Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 8, 2014

Original Article

DEVELOPMENT AND EVALUATION OF KETOROLAC TROMETHAMINE MUCOADHESIVE BUCCAL TABLETS

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Received: 12 Jun 2014 Revised and Accepted: 19 Jul 2014

ABSTRACT

Objective: The aim of the present study was to develop and evaluate buccal mucoadhesive tablets of ketorolac tromethamine.

Methods: The tablets were prepared by direct compression using bioadhesive polymers such as carbobpl 934 with hydroxypropyl methylcellulose K4M and sodium carboxymethyl cellulose. The prepared tablets were characterized by different parameters such as weight uniformity, content uniformity, hardness, swelling index, in vitro drug release studies, ex- vivo residence time and ex- vivo permeation study.

Results: F7 formulation containing Carbopol 934 and SCMC (at the ratio 1:3, respectively) showed good swelling, a convenient residence time as well as the highest amount of drug released within 6 hrs. Stability studies in natural saliva for 6 hrs, indicate that optimized F7 formulation has good stability in human saliva. In addition to the good correlation obtained between in vitro drug release and ex-vivo drug permeation study.

Conclusion: The buccal mucoadhesive tablet of ketorolac could be an alternative route to reduce the pronounced gastrointestinal irritations, and reduce dosing frequency to improve patient compliance.

Keywords: Ketorolac tromethamine, Adhesive buccal tablets, Mucoadhesive polymers.

INTRODUCTION

Mucoadhesive drug delivery system is now-a-days a booming field for research interest. These are delivery systems, which utilize the property of bioadhesion of certain polymers.

Mucoadhesive buccal drug delivery systems offer many advantages over conventional systems such as ease of administration, be promptly terminated in case of toxicity by removing the dosage form from buccal cavity and it is also possible to administer drugs to patients who cannot be dosed orally via this route[1-2].

Recently much attention has been focused on the design and evaluation of buccal drug delivery systems keeping in view their potential for future market. Therefore a buccal drug delivery system needs to be developed and optimized. An ideal buccal adhesive system must have the following properties: should adhere to the site of attachment for few hours, should release the drug in controlled manner and should provide the drug release in a unidirectional way in the mucosa[3].

The unique environment of the oral cavity offers its potential as a site for drug delivery. Through this route it is possible to realize mucosal (local effect) and transmucosal (systemic effect) drug administration. In the first case, the aim is to achieve a site-specific release of the drug on the mucosa, whereas the second case involves drug absorption through the mucosal barrier to reach the systemic circulation. Therapeutic agents administered through buccal mucosa enters directly to the systemic circulations and thereby circumvent the first pass hepatic metabolism, gastric irritation and other problems associated with conventional oral route[4-5].

Ketorolac Tromethamine (KT) is a well known non-steroidal anti-inflammatory drug with potent analgesic activity. Ketorolac is currently administered intramuscularly and orally in multiple divided doses for short-term management of post-operative pain[6]. The drug is administered via the oral route as a conventional tablet (10 mg four times a day) for management of mild to moderate pain [7]. In addition to the limitations in the available routes of administration, the half life of KT ranges from 4-6 h[6]. Therefore, frequent dosing is required to alleviate pain in postoperative patients due to its short half-life. To avoid an invasive drug delivery technique (i. e. intramuscular injection) and to decrease the gastrointestinal side effects produced by the oral tablets[8], there is a need for an alternative noninvasive mode of delivery for KT. The new delivery system should also provide sustain in the release of this medication to assist patient compliance. The buccal mucoadhesive administration may thus represent an alternative route for KT delivery.

In the present investigation, an attempt was made to design efficacious and prolonged release mucoadhesive buccal tablets of ketorolac using various polymers to reduce dosing frequency, decrease gastric irritation and to improve patient compliance.

MATERIALS AND METHODS

Materials

Ketorolac tromethamine (KT) was generously provided by Amirya Pharm. Ind. Co. (Alexandria, Egypt). Carbopol 934 (CP) (B. F., Goodrich Chemical Company, Ohio, USA), Hydroxypropyl methylcellulose (HPMC K4M); Biochemica, Switzerland, Sodium Carboxymethylcellulose (SCMC) (C. B. H. Lab Chemicals, Nottingham, U. K.), Polyvinyl pyrrolidone K30 (PVP k30): Sigma, USA. All other chemicals and solvents used were of pharmaceutical grade.

Drug excipients compatibility study

To investigate any possible interactions between the drug and the used bioadhesive polymers, infrared spectroscopy (IR) was adopted. The IR spectrum of a) pure ketorolac, b) physical mixture containing drug, CP 934 and HPMC K4M c) physical mixture containing drug, CP 934 and SCMC were taken, interpreted and compared with each other. The IR spectra were carried out using Shimadzu IR-470 spectrophotometer (Tokyo, Japan). The samples were prepared as KBr disks compressed under a pressure of 6 tones/cm2. The scanning range was 400-4000 cm^{-1}.

Preparation of Mucoadhesive Buccal Tablets

Mucoadhesive buccal tablets each containing 10 mg ketorolac were prepared by direct compression method. Composition of various formulations employing carbopol 934, SCMC and HPMC are shown in table (1) was mixed homogeneously in a glass mortar for 15 minutes. The mixture (100 mg) is compressed using 7 mm flat faced punch on 16 stages rotary tablet compress machine.

Table 1: Composition of Ketorolac Tromethamine buccal tablets

Formulation Code	Drug (mg)	Cp 934 (mg)	HPMC (mg)	SCMC (mg)	PVP K30 (mg)	D –mannitol (mg)
F1	10	35	35	-	6	14
F2	10	23	46	-	6	14
F3	10	18	54	-	6	14
F4	10	14	56	-	6	14
F5	10	35	-	35	6	14
F6	10	23	-	46	6	14
F7	10	18	-	54	6	14
F8	10	14	-	56	6	14

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The tablet was allowed to swell by keeping it in contact with 1 mL of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute[9].

Swelling index

Buccal tablets were weighed individually (W_o) and placed separately in 2% agar gel plates and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W_1) and the swelling index (S. I) was calculated using the formula[10] given in Equation 1.

Swelling index = 100 (W_1 -W_o) / W_o ……. (1)

Drug content

Five tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 ml of pH 6.8±0.5 phosphate buffer on a rotary shaker overnight. The solution was centrifuged and the supernatant was collected[11]. The absorbance was measured by using UV-visible spectrophotometer at 322 nm. Each measurement was carried out in triplicate and the average drug content in the buccal tablet was calculated.

***In vitro* drug release**

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. The dissolution medium consisted of 200 ml of phosphate buffer pH 6.8 ±0.5. The release was performed at 37°C ± 0.5°C, with a rotation speed of 50 rpm. The tablet was supposed to release drug from one side only hence a one side of tablet was fixed to glass disk with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Samples (3 mL) were withdrawn at predetermined time intervals and replaced with fresh medium[12]. The samples were filtered through filter paper and analyzed by UV spectrophotometer at 322 nm.

Release data were fitted to various mathematical models Korsmeyer-Peppa's [13], zero order, first order and Higuchi release models [14] in order to determine the release mechanism.

***Ex-vivo* mucoadhesion time**

The *ex-vivo* mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa. A segment of fresh sheep buccal mucosa (2 cm) was glued to the surface of glass slide, and a mucoadhesive buccal tablet was wetted with 1 drop of phosphate buffer pH 6.8±0.5 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 100 mL of the phosphate buffer pH 6.8, and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 8 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time[15].

***Ex- vivo* drug permeation**

The ex-vvo buccal permeation studies was carried out for optimized ketorolac buccal tablet. The permeation study of ketorolac through the excised layer of goat buccal mucosa was performed using Franz diffusion cell at 37°C ± 0.5°C. Fresh goat buccal mucosa was mounted between the donor and receptor compartments. The buccal tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 m1 of phosphate buffer pH 6.8. The receptor compartment (45 ml capacity) was filled with phosphate buffer pH 6.8 ± 0.5and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed[16]. The amount of drug permeated through the buccal mucosa was determined by withdrawing samples (1 ml) at predetermined time intervals and analyzed for drug content by UV spectrophotometer at 322 nm.

RESULTS AND DISCUSSION

FTIR studies revealed that, no interaction between the drug and the used polymers occurred as there was no shift in the IR peaks of the drug (Figure 1).

The physico-chemical characteristics of Ketorolac muacoadhesive buccal tablets are shown in Table 2. All the tablet formulations showed almost uniform weight, thickness and favorable hardness. The weight of the tablets was varied between 107.7 mg and 96.6 mg with SD values 0.4 - 0.8. The thicknesses of the various tablet formulations were observed to be in the range of 2.6 mm to 3.64 mm with SD values of 0.06-0.28.

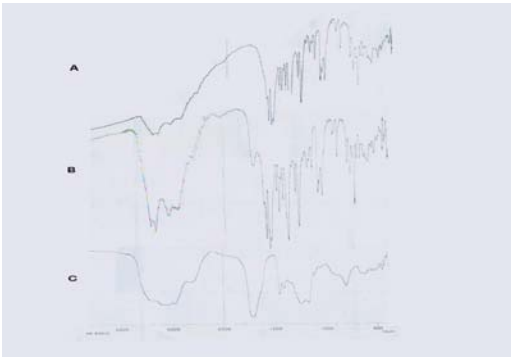

Fig. 1: a) pure ketorolac b) physical mixture of ketorolac, carbopol 934 and HPMC c) physical mixture of ketorolac, carbopol 934 and SCMC

The hardness of all the tablets was found to be in the range of 3.7 to 4.8 kg/cm2. The average drug content of the tablets was found to be within the range of 95.35% to 101.41% and the low values of standard deviation indicate uniform distribution of the drug within the prepared mucoadhesive buccal tablets. The surface pH of all the tablets was within a range of 6.4 to 7.1 (Table 2), which was close to neutral pH. Hence, it is assumed that these formulations cause no irritation in the oral cavity.

The swelling profile of different buccal tablets is shown in figures 2 and 3. The results of swelling study revealed that the swelling index of all tablets was increased by time because the polymers gradually absorb water due to hydrophilicity of the polymers. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Appropriate swelling behavior of mucoadhesive buccal system is an essential property for uniform and prolonged drug release and effective mucoadhesion. 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[17]. The swelling index was directly proportional to the concentration of the second polymer (HPMC or SCMC) and inversely proportional to CP934. The higher swelling rate and extent of buccal tablets containing SCMC can be explained due to the faster rate of water uptake by SCMC than by HPMC.

Table 2: Physicochemical properties of Ketorolac Tromethamine mucoadhesive buccal tablets

Formulation Code	Weight (mg)	Thickness (mm)	Hardness (kg/cm2)	Surface pH	Drug Content	Ex-vivo mucoadhesion time
F1	106.5±0.5	2.6±0.08	3.9±0.11	6.4 ± 0.05	95.3 ± 0. 21	> 8
F2	96.6±0.52	3.64±0.12	3.9±0.17	6.8 ± 0.1	97.2 ± 0.28	> 8
F3	99.6±0.4	2.63±0.22	3.8±0.1	6.9 ±0.05	96.7 ± 0.46	> 8
F4	104.8±0.8	2.99±0.1	3.7±0.25	7.02 ±0.15	95.5 ± 0.51	5.30 ± 0.5
F5	101.3±0.57	3.62±0.11	3.8±0.15	6.6 ±0.05	98.6 ± 0.35	> 8
F6	99.2±0.33	3.26±0.13	4.1±0.15	6.9 ±0.05	98.7 ± 0.2	5.5 ± 1.05
F7	107.7±0.45	3.36±0.06	4. 8 ±0.21	7 ± 0.1	99.1 ± 0.32	6. 5 ± 0.5
F8	100.6±0.5	2.6±0.28	4.6±0.21	7.1 ± 0.1	101.4 ± 0.25	5 ± 0.7

The swelling index after 6 hrs was in the range from 16.94% to 42.18% for buccal tablets containing CP 934 with HPMC (F1-F4), while for buccal tablets containing CP934 with SCMC (F5-F8) was in the range from 32.59% to 52.3%. Buccal tablets containing Cp934 and SCMC at the ratios of 1:2 and 1:3 exhibited the highest swelling (48.5 % and 52.3%, respectively).

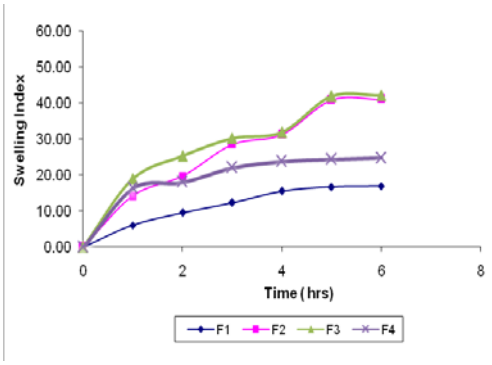

Fig. 2: Swelling study of Ketorolac tromethamine buccal tablets containing different ratios of carbopol 934and HPMC

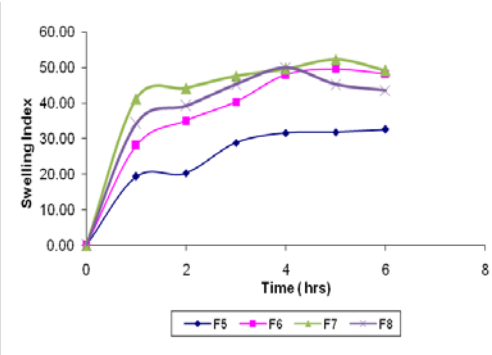

Fig. 3: Swelling study of Ketorolac tromethamine mucoadhesive buccal tablets containing different ratios of carbopol 934and SCMC

A putative and effective mucoadhesive formulation should not only be able to adhere to the mucosal surface, but also be capable of remaining in place for an extended period of time. Hence, assessing the duration of mucoadhesion of buccal tablets is critical [18]. The polymeric materials become adhesive with hydration while excessive swelling leads to reduced mucoadhesiveness because water molecules bind to polymer groups required for adhesion[19]. Ex vivo mucoadhesion time for the prepared buccal tablets (F1 to F8) varied from 5 to more than 8 hours (Table 2). The difference between the values of the ex-vivo mucoadhesion time for buccal tablets could be attributed to the combination of various amounts of the polymers, which affected the mucoadhesion. Moreover, SCMC, owing to its solubility in water and the observed higher swelling rate and extent, resulted in lower mucoadhesion time. In fact, with buccal tablets containing a higher proportion of CP, mucoadhesion time was found to be increased.

In vitro drug release studies revealed that the release of ketorolac from different formulations varies with characteristics and composition of matrix forming polymers as shown in figure 4 and 5. The drug release rate appeared to increase with decreasing carbopol 934 and increasing concentration of SCMC and HPMC. The gradual swelling of buccal tablets containing CP 934 and SCMC inevitably facilitated the release of ketorolac due to easier diffusion in the swelled region of the polymer network. The prolonged release of drug from buccal tablets containing higher percentages of CP 934 may be explained by its properties of in situ gelling and slow dissolution.

Therefore increase of carbopol content delays the drug release from tablets. The in vitro drug release of formulations F1 to F4 (containing CP 934 and HPMC at different ratios) was found to be in the range of 44.6% ± 1.5 to 63.93% ± 1.07. On the other hand formulations F5 to F8 (containing CP 934and SCMC at different ratios) was found to be in the range of 77.55% ± 2.06 to 100.1% ± 1.85. This finding was also supported by the results of swelling studies where the highest swelling index was also exhibited by the formulation containing SCMC and CP 934 (Fig. 3). It is anticipated that the high amount of water uptake by SCMC may leads to considerable swelling of the polymer matrix, allowing the drug to diffuse out at a faster rate.

Among the formulation studied F7 and F8 (containing CP 934and SCMC at ratios 1:3 and 1:4, respectively) showed the highest amount of drug released within 6 hours (100% and 98%, respectively).

Kinetics of drug release and mechanism

The obtained values of n (diffusional exponent), and r2 (correlation coefficient) are depicted in table 3. The values of n are estimated by linear regression of log (Mt/M∞) versus log (t), and these values were between 0.5 and 1.0, indicating that the release of ketorolac was found to be a non-Fickian diffusion. The only exception was formulation F2, as the 'n' value of formulation F2 is closer to 0.5, the drug release mechanism from this formulation is Fickian diffusion.

The order of drug release from all the formulations was studied, and it followed zero-order kinetics

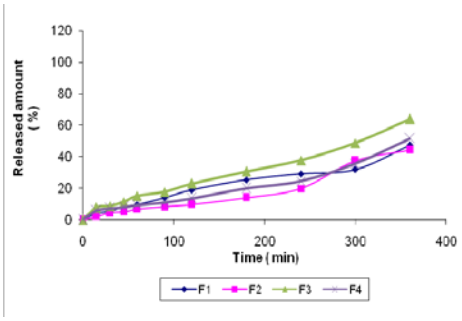

Fig. 4: *In vitro* drug release study of Ketorolac tromethamine mucoadhesive buccal tablets containing CP934 with HPMC

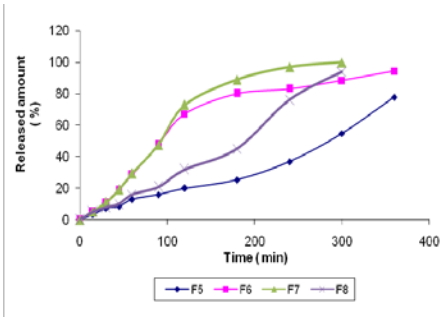

Fig. 5: *In vitro* drug release study of Ketorolac tromethamine buccal tablets containing CP 934 with SCMC

Table 3: Drug release kinetics studies of ketotolac tromethamine buccal tablets

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Hixon-crowell (R^2)	Peppas (R^2)	N
F1	0.941	0.8351	0.868	0.752	0.972	0.81
F2	0.9291	0.884	0.929	0.869	0.9391	0.47
F3	0.9940	0.992	0.926	0.826	0.965	0.674
F4	0.8044	0.733	0.86	0.772	0.923	0.671
F5	0.934	0.923	0.825	0.698	0.971	0.962
F6	0.99	0.92	0.925	0.86	0.948	0.971
F7	0.965	0.957	0.922	0.828	0.964	0.975
F8	0.978	0.970	0.865	0.735	0.946	0.999

On the basis of above result F7 formulation was selected for ex vivo drug permeation studies. The results of drug permeation from buccal tablets through the sheep buccal mucosa showed 53.16% ± 2.02% (Fig. 6) drug permeated during 6 hours. Good correlation was obtained between in vitro drug release and ex-vivo drug permeation study with the correlation coefficient of 0.974. The stability of mucoadhesive buccal tablets was examined in natural human saliva.

The obtained data are presented in Table 4. Buccal tablets did not exhibit change in color or shape. Physical properties of the buccal tablets such as diameter increased slightly owing to swelling of the buccal tablets in human saliva. But the buccal tablets did not collapse in the human saliva until the end of the study. No change in drug content was observed over the period of 6 hours in human saliva, the drug content was in the range of 97 % to 99.2%.

Table 4: Stability study of the selected F7 ketorolac buccal tablet formulation in normal human saliva

Sampling Time (hours)	Color changes*	Change in shape Diameter(mm)**	Collapsing	Drug Recovered (%)**
0	No	9	No	99.2
1	No	10	No	97
3	No	11	No	98.5
6	No	11	No	97.6

*Visual observation **Mean of three readings

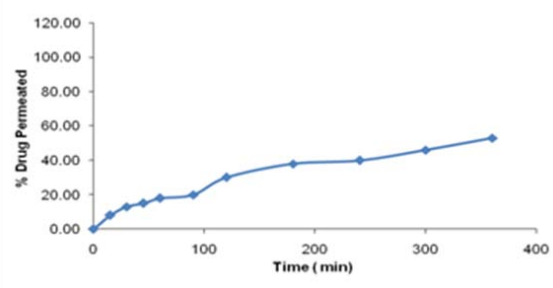

Fig. 6: Drug permeation % of the selected F7 formulation

CONCLUSION

It was concluded that development of muoadhesive buccal tablets of ketorolac was one of the alternative routes of administration to avoid gastrointestinal irritation as it is the most pronounced adverse effects associated with its use. In addition, these formulations reduce the need of frequent administration and enhance patient compliance. F7 formulation containing Carbopol 934 and SCMC (at the ratio 1:3, respectively) showed good swelling, a convenient residence time as well as promising drug release pattern. In addition to the good correlation obtained between in vitro drug release and ex-vivo drug permeation study with the correlation coefficient of 0.974.

CONFLICT OF INTERESTS

Declared None

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