Research Article

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FORMULATION AND EVALUATION OF BUCCAL FILMS OF KETOROLAC TROMETHAMINE

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ABSTRACT

The aim of the present study was to formulate the buccal films and selection of most satisfactory formulation by in-vitro evaluation. Ketorolac tromethamine is a NSAID with potent analgesic activity, having a less biological half-life of 4 to 6 hrs (and bioavailability of 90%) and it has the potential of causing serious gastro intestinal side effects. Hence the present investigation was done to formulate buccal films of Ketorolac tromethamine with an objective to improve therapeutic efficacy, patient compliance, half life and to overcome the gastro intestinal side effects produced by the drug. Mucoadhesive films of Ketorolac tromethamine composed of polymers like HPMC K 100M, HPMC E15, HPMC E50, Eudragit RLPO were developed by solvent casting method. The patches were evaluated for their physical appearance, texture, thickness, folding endurance, weight and content uniformity, swelling behaviour, mucoadhesive strength, surface pH, moisture absorption, moisture loss, tensile strength, in vitro release studies and mucoadhesion time. All the prepared films have smooth surface and elegant texture. The drug release mechanism was found to follow non-fickian diffusion release. Formulation F5 exhibited best mucoadhesive performance and matrix controlled release. Swelling behaviour and duration of mucoadhesion are critical factors in the selection of satisfactory formulation.

Keywords: *Mucoadhesive films, Mucoadhesive strength, Solvent casting method, swelling behaviour.*

INTRODUCTION

For many decades, treatment of an acute disease or a chronic illness has been mostly accomplished by delivering drugs using various pharmaceutical dosage forms, including tablets, capsules, Suppositories, creams, liquids, aerosols, and injectables as carriers. Amongst various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike[1]. The blood that drains the GIT carries the drug directly to the liver leading to first pass metabolism resulting in poor bioavailability.

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The inherent problems associated with the drug, can be solved by modifying the formulation or by changing the routes of administration. Parenteral, mucosal and transdermal routes circumvent hepatic first pass metabolism and offer alternative routes for the systemic delivery of drugs[2]. Hence buccal route of drug administration was preferred.

Mucoadhesive drug delivery

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption[3-5]. Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity

offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect).

Buccal route of administration:

The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bioadhesive buccal delivery systems.

Direct access to the systemic circulation through internal jugular vein by passes drugs from hepatic first pass metabolism leading to high bioavailability. Oral mucosa of the oral cavity is easily accessible for administration of drugs. Ketorolac tromethamine is a non-steroidal anti-inflammatory drug with potent analgesic activity. In the present study Ketorolac tromethamine which is having half-life of 4-6 hrs with very low first pass metabolism is selected for the study. The present investigation is concerned with the development of mucoadhesive buccal films to prolong the buccal residence time, to increase penetration through the buccal mucosa and to increase its half-life.

MATERIALS AND METHODS

Table 1: List of chemicals used.

S. No.	Material used
1	Ketorolac tromethamine
2	Methanol
3	Ethanol
4	Eudragit RLPO
5	HPMC E15
6	HPMC E 50
7	Polysorbate 80
8	Glycerine
9	Dialysis Membrane
10	Potassium dihydrogen ortho phosphate

Analytical method

i. Determination of λ max

The absorption maxima were found to be 323 nm.

ii. Calibration curve of Ketorolac tromethamine

Calibration curve of Ketorolac tromethamine in phosphate buffer (pH 6.8) were obtained at 323 nm with UV-VISIBLE spectrometer. Using concentration and absorbance data, a calibration curve was obtained.

Pre formulation studies

The overall objective of the pre formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms.

FT- IR spectrum interpretation

The pure drug and polymers were subjected to FT-IR studies alone and in combination, to study the interference of polymers and drug.

Formulation of buccal films

The buccal films of Ketorolac tromethamine were prepared by using various polymers (HPMC and Eudragit RLPO) with glycerine as plasticizer.

Method of preparation of buccal films

Buccal films of Ketorolac tromethamine were prepared by solvent casting technique using film forming mucoadhesive polymers (Table 1). HPMC and Eudragit RL PO were weighed accurately and HPMC was dissolved in 2 ml of ethanol. The beaker containing polymer and ethanol was kept aside for 5 min for swelling of the polymer.

Further 6 ml of ethanol was added to the above polymer solution and Eudragit RL PO was added and the dispersion was stirred. Then plasticizer was added to the polymer solution. Simultaneously Ketorolac tromethamin was accurately weighed in quantity such that 2 cm^2 film contained 10 mg and then dissolved in 3 ml of Methanol in another beaker. Drug was calculated on the basis of area. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer.

The whole solution was poured into the glass Petri dish placed over a flat surface. The mould containing polymeric solution of drug was kept 24 hrs and at room temperature for drying. After drying, the films were observed and checked for possible imperfections upon their removal from the moulds.

Total area of Petridish =38 cm^2

Drug required in 2 cm^2 =10 mg

Total drug loaded =190 mg

Evaluation of mucoadhesive buccal films

Physical appearance, Surface texture, Uniformity of weight, Thickness uniformity, swelling studies of the films, Surface pH, Folding endurance, Bio adhesive strength, Drug content uniformity, Moisture content and moisture absorption, Tensile Strength, *In Vitro* drug release Study, Mucoadhesive time, Kinetics of drug release were evaluated and tabulated.

RESULTS & DISCUSSION

The IR spectrum of Ketorolac tromethamine exhibited peaks at 3350.01cm^{-1} due to N-H and NH_2 stretching and peaks at 1469.43 cm^{-1} and 1430.88 cm^{-1} due to C=C aromatic and aliphatic stretching, peak at 1383.19cm^{-1} is due to -C-N vibrations, peak at 1047.59 cm^{-1} is due to -OH bending confirms presence of alcoholic group, peaks at 702.09 cm^{-1}, 725.54 cm^{-1}, 771.71 cm^{-1}, 798.11 cm^{-1} confirms C-H bending (Aromatic) thus confirms structure of Ketorolac tromethamine. IR studies show no interaction between drug and excipients. However, additional peaks were absorbed in physical mixtures which could be due to the presence of polymers and indicated that there was no chemical interaction between Ketorolac tromethamine and other excipients.

The spectra showed no incompatibility between the polymers and Ketorolac tromethamine drug. The spectra of the polymers and the pure drug are given in the figures 1, 2, 3, 4, 5.

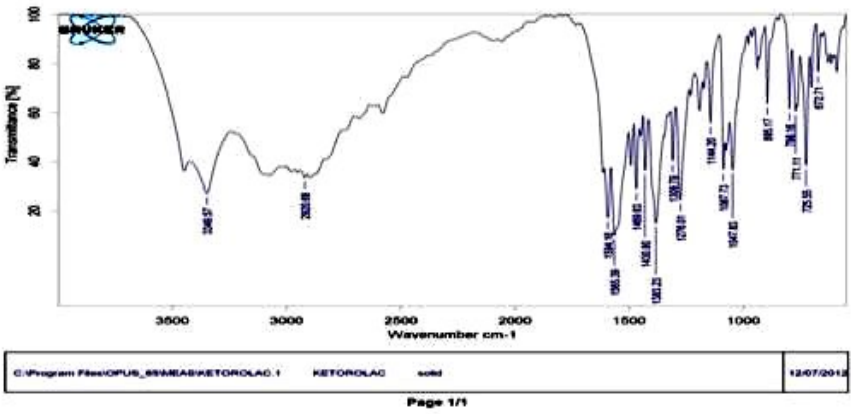

Fig. 1: IR Spectra of pure drug Ketorolac tromethamine

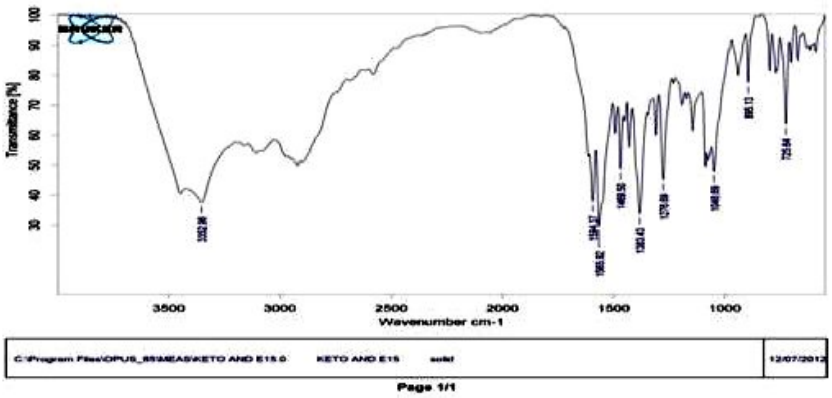

Fig. 2: IR Spectra of Ketorolac and HPMC E15

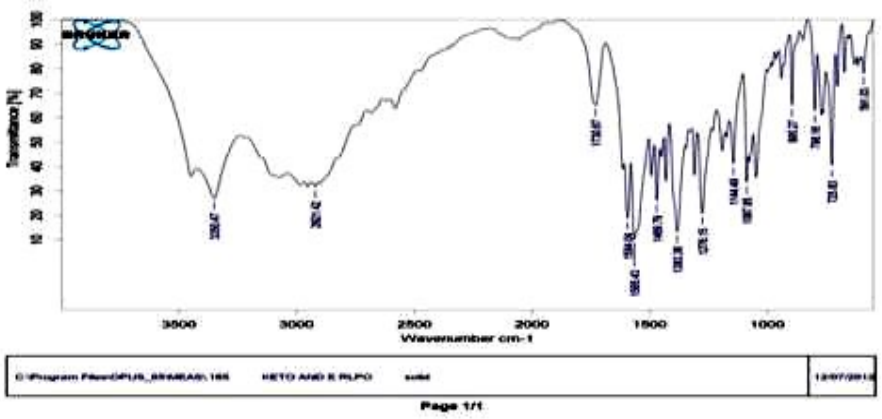

Fig. 3: IR Spectra of Ketorolac and Eudragit RL PO

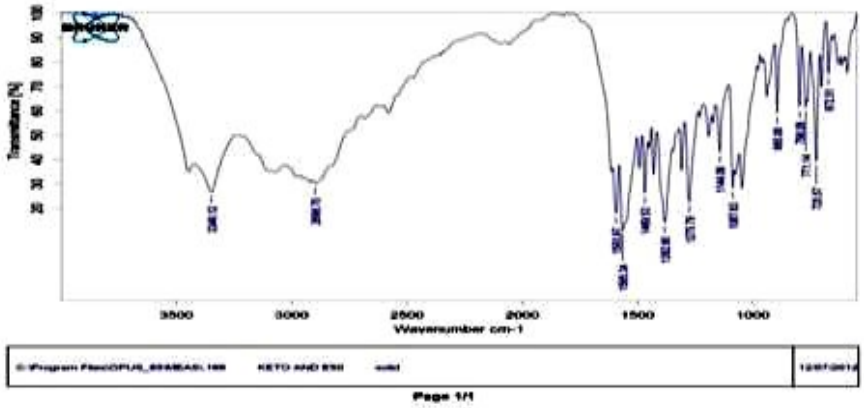

Fig. 4: IR Result of Ketorolac and HPMC E50

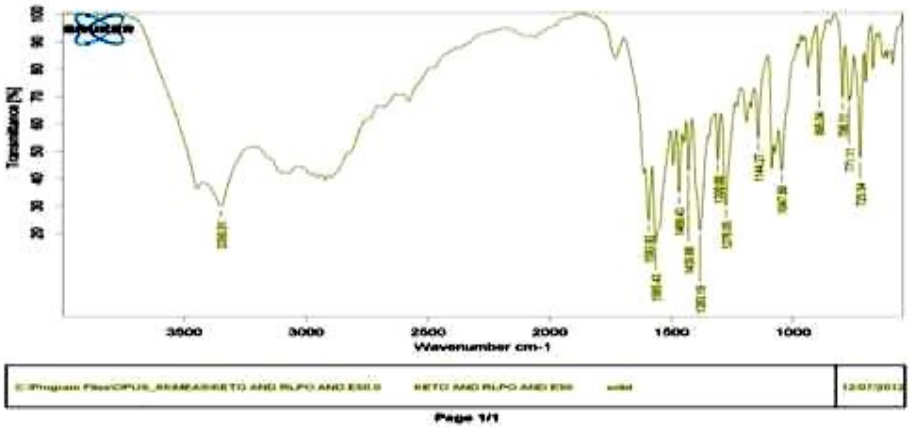

Fig. 5: IR Spectra of Ketorolac, Eudragit RL PO and HPMC E

Batch code	Drug in mg	Polymer					Glycerine (ml)	Methanol ml	Ethanol ml
		HPMC K-100M	HPMC E-50	HPMC E-15	Polysor bate (ml)	Eudragit RLPO (mg)			
F 1	190	300mg	-	-	-	-	0.1	10	-
F 2	190	150	-	-	-	-	0.1	3	8
F 3	190	-	75	75	0.05	-	0.1	3	8
F 4	190	-	150	-	0.1	-	0.1	3	8
F 5	190	-	200	-	0.1	50	0.1	3	8
F 6	190	-	200	-	0.1	70	0.1	3	8
F7	190	-	200	-	0.1	90	0.1	3	8
F 8	190	-	250	-	0.1	100	0.1	3	8
F 9	190	-	280	-	0.1	70	0.1	3	8
F 10	190	-	300	-	0.1	70	0.1	3	8

Table No 2: Formulae of Ketorolac tromethamine buccal films

Patch code	Appearance	Surface texture	TN (mm) (mean*± Std)	WU (mg) (mean*± Std)	Surface pH (mean*± Std)	CU (mean*± Std)	FE (mean*± Std)
F 1	+	Very smooth	0.3±0.01	45±1.89	6.16±0.03	91.2	186±4.0
F 2	+	Very smooth	0.10±0.01	37.1±1.44	6.82±0.02	89.4	182±2.51
F 3	+	Smooth	0.08±0.005	38.5±1.80	6.42±0.09	89.1	174±5.29
F 4	+	Very smooth	0.12±0.017	39.8±1.75	6.01±0.12	94.0	199±6.55
F 5	+	Very smooth	0.24±0.015	40.8±1.25	6.57±0.13	94.9	281±7.09
F 6	+	Smooth	0.18±0.005	42.1±1.04	6.70±0.03	90.1	189±3.51
F 7	+	Very smooth	0.26±0.02	48.5±1.5	6.68±0.015	93.0	305±8.14
F 8	+	Very smooth	0.23±0.015	49.8±1.25	6.56±0.04	90.7	206±8.08
F 9	+	Smooth	0.46±0.04	52.6±1.50	6.64±0.04	96.7	206±7.63
F 10	+	Smooth	0.37±0.03	55.1±2.84	6.82±0.02	88.4	215±3.51

Table 3: Physiochemical evaluation data of Ketorolac tromethamine buccal patches

TN= thickness, WU= weight uniformity, SI= Percent swelling index,
MS = mucoadhesive strength, CU = content uniformity, FE = folding endurance respectively.

*Each value is an average of three determinations.
(+: Transparent).

Time (min)	S.I. of F1 (%)	S.I. of F2 (%)	S.I. of F3 (%)	S.I. of F4 (%)	S.I. of F5 (%)	S.I. of F6 (%)	S.I. of F7 (%)	S.I. of F8 (%)	S.I. of F9 (%)	S.I. of F10 (%)
0	0	0	0	0	0	0	0	0	0	0
5	9.21	7.94	7.21	6.47	3.40	6.90	4.01	5.12	5.19	3.62
10	15.49	11.47	9.86	9.07	9.21	9.90	9.25	9.10	7.57	9.50
15	19.51	20.82	21.64	18.5	15.58	20.30	15.80	12.24	11.86	11.21
20	34.5	32.05	27.22	31.50	18.41	23.01	19.29	18.12	18.20	15.10
30	Eroded	Eroded	29.20	Eroded	19.50	23.50	22.20	20.12	24.31	25.20

Table 4: Swelling index (SI) of Ketorolac tromethamine buccal patches

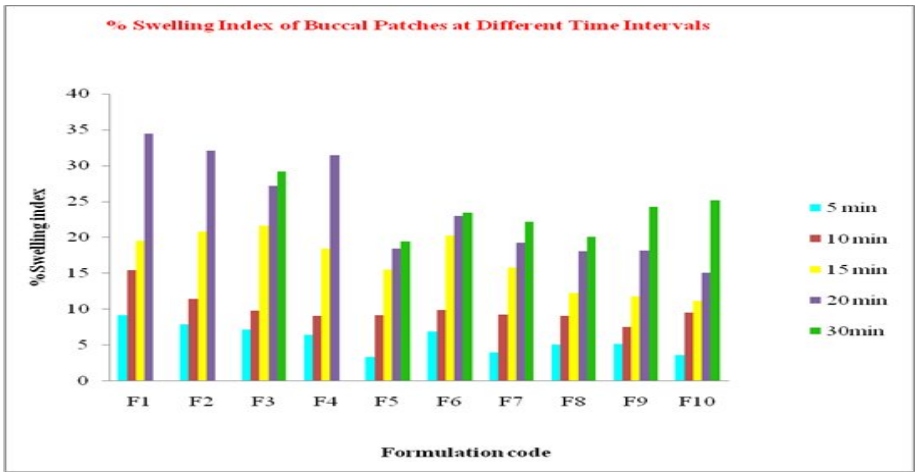

Fig 6: Percentage swelling index of buccal patches at different time intervals

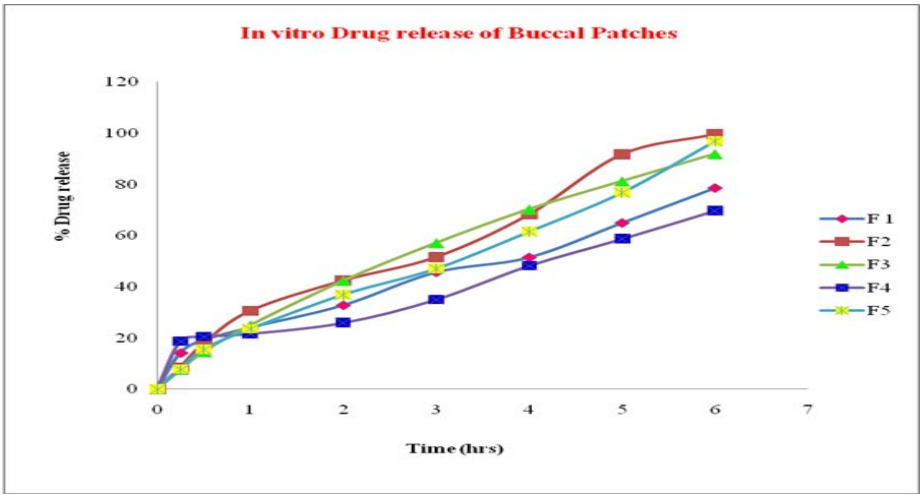

Fig 7: *In-vitro* drug release profile of F1, F2, F3, F4, F5 in pH 6.8 buffer

Time in (hrs)	Square root of time	Log time	Cum % release	Log cum % release	Cum % retained	Log cum % retained
0	0	-	0		100	2.000
0.25	0.500	-0.602	7.850417	0.895	92.14958	1.964
0.5	0.707	-0.301	15.59942	1.193	84.40058	1.926
1	1.000	0.000	23.53133	1.372	76.46867	1.883
2	1.414	0.301	36.95038	1.568	63.04962	1.800
3	1.732	0.477	47.09163	1.673	52.90837	1.724
4	2.000	0.602	61.56103	1.789	38.43897	1.585
5	2.236	0.699	76.80913	1.885	23.19087	1.365
6	2.449	0.778	96.91054	1.986	3.08946	0.490

Table 5: *In-vitro* diffusion studies of Ketorolac tromethamine (F5)

Zero order		First order		Higuchi model		Korsmeyer-Peppas model		
R^2	Y	R^2	Y	R^2	Y	R^2	Y	n
0.990	14.83x + 4.841	0.781	-0.191x + 2.099	0.946	38.00x - 10.13	0.991	0.738x + 1.364	0.738

Table 6: Release kinetics of optimized formulation (F5)

Fig. 8: Ketorolac tromethamine buccal patches

CONCLUSION

The main objective of formulating the buccal system was to prolong the drug release time, reduce the frequency of administration and to improve patient compliance. IR study shows that there is no incompatibility between drug and polymers. The buccal patches of Ketorolac tromethamine containing 190mg of drug were prepared successfully by solvent casting method using HPMC K-100, HPMC E-50, HPMC E-15 and Eudragit RL PO as polymers in various ratios.

Additives such as Ethanol, methanol as solvent, glycerine as plasticizer and polysorbate 80 as penetration enhancer was included in the formulation. Total 12 formulations were prepared. Based on the observations, F5 formulation was exhibited satisfactory characteristics regarding to surface texture, physical appearance, content uniformity, thickness, surface pH, folding endurance, bioadhesive strength, bioadhesion time, invitro release studies, swelling studies and other quality control parameters.

Higuchi's plot for the formulation revealed that the predominant mechanism of drug release is diffusion. From Peppa's plot the 'n' value for F5, F6, F7 and F9 was found to be 0.738, 0.925, 0.699, and 0.997, thus indicating non-fickian diffusion (anomalous behavior). The releases of Ketorolac from the patches were diffusion rate controlled. The present study was a satisfactory attempt to develop erodible buccoadhesive films, which will overcome the inherent drawbacks (such as gastric irritation and ulceration) associated with delivery of Ketorolac tromethamine and will provide an improved therapeutic efficacy and patient compliance.

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