7.09) which reflects no improvement in pain relief with no significant difference ($p > 0.05$). In the mean time, a highly significant difference ($p < 0.001$) between the two groups was observed as shown in Fig. 3 and 4. This confirms the efficient pain relief properties of the KT film (K10) compared to placebo. However, on the basis of the intention to treat the KT film was applied to the placebo group at that time (1 h). After 1 h the mean PI decreased in this group from 7.09 to 0.82 which reflects efficient pain relief. At that time and up to 24 h both of the two groups have shown a low score of PI values with no significant difference between the two groups. In the

Table 4: Baseline demographic characteristics, surgical characteristics and pain intensity of the clinical post-operative patients

Surgical treatment	Age range	Treatment	Sex		Baseline pain intensity
			Male	Female	
Endodontic surgery	23–65	KT film	3	3	Moderate
		Placebo	4	3	Moderate
Periodontal surgery	18–61	KT film	6	3	Moderate
		Placebo	5	3	Moderate
Oral surgery	21–60	KT film	6	4	Severe
		Placebo	5	4	Severe
Ortho surgery	23–60	KT film	7	3	Moderate
		Placebo	6	3	Moderate

Total number of patients received KT film is 35
Total number of patients received Placebo is 35

Table 5: Results of the patients' post-operative pain intensity for the KT film and placebo group

Time (h)	Group	Patients number	Pain intensity
0	KT film	35	6.85 ± 0.24
	Placebo	33	7.12 ± 0.21
1	KT film	35	1.14 ± 0.23
	Placebo	33	7.09 ± 0.27
1*	KT film	35	1.14 ± 0.23
	KT film applied to placebo	33	0.82 ± 0.21
4*	KT film	35	0.51 ± 0.12
	KT film applied to placebo	33	0.24 ± 0.08
6*	KT film	35	0.26 ± 0.08
	KT film applied to placebo	33	0.45 ± 0.18
24*	KT film	35	–
	KT film applied to placebo	33	–

* KT film was applied to placebo group
– donates no pain recorded

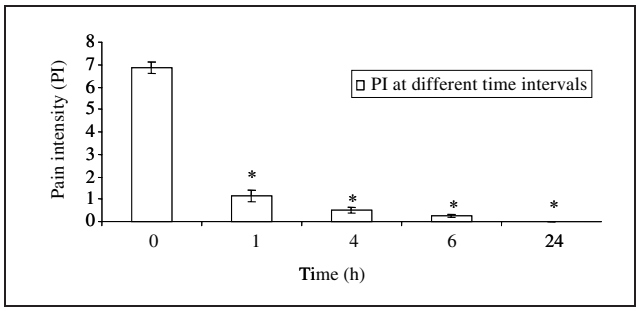


Fig. 3: Results of the post-operative pain intensity after KT film application donates statistically significant difference of time intervals from zero time

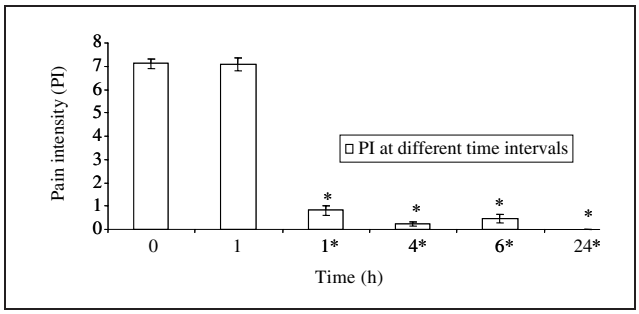


Fig. 4: Results of the post-operative pain intensity of placebo group and after KT film application.
, 4, 6* and 24* pain recorded for the placebo group after KT administration

mean time, significant difference within each group was observed after 1h from the application of KT film compared with zero time. This significant difference lasts for the period of the study (24 h) as shown in Figure 4, which indicates the efficacy of the prepared KT film for an extended period of time. The usual dosage regimen of oral KT is 10 mg four times daily.

The buccoadhesive KT film investigated in this study was excellently tolerated in all patients and no complaints of GI side effects were reported. It could be concluded from this clinical trial that KT formulated into buccoadhesive films is effective as analgesic in postoperative oral surgery in a single dose of 30 mg with minimal GI side effects and comfortable application of such film.

3. Experimental

3.1. Materials

Ketorolac tromethamine (KT) was generously obtained from Amirya Pharm. Ind. Co. (Alexandria, Egypt). Hydroxypropyl methyl cellulose (HPMC) was purchased from Dow Chemical Company (Midland, Michigan, USA). Carbopol 934P was supplied from Sorgan Co. (Wiedelberg, Germany). Polyvinylpyrolidene K90 (PVP) was obtained from Serva GmbH & Co. (Heidelberg, Germany). All other chemicals and solvents used were of pharmaceutical grade.

3.2. Methods

3.2.1. Preparation of the polymeric film containing ketorolac

Ketorolac buccoadhesive film was prepared by the method previously reported (Alanazi et al. 2006). Hydrophilic bioadhesive polymers (HPMC and Carbopal 934) were used to prepare the film. In addition, film forming agent (PVP) and plasticizer (PG) were added. The schematic diagram for the preparation steps of KT buccoadhesive film and a list of formulation is presented in Figure 5. The film constituents were examined for their compatibility using infrared spectroscopy (IR), differential scanning calorimetery (DSC) and UV spectrophotometery.

3.2.2. Pharmaceutical evaluation of the prepared buccoadhesive film

The actual content of KT in the prepared film was determined by HPLC (Gu et al. 1988). The prepared film was also evaluated for its physio-mechanical elongation such as the tensile strength (TS), the modulus of elasticity (EM) and mechanical observation. The hydration characteristic of the prepared film was evaluated by swelling behavior method (Peh et al. 1999). The surface pH of the prepared film was determined after soaking the film (1 cm^2) in distilled water (1 ml) for 15 min. *In vitro* bioadhesion of the prepared films was examined using chicken pouch as a model mucosal membrane (Agarwal et al. 1999). The *in vitro* release profile of KT from the prepared film was studied. The permeation of KT from the prepared buccal film through bovine buccal membrane was carried out using a Franz diffusion cell. The *in situ* release of KT from the prepared film was investigated using a home-made open, continuous flow through cell (Alanazi et al. 2006).

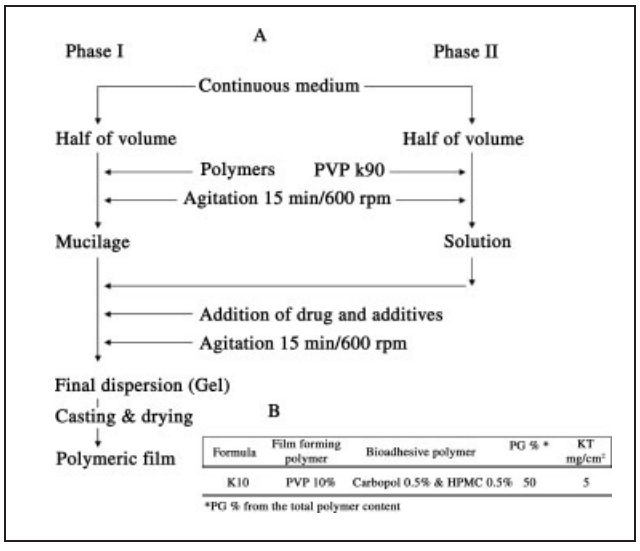


Fig. 5: Schematic diagram for preparation steps of ketorolac buccoadhesive film (A), a list of film constituent (B)

3.2.3. In vivo release evaluation of the prepared buccoadhesive film using human volunteers

The *in vivo* release study was performed under medical supervision on six human healthy volunteers (3 males and 3 females) capable of consent aged between 18–40 years and weighing 70–90 kg. A rectangular piece of the prepared film was stuck to the wall of the buccal cavity by finger and adhered to the gum. Eating and drinking was prohibited during the first 3 h. After application, saliva samples (~1.0 ml) were collected periodically every 30 min up to 8 h after adhering the medication. The collected saliva samples were stored at −20 °C in a deep freezer bending to analysis by HPLC for determining drug content.

3.2.4. Investigation of the anti-inflammatory efficacy of the prepared buccoadhesive film using hind-paw induced oedema method in rats

The anti-inflammatory efficacy of the prepared film was evaluated. Male rats (5 per group) weighing 200 ± 20 g were used for evaluation. The rats in each group were selected so that the average body weight among the groups was as close as possible. The rats were fasted with free access to water for 12 h prior to the test. The rats were anaesthetized with urethane (intra-peritoneal). Oedema was induced by subcutaneous injection of 10% Kaolin suspension in pyrogen free saline solution into the right subplanatar region (Winter 1964; Vinegar 1968). One hour after induction of oedema, the first group of rats were given 1/2 KT tablet containing 5 mg KT (after suspension in 1.0 ml of water) by an esophageal tube. The second group received 1.0 cm^2 of the prepared film (contains 5 mg KT) stuck to the buccal area, the third group received 1.0 cm^2 of the prepared film, applied topically on the inflamed area. The last group received 1.0 cm^2 of non-medicated film, as control, stuck to the buccal area.

The thickness of the rat hind paw was measured by a vernier caliper (SMEC, China) before Kaolin injection, immediately after giving the drug (1 h after Kaolin injection and then after 0.5, 1, 2, 3, 4 and 5 h. The percent swelling of the paw was calculated using Eq. (1):

$$\% \text{ swelling} = \frac{V - V_i}{V_i} \quad (1)$$

where V = the paw thickness at each time interval and V_i = the initial paw thickness (before kaolin injection) (Chi et al. 1990).

The average paw swelling in the treated rats was compared with that of control rats and the percent inhibition of oedema was calculated using Eq. (2):

$$\% \text{ Inhibition} = \left(1 - \frac{S}{S_i}\right) \times 100 \quad (2)$$

where S = % swelling of KT treated group and S_i = % swelling of control group (Chi et al. 1990). A multiple range T-Test was adopted to statistically compare the differences in the anti-inflammatory activity observed after application of the investigated formulations.

3.2.5. Investigation of the analgesic activity of the prepared KT buccoadhesive film using the hot-plate method in mice

Hot Plate Test was used in this study to investigate the analgesic activity of the prepared KT buccoadhesive film (Raza et al. 2000). Male Swiss albino mice weighing 20–30 g were used and the mice in each group were selected so that the average body weight among the groups was as close as possible. Eight animals were used in each group. The animals were fasted with free access to water for 12 h prior to the test.

The first group of mice received 2 mg KT orally (0.2 ml of 10 mg/ml KT solution in distilled water) by an esophageal tube. The second group received a piece of the prepared film contains 2 mg KT by sticking in the buccal cavity. The film (0.2 cm^2 area and 25 mg in weight) was adhered to the oral cavity of the mouse by means of forceps. The third group treated as group two but using non-medicated buccal film and used as control group.

The analgesic response was determined by a hot plate maintained at a temperature of 56 ± 0.5 °C (DS 30 socnel ugobasile Biological Research Suppliers Co. Italy). The latency to forepaw licking or jumping off the hot plate was recorded for every individual animal in each group at time intervals of 0.5, 1.0, 3.0, 4.0, 6.0, 9.0, 12.0 and 24.0 h.

3.2.6. Clinical evaluation of the prepared buccoadhesive films in dental post-operative patients

Eligible patients were healthy men and women, aged 18 to 64 years, undergoing oral dental surgery (Dental Clinic, College of Dentistry, King Saud University). The demographic characteristics, surgical characteristics, and baseline pain intensity are shown in Table 3. Before enrollment, patients had to experience moderate to severe postoperative pain (intensity >5.0 cm on a 10.0 cm isual analog scale [VAS]) (Scott J 16). Exclusions included a history of upper GI ulceration or bleeding within the past

6 months or current significant upper GI complains. Pregnant women and patients who had taken analgesics or other agents that could confound the analgesic response (e.g. tricyclic antipressants, narcotic analgesics, antihistamines, tranquilizers, hypnotics, sedatives, NSAIDs, or corticosteroids) in the 6 h before surgery were also excluded from the study. All patients gave written informed consent prior admission to the studies which were approved by Human Studies Committee and College of Dentistry Research Center Sub-committee on Ethics, King Saud University.

The method used was a double-blind, randomized parallel-group, placebo- and active drug, single-dose, single-center trail. Patients experiencing moderate to severe post-operative pain after the oral surgery were randomized to receive a single 30 mg dose of the prepared buccoadhesive KT film or placebo (the same film formula without the drug) to be applied in the oral cavity over the site of surgery. Patients assessed pain intensity (PI) at baseline and at designated intervals for 24 h after administration of the investigated buccoadhesive KT film. The study was based on the intention to treat, so, after the first hour, the patients in the placebo group who showed moderate to severe postoperative pain (intensity >5.0 cm on a 10.0 cm visual analog scale) were applying the prepared film containing KT and the analgesic efficacy was assessed in terms of pain intensity (PI) relief as in the drug treated group.

Study design was a double-blind, randomized, parallel-group, placebo-controlled, single-dose, single-center trail performed at college of dentistry, King Saud University, Riyadh, Saudi Arabia. Patients were randomized to study treatment. During the pretreatment period, defined as the 14 days before application of study medication film, patients gave their written informed consent. A medical history was obtained, and physical examination and clinical laboratory testing were performed, including an urine pregnancy test for women of childbearing potential. A second urine pregnancy test was not performed on the day of surgery.

The treatment period began with application of a single dose of study medication film in the buccal cavity after the patient had undergone oral surgery and developed moderate to serve postoperative pain. One dose of active medication film or 1 dose of placebo film was applied in the oral cavity after randomization. Patients remained at the study site and were monitored for 6 h according to post operative care standard.

During the treatment period, patients assessed pain intensity (PI) as baseline (immediately before taking medication) and pain intensity (PI) at 1, 2, 4, 6 and 24 h there after, or immediately before taking rescue medication. All assessments were recorded in a patient diary, which was kept at the study site. Pain intensity assessments were made using a categorical scale and a standard visual analog scale (VAS). The categorical pain intensity assessment employed a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). In the VAS assessment of pain intensity, patients placed a vertical mark along a 10.0 cm scale from 0 cm (no pain) to 10.0 cm (worst pain).

For Clinical Safety Assessments, patients were monitored throughout the treatment and post treatment periods (24 and 72 h) for the fear of development of adverse events. Vital signs were recorded for the treated patients and routine clinical laboratory assessments performed before and after surgery prior to patient discharge from the study unit (Dental Clinic, College of Dentistry, King Saud University).

3.2.7. Statistical analysis

Efficacy analysis was performed on the intent-to-treat population. So patients who required rescue medication within 1 h after receiving placebo were given the active study medication film. Based on that, unpaired t- test was used to compare the results of the two groups and paired t-test was used to compare the results within each group.

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