

Development and Evaluation of Mucoadhesive Buccal Tablets of Ketorolac Tromethamine

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Submission Date: 26-9-2013; Review completed: 22-10-2013; Accepted Date: 21-11-2013

ABSTRACT

Buccal route offers excellent opportunities and potential advantages for systemic drug delivery as compared to per-oral administration. The objective of this study was to prepare mucoadhesive tablets of Ketorolac tromethamine in order to circumvent the gastric irritation associated with the drug. The tablets were prepared using various hydrophilic polymers like Hydroxy propyl methyl cellulose K4M (HPMC), Carbopol 934P (CP) and xanthan gum singly and in combination, by direct compression followed by coating with impervious backing layer of ethyl cellulose to obtain unidirectional release of drug. Tablets were evaluated for physical properties, drug content, swelling index, mucoadhesion, and *in vitro* dissolution studies. The formulation containing CP-HPMC combinations were found to be uniform in thickness, weight, drug content and adequate mucoadhesive strength and swelling index. The higher swelling index for tablets of CP-HPMC combinations may be attributed to the relatively higher hydrophilicity of carbopol. Histological studies revealed no damage to buccal mucosa. It can be concluded that buccal route is a promising alternative for administration of Ketorolac tromethamine.

Keywords: Ketorolac tromethamine, mucoadhesive, swelling index, direct compression.

INTRODUCTION

Drugs can be administered by different routes to produce a systemic pharmacological effect. Almost 90% of the drugs are given by the oral route. However the main impediment for the oral delivery of many drugs as a potential therapeutic agent is there extensive presystemic metabolism, instability in acidic environment resulting in inadequate and erratic oral absorption.¹ Transmucosal routes of drug delivery which comprise of the mucosal linings of the nasal, rectal, vaginal, ocular and oral cavity offer excellent opportunities and potential advantages over per-oral administration for systemic drug delivery. Oral mucosa is relatively permeable with a rich blood supply; it is robust and shows short recovery times after stress or damage. The virtual lack of Langerhans

cells makes the oral mucosa tolerant to potential allergens.²

Over the last few decades pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal route as an alternative to the injectable routes. Currently research is focused on development of suitable delivery system for drugs that undergo first pass metabolism, such as cardiovascular drugs, beta-blocking agents, analgesics and peptides. Buccal route of drug delivery has received greater attention because of its unique advantages over other transmucosal routes such as accessibility, patient compliance, rapid cellular recovery following local stress and ability to withstand environmental extremes like change in pH, temperature etc.³

Arthritis is a common joint disorder characterized by joint weakness, instability

DOI: 10.5530/ijper.48.1.11

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and deformities that can interfere with the most basic daily tasks. The treatment of arthritis includes corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), narcotic painkillers and disease modifying anti-rheumatic drugs (DMARDs). NSAID's are more commonly prescribed but show side effects like heartburn, indigestion, stomach cramps and nausea. NSAIDs can disturb the protective lining of the stomach making patients prone to ulcers and bleeding. Ketorolac tromethamine (KT) is one such NSAID used for providing symptomatic relief to arthritic and cancer patients. The drug is administered via oral route as a conventional tablet (10mg four times a day) and also intra muscularly, for management of mild to moderate pain.⁴ Various drug delivery systems that have been previously investigated include osmotic pump⁵ and floating delivery systems.^{6,7}

The half life of KT ranges from 4–6h and therefore, frequent dosing is required to alleviate pain.⁴ To avoid invasive drug delivery technique (intramuscular injection) and to decrease the gastrointestinal side effects produced by oral tablets, there is a need for an alternative non invasive mode of delivery for KT.⁸

The objective of this study was to prepare mucoadhesive tablets of KT in order to avoid the gastric irritation associated with the drug. KT is a good candidate for buccal application for both topical and systemic effects because of its high potency, excellent water solubility and absence of bitter taste.^{9,10} Various bioadhesive polymers such as hydroxyl propyl methyl cellulose K4M, carbopol 934P and xanthan gum were investigated singly as well as in combination.

MATERIALS

Ketorolac tromethamine was generously provided by Cipla, Mumbai, India. Hydroxy propyl methyl cellulose (HPMC K4M) was provided by Colorcon Asia Ltd., Goa, India. Carbopol 934P (CP 934P) was supplied by Loba Chemicals, Mumbai, India. Ethyl cellulose (EC) and xanthan gum (XG) were procured from SD Fine-Chem. Pvt.Ltd., Mumbai. PEG 6000 was obtained from Loba Chemicals, Mumbai, India. All chemicals and solvents used were of pharmaceutical grade.

METHOD

Buccal tablets of KT using HPMC K4M, CP 934P and xanthan gum as mucoadhesive polymers singly and in combination were prepared using direct compression method¹. The compatibility of KT with various excipients was determined by FTIR. Nine tablet formulations were prepared containing

various mucoadhesive polymers. All the ingredients including drug, polymer and other tablet excipients were weighed accurately according to the batch formula (Table 1). The drug and excipients except lubricant were mixed by geometric mixing in order of their ascending weights and blended for 10min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2min. The tablet blends were compressed using 6mm punches on a single stroke Mini Press-II MT (Make: Rimek) tablet compression machine. Tablets were coated with impermeable ethyl cellulose for unidirectional release using a modified coating method leaving one surface of the tablets uncoated.

EVALUATION OF TABLETS

Tablet parameters

All tablets were evaluated for thickness, hardness, friability and uniformity of weight as described in Indian Pharmacopoeia 1996.¹¹ The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm². Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated. The thickness of three randomly selected tablets from each formulation was determined inmm using a digital vernier caliper. The friability of uncoated tablets was determined using Roche Friabilator. Twenty tablets were initially weighed ($W_{initial}$) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes. The tablets were dusted and weighed again (W_{final}). The percentage friability was then calculated by,

$$\frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Table 1: Composition of Buccal Tablet*

Ingredient	X1	X2	X3	X4	X5	X6	X7	X8	X9
KT	5	5	5	5	5	5	5	5	5
HPMC K4M	30	40	50	30	30	30	30	30	30
CP 934P	–	–	–	30	40	50	–	–	–
Xanthan gum	–	–	–	–	–	–	30	40	50
Magnesium stearate	2	2	2	2	2	2	2	2	2
PEG 6000	62	52	42	32	22	12	32	22	12
Talc	1	1	1	1	1	1	1	1	1
Total	100	100	100	100	100	100	100	100	100

*All quantities are in mg.

The weight variation test was performed as per IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting off each tablet and weighing in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Drug content

Five uncoated tablets were powdered in a glass mortar and powder equivalent to 5mg of drug was placed in a stoppered 10ml conical flask. The drug was extracted with distilled water with vigorous shaking on orbital shaker (100rpm) for 1h and filtered into 10ml volumetric flask. Further appropriate dilutions were made by using phosphate buffer pH 6.8 and the drug content was determined by UV spectroscopy at 320nm in triplicate.¹²

Surface pH study¹³

The surface pH of the buccal tablets was determined in order to investigate the possibility of any *in vivo* side effects. The tablets were allowed to swell by keeping them in contact with 1ml of phosphate buffer pH 6.8 for 2h at room temperature. The surface pH was measured using pH meter.

Swelling Index¹³

KT tablets were weighed individually (designated as W_1) and placed separately in petriplates containing 4ml of phosphate buffer pH6.8. At regular intervals of 1, 2, 3, 4 and 5h, excess water from the tablets was removed carefully by using filter paper and swollen tablets were reweighed (W_2). The swelling index of each system was calculated using the following formula:

$$\text{Swelling Index} = \frac{W_2 - W_1}{W_1}$$

In vitro drug release study

The study was carried out in USP XXIII tablet dissolution test apparatus-II (LABINDIA DS 8000), employing paddle stirrer at 50rpm and using 500ml of phosphate buffer pH 6.8 as dissolution medium maintained at $37 \pm 0.5^\circ\text{C}$. Since the tablets were designed for unidirectional drug release, one side of tablets was fixed to glass disk with cyanoacrylate adhesive.¹⁰ The disk was placed at the bottom of the dissolution vessel. At different time intervals, 5ml aliquots were withdrawn and filtered through Whatman filter paper and analyzed for KT after appropriate dilution at 320nm using Jasco-V530 UV-Visible spectrophotometer.

Ex vivo residence time

The *ex vivo* residence time of tablets was evaluated by assessing the time required to detach the tablet from

sheep buccal mucosa in a beaker filled with 500ml phosphate buffer pH 6.8 at 37°C . The mucosal membrane was fixed on the inner side of the beaker with cyanoacrylate glue.¹⁴ The tablets were attached to the membrane by applying light force with finger tip for 60s. The beaker was then magnetically stirred at the rate of 150rpm to simulate buccal and salivary movement. The time necessary for complete erosion or detachment of the tablets from the mucosal membrane was taken as an indication of the *ex vivo* residence time.

Mucoadhesion study¹⁴

Mucoadhesion was evaluated using a texture analyzer (CEB Texture Analyzer, Make-Brookfield Engineering Labs, Texture Pro CT 3). Sheep buccal mucosa was utilized as the model membrane and it was affixed to the lower platen of the instrument. A tablet was carefully attached to the 10mm cylindrical probe (TA probe) using doubleface tape. The probe with the tablet was lowered onto the mucosal surface at a constant speed of 0.5mm/s and a predetermined compressive force of 1N was applied for 60s to allow the tablet to adhere to the mucosa. The probe was then removed at 5mm/s to a distance of 15mm and maximum detachment force (g) was determined for each sample. For each new sample, a different mucosa sample was used.

Histological evaluation of buccal mucosa

To assess the biocompatibility of KT and polymer combinations with buccal mucosa, sub acute toxicity studies were conducted on sheep buccal mucosa. The mucosa was cut into uniform dimensions and divided into 03 groups. The buccal tablet (X6) was affixed onto a set of 02 mucosa of one group. The second set of mucosa were brought in contact with drug solution (all equivalent to 5mg of KT 3 times day) and the third group was taken as negative control. The study was carried as per OECD guidelines¹⁵ for a period of 28 days. The samples were then subjected to histological evaluation.

Stability studies

The formulation X6 was subjected to stability studies wherein the tablets were exposed to ambient temperature and accelerated conditions of 40°C and 75% RH for 03 months. The tablets were then evaluated for mucoadhesion, *in vitro* drug release and drug content.

RESULTS AND DISCUSSION

Compatibility studies and tablet parameters

The FTIR spectra of binary mixtures of KT with various potential excipients revealed no gross changes in the peak height and intensity indicating compatibility between the drug and excipients. Any shifting of

peaks are insignificant and point to the dilution effect of excipients (Fig. 1). The physical characteristics of the KT buccal tablets are shown in Table 2. All the formulations showed almost uniform weight and thickness and drug content was found to be between 91 to 97%. The weight of the tablets varied between 98 ± 0.4 and 100 ± 0.5 mg and thickness ranged between 4.92 ± 0.05 and 4.98 ± 0.03 mm. Friability of all the formulations was found to be less than 1%, which is an indication of good mechanical resistance of tablets.

Swelling index

The swelling indices for all the tablets are represented in Figure 2. The swelling index of all the tablets was found to increase with time. Direct relationship was observed between swelling index and amount of HPMC in case of X1–X3, CP in case X4–X6 and xanthan gum in case of X7–X9. The magnitude of swelling was higher when CP was combined with HPMC (X4–X6). The greater swelling index for tablets of CP-HPMC combinations may

be attributed to the relatively higher hydrophilicity of CP. However the tablets with combination of xanthan gum with HPMC (X7–X9) exhibited marginally lower swelling index than the other formulations.

In vitro drug release

In vitro release of KT buccal tablets is shown in Figure 3. Maximum release was observed from formulation X6 which contains higher proportion of CP. This could be due to ionization at environment pH which leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counter ion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate.¹⁶ PEG 6000 is reported to increase porosity of the matrix and produce channels, which

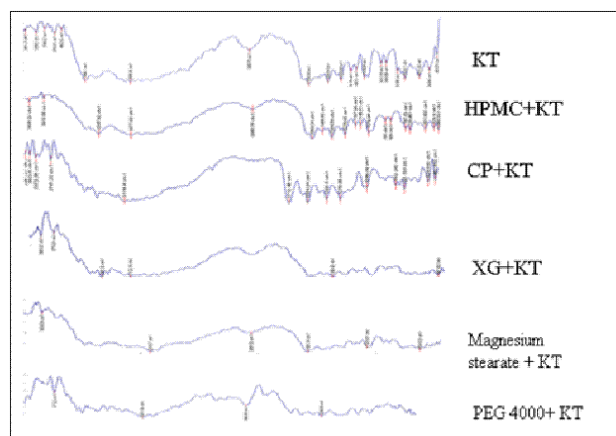


Figure 1: FTIR Spectrum of KT and excipients.

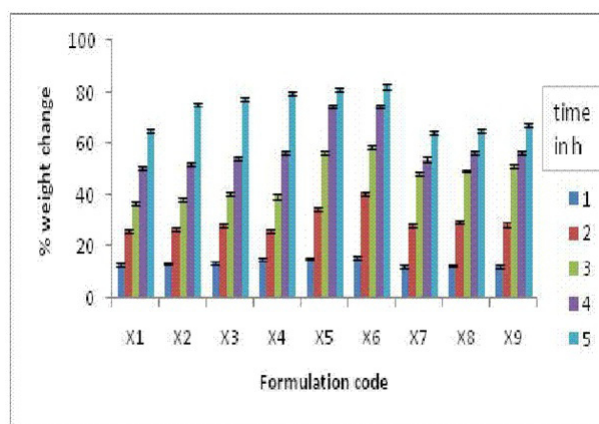


Figure 2: Swelling data of mucoadhesive buccal tablets of KT.

Table 2: Evaluation of Buccal Tablets (n=3)							
Formulation code	Weight variation (mg)	Hardness (kg/cm ²)	Thickness (mm)	Friability (% loss)	Surface pH	Drug content (%)	Ex vivo Residence Time (min)
X1	98±0.50	4.8±0.55	4.92±0.65	0.41	6.29±0.30	96.19±1.25	293±0.80
X2	99±0.80	4.9±0.50	4.98±0.35	0.43	6.02±0.49	95.87±1.56	288±1.21
X3	100±1.00	4.7±0.65	4.95±0.45	0.42	6.32±0.38	96.95±1.42	280±1.34
X4	98±0.60	4.7±0.50	4.89±0.80	0.43	6.01±0.22	96.06±1.52	340±1.25
X5	99±0.75	4.6±0.80	4.82±0.65	0.43	6.43±0.27	97.45±0.85	344±1.56
X6	99±0.50	4.9±0.60	4.82±0.80	0.43	6.47±0.20	98.32±0.98	354±1.45
X7	98±0.80	4.3±0.55	4.87±0.95	0.44	6.17±0.19	94.67±1.20	330±0.81
X8	99±0.90	4.7±0.70	4.92±0.68	0.42	6.57±0.33	96.49±1.74	321±1.74
X9	100±0.90	4.8±0.60	4.98±0.84	0.47	6.19±0.30	97.00±2.10	303±1.47

in turn facilitates the dissolution medium to penetrate the matrix and dissolve the drug more rapidly, thereby enhancing drug release.

Mucoadhesion study

In the current investigation, the mucoadhesive strength indicates force with which polymer binds to buccal mucosal surface under physiological conditions. This has a direct impact on the residence time of the tablets. Assessment of the mucoadhesive strength in terms of detachment stress showed that the HPMC tablets possessed adhesive properties that increased with increase in CP concentration. Formulations X6 showed highest mucoadhesive strength. Comparison of formulations X1–X3 showed that mucoadhesive strength increased with increasing concentration of HPMC but the magnitude of effect was less. The tablets containing a higher proportion of CP showed higher mucoadhesive strength (Fig. 4). Correlating the mucoadhesive strength with swelling index revealed that tablet with higher degree of swelling displayed greater mucoadhesive strength.

Ex vivo residence time

Ex vivo residence time is the time necessary for complete detachment of tablet from mucosal surface without losing integrity. The correlation between mucoadhesion and residence time cannot be understated. Tablets containing a higher proportion of CP showed higher mucoadhesion (Table. 2). The reason might be ionization of CP at salivary pH and formation of secondary bonds with mucin because of rapid swelling and interpenetration of the polymer chains in the interfacial region, which leads to improved attachment of the tablet to mucosal surface, while xanthan gum undergoes superficial bioadhesion. This indicates that the bioadhesive strength of CP is greater than xanthan gum.^{17,18} All the formulations showed a residence time of 4.5 to 6.5h. The tablets containing combination of HPMC K4M and CP 934P showed a residence time greater than 5h.

Histological evaluation of buccal mucosa

Histological investigation is imperative to assess the biocompatibility of KT and other formulation components with buccal mucosa. Tablets of X6 batch were subjected to histological evaluation as it displayed better mucoadhesive strength and residence time as compared to other formulations. The microscopic observations indicated that the final formulation containing 5mg KT had no significant effect on the cellular structure of mucosa. As shown in Figure 5, no cell necrosis was observed. Cellular membrane was intact and no damage was observed to the treated sheep buccal mucosa. Thus, formulation containing KT appeared to be safe with respect to buccal administration.

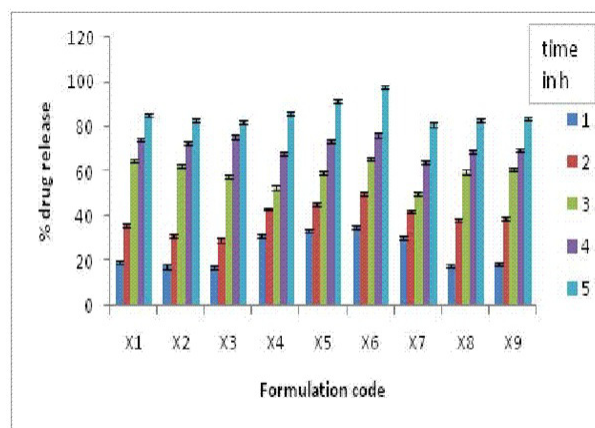


Figure 3: *In vitro* release data of mucoadhesive buccal tablets of KT.

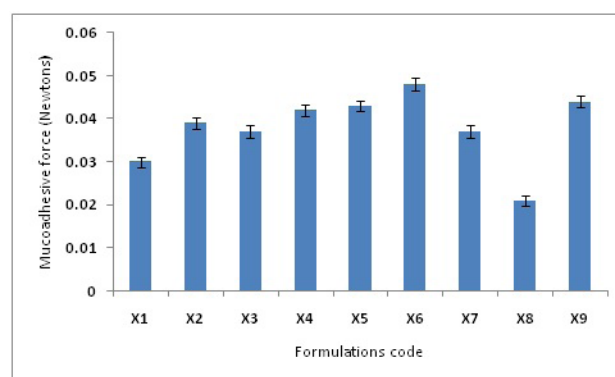


Figure 4: Mucoadhesive strength of buccal tablets of KT.

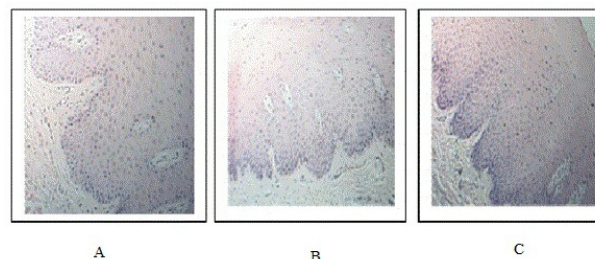


Figure 5: Histological Evaluation of Buccal mucosa A) positive control B) negative control C) Buccal tablet (X6).

Stability studies

The stability studies of the X6 buccoadhesive tablets revealed that there are no significant changes in the physical parameters when stored at of $40 \pm 2^\circ\text{C}/75 \pm 5\%$ RH and in ambient conditions. No significant reduction in the content of the active drug, *in vitro* drug release and mucoadhesive strength was observed over a period of three months.

CONCLUSION

It may be concluded that buccal route is a promising alternative for administration of Ketorolac

tromethamine in order to circumvent the gastric irritation associated with the drug. The results showed that mucoadhesive buccal tablet formulation (X6) containing HPMC and CP produces good mucoadhesive strength and *in vitro* drug release through buccal mucosa without causing any tissue damage.

ACKNOWLEDGEMENT

The authors are thankful to Cipla Pvt. Ltd. (Mumbai, India) for providing drug and Dr. Ashwini Madgulkar, Principal AISSMS College of Pharmacy for providing the facilities for carrying out the research project.

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