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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLETS OF KETOROLAC TROMETHAMINE

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Abstract:

Among the various routes of drug delivery, the oral route is perhaps the most preferred by patients and clinicians alike. Ketorolac is currently administered intramuscularly (30 mg) and orally as conventional tablet (10 mg) for short-term management of post-operative pain and moderate to severe pain. It is a non-steroidal anti-inflammatory cyclooxygenase inhibitor. It acts by inhibiting the synthesis of prostaglandins. The major side effects of Ketorolac are gastric mucosal erosions, ulcers and gastric bleeding. The aim of this study was to prepare a new mucoadhesive tablet formulation of Ketorolac Tromethamine in view of attaining prolonged effect of drug for better therapy with reduced dosing frequency.

In present work, an attempt has been made to formulate buccoadhesive tabletof model drug and preparation of tablets using hydrophilic polymers like HPMC K15M, HPMC K4M and carbopol934.

The buccal tablets were characterized on the basis of their physical parameters (hardness, thickness, weight variation) drug content, surface pH, swelling index, mucoadhesive strength, in vitro drug release were studied.

Key words: *Ketorolac Tromethamine, non-steroidal anti-inflammatory, mucoadhesive tablet, HPMC K15M, HPMC K4M and carbopol934.*

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INTRODUCTION:

Buccal tissue is richly supplied with perfused blood capillaries hence this route has certain advantages such as avoidance of irritation of the gastrointestinal membrane, relative permeability due to rich blood supply, reduced risk of overdose, non-invasive administration, ease of convenience and self-medication, improved patient compliance, higher bioavailability allowing lower doses, avoidance of liver or gastrointestinal metabolism, feasibility of beneficial adjunct product to existing product and reduced risk of infectious disease transmission leading to the acceptance of buccal delivery as an alternative dosage form [1].

The buccoadhesive drug delivery systems have been developed basically to increase the retention of drug in the buccal cavity. The route provides intimate contact between a dosage forms and absorbing tissue thereby resulting in high drug concentration in a local area and hence continuous release of drug from the medication towards medium from where it is constantlyremoved [2].

Model drug is currently administered intramuscularly and orally as conventional tablet for short-term management of post-operative pain and moderate to severe pain. It is a non- steroidal anti-inflammatory cyclooxygenase inhibitor [3]. It acts by inhibiting the synthesis of prostaglandins. It is a member of the pyrrolo-pyrrole group of NSAIDS. It is a racemic mixture of (-) S and (+) R Ketorolac Tromethamine of which S-form is active [4].

The aim of this study was to prepare a new mucoadhesive tablet formulation of Ketorolac Tromethamine in view of attaining prolonged effect of drug for better therapy with reduced dosing frequency.

In this regard,buccoadhesive drug delivery have emerged as an effective tool to increase drug release rate and incorporated in sustained-release matrix-type systems made of different polymers, Actually, Various types of polymers can be used in the Hydrophilic matrix and the hydration of these polymers results in the formation of an outer gel layer that controls drugs release. HPMC, the nonionic cellulose is commonly used in the formulation of hydrophilic matrix systems. On the other hand, acrylic acid derivatives Carbopols have also attracted interest in their use in controlled drug delivery.

In present work, an attempt has been made to formulate buccoadhesive tabletof model drug and preparation of tablets using hydrophilic polymers like HPMC K15M, HPMC K4M and carbopol934.

MATERIALS AND METHODS:

The following materials that were either AR/LR grade were used as supplied by the manufacturer:
Ketorolac Tromethamine, Mannitol , Magnesium stearate, Ethyl cellulose, Tartrazine colour were supplied by MSN labs Pvt. Ltd, Hyderabad and HPMC K4M, HPMC K15M, Carbopol 934 were supplied by Colorcon Asia Pvt. Ltd., Goa.

Preformulation Studies

Preformulation studies on drug include: Colour, Taste, Solubility Analysis, Melting Point Determination and Compatibility Studies.

Identification of Pure Drug

a) Determination of meltingpoint: Melting point of Ketorolac Troethamine was determined by capillary method.

b) IR spectroscopy:

The FT-IR spectrum of the obtained gift sample was compared with the reference standard FT-IR spectrum of KetorolacTromethamine by potassium bromide method.

Compatibilitystudy

FTIRspectroscopy:

Compatibility of test Drug with polymer and excipients was established by infrared spectral analysis. I.R spectral analysis of samples (Pure Ketorolac Tromethamine, mixture of pure drug, carbopol 934, HPMC (K15M, K4M) and excipients was performed to check the compatibility of drug after combining it with the excipients by potassium bromide method.

Preparation of Standard Stock Solution

Preparation of phosphate buffer pH 6.8:

In preparation of phosphate buffer pH 6.8 250 ml of 0.2 M potassium di hydrogen phosphate solution was placed in a 1000 ml of volumetric flask to it 112.0 ml of 0.2 M sodium hydroxide was added, to the volume was then made up to 1000 ml with distilled water.

Spectrophotometric:

Characterization of Ketorolac Tromethamine

Determination of λmax:

Stock solution (100µg/ml) of Ketorolac Tromethamine was prepared in methanol. This solution was appropriately diluted with phosphate buffer pH 6.8 to obtain a concentration of 10µg/ml. The solution was kept in a fused silica cuvette 10 mm. The UV spectrum was

recorded in the range of 200-400 nm on double beam UV-visible spectrophotometer.

Preparation of Standard Calibration Curve of Ketorolac Tromethamine

Initially 100 mg of Ketorolac Tromethamine was weighed accurately and transferred to a 100 ml volumetric flask. This was dissolved in methanol and volume was made up to 100 ml. This solution was treated as the stock solution and contains 1000µg/ml of Model drug solution. From this stock solution 0.2, 0.4, 0.6, 0.8, 1.0, and 1.2 ml were withdrawn and diluted the each sample with phosphate buffer pH 6.8 to obtain concentrations of 2, 4, 6, 8, 10, and 12 µg/ml. Absorbance of these solutions were measured at 323 nm against blank solution i.e., phosphate buffer pH 6.8.

Beers Range:

Beers range of Ketorolac Tromethamine is 2-12 µg/ml.

Method of Preparation of Mucoadhesive tablets: [5,6]

Preparation:

Direct compression method has been employed to prepare buccal tablets of Ketorolac Tromethamine using Carbopol 934, HPMC K15M and HPMC K4M as polymers. Total weight of tablet is 150 mg in which backing layer ethyl cellulose weight is 30 mg and Tartrazine as colouring agent of quantity sufficient.

Procedure: All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table-1). The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (150 mg) of each formulation was pre-compressed on 10-station rotatory tablet punching machine at a pressure of 50 kg/cm^2 for 5 seconds to form single layered flat-faced tablet of 8 mm diameter. Then 30 mg of ethyl cellulose powder mixed with tartrazine was added and final compression was done at a pressure of 75 kg/cm^2 for 10 seconds to get bilayertablet.

Table 1: Composition of Buccal Tablet

S.no	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	11	F12
1	KT	10	10	10	10	10	10	10	10	10	10	10	10
2	Mannitol	78	68	58	48	78	68	58	48	78	68	58	48
3	Carbopol 934	30	40	50	60	-	-	-	-	-	-	-	-
4	HPMC K15M	-	-	-	-	30	40	50	60	-	-	-	-
5	HPMC K4M	-	-	-	-	-	-	-	-	30	40	50	60
6	Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
7	Ethyl cellulose	30	30	30	30	30	30	30	30	30	30	30	30
8	Tartarazine	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

- All Values are in mg. (Tabletweight=150mg)

Evaluation of Buccal Tablets of Ketorolac Tromethamine:

Trial batches of different formulations of Mucoadhesive buccal tablets were prepared and evaluated for the following parameters

Pre-compression evaluation parameters:

Angle of repose: [7]

Angle of repose was determined using fixed funnel method. The blend was poured through a funnel than can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (ɵ) was calculated using the formula, $\theta = \tan^{-1}(h/r)$

Bulk density: [7]

Bulk density of model drug was determined by pouring blend gently through a glass funnel into graduated cylinder. The volumes occupied by the samples were recorded. Bulk density was calculated as:

Bulk density = weight of sample in gram /volume occupied by the sample

Tapped density: [7]

Tapped density was determined by using Electro lab density tester, which consists of a graduated cylinder mounted on a mechanical tapping device. An accurately weighed sample of powder was carefully added to the cylinder with the aid of a funnel. Typically, the initial volume was noted, and the sample is then tapped (500, 750 or 1250 tapping) until no further reduction in volume is noted or the percentage of difference is not more than 2%.

Tapped density = Weight of sample in gram / Tapped volume

Hausner'sratio:

The Hausner's ratio is an indirect index of ease of powder flow. It is calculated by following formula,

Hauser's Ratio = Tapped Density / Bulk Density

Compressibility index:

The simplest way for measurement of free flow of powder is compressibility, which is an indication of the ease with which a material can be induced to flow. Itis given by compressibility index (I) which is calculated as follows,

I = Tapped density-bulk density/tapped density x100

Post-Compression Evaluation Parameters:

General appearance:

Mucoadhesive tablets morphological characterization includes size, shape, colour, presence or absence of odour, taste, surface texture was determined.

Thickness: [8]

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper. Average thickness and standard deviation values were calculated.

Hardness: [9]

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability Test: [9]

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, dedusted and reweighed. The friability was calculated as the percentage weight loss. friability was calculated as follows:

% Friability = $(W_1 - W_2) \times 100/W_1$

Where, W_1 = Initial weight of the 20 tablets.

W_2 = Final weight of the 20 tablets after testing.Friability values below 0.8% are generally acceptable.

Weight Variation Test: [9]

To study weight variation individual weights (W_I) of 20 tablets from each formulation were noted using electronic balance. Their average weight (W_A) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

% weight variation = $(W_A - W_I) \times 100/ W_A$

Drug Content (Assay): [9]

The drug content of the matrix tablets was determined according to in-house standards and it meets the requirements if the amount of the active

ingredient in each of the 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 50 mg of Model drug was transferred to a 100 mL volumetric flask containing 70 mL of 6.8pH phosphate buffer. It was shaken by mechanical means for 1h.Then it was filtered through a whatman filter paper (No.1) and diluted to 100 mL with 6.8pH phosphate buffer. From this resulted solution 1 mL was taken, diluted to 50 mL with 6.8pH phosphate buffer and absorbance was measured against blank at 323nm.

Tablet surface pH evaluation: [10]
The surface pH of the tablets was determined in order to investigate the possibility of any side effect, in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was our attempt to keep surface pH as close to neutral as possible.

Swelling Index: [11,12]
The swelling rate of the buccal tablet is evaluated by using of pH 6.8 phosphate buffer. The initial weight of the tablet is determined (w_1). The tablets is placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at 37 ° C and tablet is removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0 h), blotted with filter paper and reweighed (w_2). The swelling index is calculated by the formula:

Swelling index = $100 (w_2-w_1) / w_1$.

Mucoadhesion strength: [13-15]
The apparatus used for testing bio adhesion was assembled in the laboratory . Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by Gupta et al using the porcine buccal mucosa as model mucosal membrane.

Method:
The balance adjusted as described above was used for the study. The porcine buccal mucosa, excised and washed was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker. This beaker suitably weighted was lowered into 500 ml beaker, which was then filled with isotonic phosphate buffer (pH 6.8) kept at 37° C such that the buffer reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). The 5gm on right hand side is removed; this causes application of 5 gm of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 minutes and then slowly weights were increased on the right pan, till tablet separates from mucosal membrane. The total weight on right pan minus 5 gm gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before reading a new tablet of same formulation toget reproducible multiple results for theformulation

***In vitro* Dissolution studies: [16,17]**
In vitro dissolution studies of buccal tablets of Model drug were carried out in USP TDT tablet dissolution test apparatus-II (Electrolab), employing a paddle stirrer at 50 rpm using 900ml of pH 6.8 Phosphate buffer solution at 37 ±0.5°C as dissolution medium. One tablet was used in each test. The tablets were supposed to release drug from one side only; therefore an impermeable backing membrane side of tablet was fixed to a 2×2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in dissolution apparatus.

At predetermined time intervals 5ml of the samples were withdrawn by means of a syringe fitted with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5°C. The samples were analyzed for drug release by measuring the absorbance at 263.4 nm using UV-Visible spectrophotometer after suitabledilutions.

Stability studies: [18]
Stability studies were performed at a temperature of 40^0 C at 75 % RH, over a period of three months (60 days) on the promising buccal tablets of Model drug optimized formulation. Sufficient number of tablets (15) were packed in amber colored screw capped bottles and kept in stability chamber maintained at $40^0 \pm 1^0$C and 75 % RH. Samples were taken at monthly intervals for drug content estimation. At the end of two months period, dissolution test and drug content studies were performed to determine the drug release profiles and drug content.

RESULTS AND DISCUSSION:

Table 2: Comparisons Of Ftir Spectral Peaks

Functional Groups	Reported Frequencies (cm^{-1})	Observed Frequencies (cm^{-1})			
		Pure Drug	Drug + Carbopol 934	Drug + HPMC K 15M	Drug + HPMC K4M
Aromatic C=C	1590-1620	1608.63	1618.28	1606.70	1593.20
C-H in $-CH_2$	2875-2877	2877.79	2879.72	2877.79	2875.86
N=C	3440-3462	3446.79	3441.01	3449.79	3461.93
O-H	3500-3524	3502.73	3501.63	3523.95	3502.73
=C-H	2938-2975	2945.50	2938.21	2953.02	2975.86

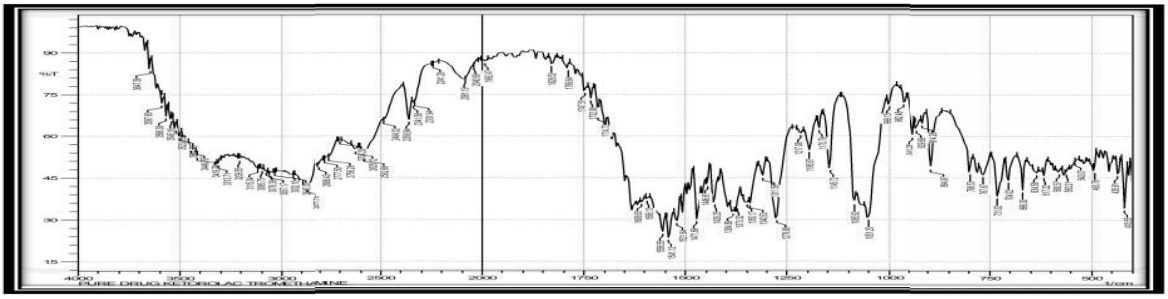

Fig.1: IR spectrum of pure Ketorolac Tromethamine

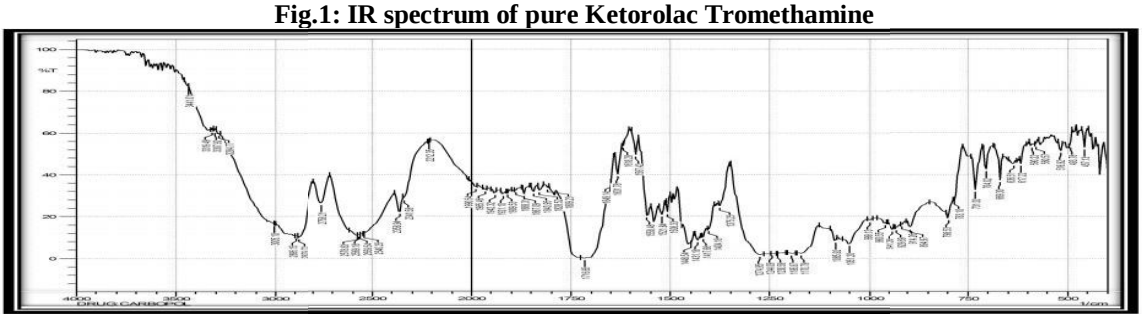

Fig. 2: IR spectrum of Ketorolac Tromethamine +Carbopol 934

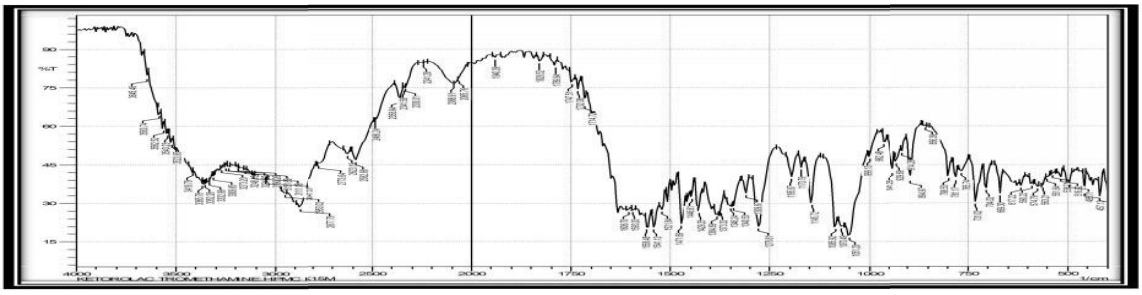

Fig. 3: IR spectrum of Ketorolac Tromethamine +HPMC K15M

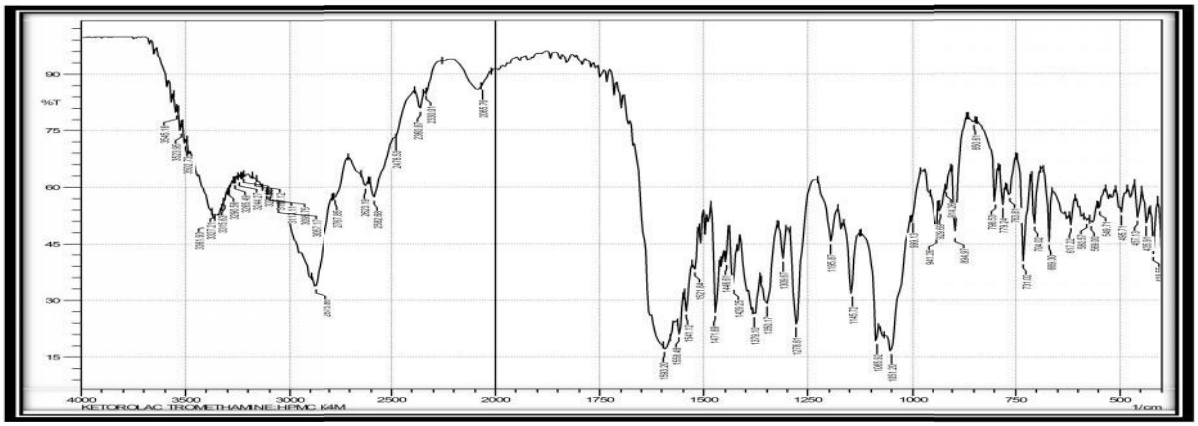

Fig. 4: IR spectrum of Ketorolac Tromethamine +HPMC K4M

Table 3: Standard Calibration Curve Of Ketorolac Tromethamine

Concentration (mcg/ml)	Absorbance
0	0
2	**0.090**
4	**0.185**
6	**0.249**
8	**0.332**
10	**0.406**
12	**0.482**

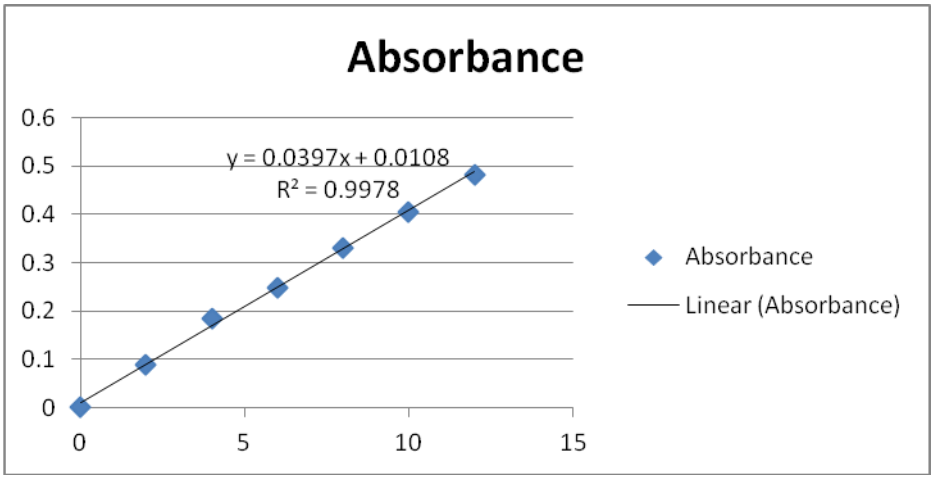

Fig.5: Standard calibration curve of Ketorolac Tromethamine

Table 4: Pre Compression Evaluation Of Drug/Polymer Mixture

Formulation code (Drug: polymer)	Angle of repose (°)	Bulk density (gm./cm 3)	Tapped density (gm./cm3)	Carr's index (%)	Hausner's ratio
F1 (1:3)	25.49±1.151	0.214±0.0498	0.251±0.0381	14.74±0.4924	1.172±0.00653
F2 (1:4)	26.24±0.989	0.308±0.0221	0.364±0.0423	15.38±0.296	1.181±0.00374
F3 (1:5)	29.05±1.675	0.276±0.051	0.322±0.062	14.28±1.077	1.166±0.01327
F4 (1:6)	33.65±1.755	0.521±0.0105	0.629±0.0255	17.17±0.195	1.207±0.00244
F5 (1:3)	29.25±0.734	0.324±0.0210	0.376±0.0245	13.82±1.0539	1.160±0.01314
F6 (1:4)	32.27±1.0715	0.320±0.03159	0.397±0.0255	19.39±0.4724	1.240±0.06164
F7 (1:5)	26.97±0.979	0.341±0.0398	0.388±0.0523	12.11±0.4924	1.13±0.0452
F8 (1:6)	33.21±0.722	0.518±0.0421	0.627±0.0234	17.38±0.296	1.21±0.00324
F9 (1:3)	26.56±1.575	0.422±0.051	0.506±0.0585	16.60±1.077	1.199±0.0232
F10 (1:4)	28.56±1.724	0.481±0.0105	0.572±0.0130	15.90±0.195	1.180±0.00545
F11 (1:5)	27.33±0.834	0.475±0.0310	0.566±0.0296	16.07±1.0539	1.191±0.01215
F1 (1:6)	33.65±1.715	0.521±0.0169	0.629±0.03826	17.15±0.4724	1.20±0.06254

Averages of triplicate were reported (n=3) **(MEAN ±SD)**

Table 5: Post Compression Evaluation Of Prepared Tablets

Formulaton code (Drug: polymer)	Uniformity of thickness (n=20)mm	Hardness (n=10) (kg/cm^2)	Friability %	Uniformity of weight (n=20) mg	Content uniformity (n=10) %
F1 (1:3)	2.89±0.17	3.49±0.44	0.34±0.01	152.1±1.48	99.62±1.37
F2 (1:4)	2.97±0.25	3.68±0.31	0.40±0.01	151.8±0.54	100.12±0.80
F3 (1:5)	2.93±0.80	3.45±0.40	0.39±0.01	151.2±0.41	97.62±2.47
F4 (1:6)	2.99±0.20	3.98±0.55	0.45±0.02	150.9±1.64	98.12±0.88
F5 (1:3)	2.84±0.66	4.19±0.57	0.59±0.01	151.3±1.14	96.86±1.25
F6 (1:4)	2.85±0.25	4.47±0.30	0.53±0.03	152.4±0.83	99.12±1.87
F7 (1:5)	2.91±0.71	4.08±0.57	0.36±0.98	150.1±0.67	98.62±1.99
F8 (1:6)	3.00±0.89	3.76±0.60	0.32±0.02	150.4±0.43	100.37±1.14
F9 (1:3)	2.95±0.73	3.66±0.44	0.52±0.87	152.7±0.80	97.87±2.18
F10 (1:4)	2.83±0.68	4.58±0.31	0.38±0.67	151.85±0.83	96.12±0.98
F11 (1:5)	2.81±0.88	4.39±0.37	0.44±0.01	151.7±0.93	98.37±0.43
F12 (1:6)	2.86±0.25	4.85±0.65	0.36±0.02	152.2±0.83	99.12±1.87

Averages of triplicate were reported (n=3) **(MEAN ±SD)**

Table 6: Surface P^H, Swelling Index and Mucoadhesive Strength Evaluation

Formulation Code (Drug: polymer)	Surface PH	Mucoadhesive strength (g)	Swelling index (%)
F1 (1:3)	6.50±0.11	19±0.10	79.33±3.37
F2 (1:4)	6.60±0.06	23±0.35	97.64±1.48
F3 (1:5)	6.52±0.06	30±0.20	100.92±4.14
F4 (1:6)	5.35±0.04	36±0.30	120.95±4.96
F5 (1:3)	6.51±0.03	13±0.25	78.31±4.19
F6 (1:4)	6.36±0.11	18±0.21	90.31±2.33
F7 (1:5)	6.32±0.03	24±0.35	93.83±2.52
F8 (1:6)	6.42±0.05	26±0.10	107.52±1.29
F9 (1:3)	6.38±0.03	11±0.25	69.12±4.19
F10 (1:4)	6.45±0.11	14±0.21	73.21±2.33
F11 (1:5)	6.58±0.03	16±0.35	80.10±2.52
F1 (1:6)	6.81±0.05	21±0.10	84.25±1.29

Averages of triplicate were reported (n=3) **(MEAN ±SD)**

Table 7: *in vitro* dissolution profile of formulation f1 (drug+ carbopol 934 in 1:3 ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.019	0.288	0.0288	2.59	0	2.59	26.04
2	0.024	0.413	0.0413	3.71	0.0288	3.74	37.56
3	0.026	0.463	0.0463	4.16	0.0700	4.23	42.49
4	0.031	0.588	0.0588	5.28	0.1163	5.40	54.25
5	0.035	0.688	0.0688	6.18	0.1750	6.36	63.88
6	0.038	0.763	0.0763	6.86	0.2438	7.11	71.35
7	0.042	0.863	0.0863	7.76	0.3200	8.08	81.35
8	0.045	0.938	0.0938	8.43	0.4063	8.84	88.79

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 8: *In Vitro* Dissolution Profile of Formulation F2 (Drug+ Carbopol 934 in 1:4 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.013	0.138	0.0138	1.24	0	1.24	12.38
2	0.016	0.213	0.0213	1.81	0.0138	1.93	19.24
3	0.021	0.338	0.0338	3.04	0.0350	3.07	30.69
4	0.026	0.463	0.0463	4.16	0.0688	4.23	42.27
5	0.030	0.563	0.0563	5.06	0.1150	5.18	51.72
6	0.036	0.713	0.0713	6.41	0.1713	6.58	65.77
7	0.038	0.763	0.0763	6.86	0.2425	7.10	70.98
8	0.041	0.838	0.0838	7.54	0.3188	7.86	78.48

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 9: *In Vitro* Dissolution Profile of Formulation F3 (Drug+ Carbopol 934 In 1:5 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.011	0.088	0.0088	0.79	0	0.79	8.09
2	0.015	0.188	0.0188	1.69	0.0088	1.70	17.38
3	0.018	0.263	0.0263	2.36	0.0275	2.39	24.49
4	0.021	0.338	0.0338	3.04	0.0538	3.09	31.67
5	0.024	0.413	0.0413	3.71	0.0875	3.80	38.93
6	0.026	0.463	0.0463	4.16	0.1288	4.29	43.97
7	0.031	0.588	0.0588	5.29	0.1750	5.46	55.97
8	0.035	0.688	0.0688	6.19	0.2338	6.42	65.79

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 10: *In Vitro* Dissolution Profile of Formulation F4 (Drug+ Carbopol 934 In 1:6 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.009	0.038	0.0038	0.34	0	0.34	3.46
2	0.011	0.088	0.0088	0.79	0.0038	0.79	8.07
3	0.013	0.138	0.0138	1.24	0.0125	1.25	12.74
4	0.018	0.263	0.0263	2.36	0.0263	2.39	24.35
5	0.021	0.338	0.0338	3.04	0.0525	3.09	31.50
6	0.023	0.388	0.0388	3.49	0.0863	3.57	36.43
7	0.025	0.438	0.0438	3.94	0.1250	4.06	41.41
8	0.028	0.513	0.0513	4.16	0.1688	4.78	48.74

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 11: *In Vitro* Dissolution Profile of Formulation F5 (Drug+ Hpmc K15m In 1:3 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.016	0.213	0.0213	1.91	0	1.91	19.73
2	0.022	0.363	0.0363	3.26	0.0213	3.28	33.92
3	0.027	0.488	0.0488	4.39	0.0575	4.45	45.92
4	0.032	0.613	0.0613	5.51	0.1063	5.62	58.04
5	0.036	0.713	0.0713	6.41	0.1675	6.58	67.98
6	0.039	0.788	0.0788	7.09	0.2388	7.33	75.68
7	0.043	0.888	0.0888	7.99	0.3175	8.31	85.80
8	0.045	0.938	0.0938	8.44	0.4063	8.84	91.36

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 12: *In Vitro* Dissolution Profile of Formulation F6 (Drug+ Hpmc K15m In 1:4 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.012	0.113	0.0113	1.01	0	1.01	10.19
2	0.018	0.263	0.0263	2.36	0.0113	2.37	23.95
3	0.021	0.338	0.0338	3.04	0.0375	3.08	31.03
4	0.026	0.463	0.0463	4.16	0.0713	4.23	42.72
5	0.029	0.538	0.0538	4.84	0.1175	4.96	50.00
6	0.035	0.688	0.0688	6.19	0.1713	6.36	64.16
7	0.041	0.838	0.0838	7.54	0.2400	7.78	78.48
8	0.046	0.963	0.0963	8.66	0.3238	8.99	90.68

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 13: *In Vitro* Dissolution Profile of Formulation F7 (Drug+ Hpmc K15m In 1:5 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.011	0.088	0.0088	0.79	0	0.79	8.01
2	0.014	0.163	0.0163	1.46	0.0088	1.47	14.92
3	0.018	0.263	0.0263	2.36	0.0250	2.39	24.21
4	0.023	0.388	0.0388	3.49	0.0513	3.54	35.89
5	0.029	0.538	0.0538	4.84	0.0900	4.93	49.97
6	0.035	0.688	0.0688	6.19	0.1438	6.33	64.21
7	0.039	0.788	0.0788	7.09	0.2125	7.30	74.04
8	0.046	0.963	0.0963	8.66	0.2913	8.95	90.81

Averages of triplicate were reported (n=3) CLA- Cumulative loss added ;CDR- Cumulative drug release

Table 14: *In Vitro* Dissolution Profile of Formulation F8 (Drug+ Hpmc K15m In 1:6 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.009	0.038	0.0038	0.34	0	0.34	3.38
2	0.012	0.113	0.0113	1.01	0.0038	1.02	10.13
3	0.015	0.188	0.0188	1.69	0.0150	1.70	16.97
4	0.018	0.263	0.0263	2.36	0.0338	2.40	23.89
5	0.022	0.363	0.0363	3.26	0.0600	3.32	33.13
6	0.025	0.438	0.0438	3.94	0.0963	4.03	40.22
7	0.031	0.588	0.0588	5.29	0.1400	5.43	54.11
8	0.036	0.713	0.0713	6.41	0.1988	6.61	65.91

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 15: *In Vitro* Dissolution Profile of Formulation F9 (Drug+ Hpmc K4m in 1:3 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.019	0.288	0.0288	2.59	0	2.59	26.48
2	0.026	0.463	0.0463	4.16	0.0288	4.19	42.86
3	0.032	0.613	0.0613	5.51	0.0750	5.59	57.13
4	0.035	0.688	0.0688	6.19	0.1363	6.32	64.66
5	0.038	0.763	0.0763	6.86	0.2050	7.07	72.26
6	0.043	0.888	0.0888	7.99	0.2813	8.27	84.55
7	0.047	0.988	0.0988	8.89	0.3700	9.26	94.66
8	0.047	0.988	0.0988	8.89	0.4688	9.36	95.67

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 16: *In Vitro* Dissolution Profile Of Formulation F10 (Drug+ Hpmc K4m In 1:4 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.017	0.238	0.0238	2.14	0	2.14	22.26
2	0.021	0.338	0.0338	3.04	0.0238	3.06	31.85
3	0.026	0.463	0.0463	4.16	0.0575	4.22	43.91
4	0.029	0.538	0.0538	4.84	0.1038	4.94	51.42
5	0.034	0.663	0.0663	5.96	0.1575	6.12	63.68
6	0.039	0.788	0.0788	7.09	0.2238	7.31	76.08
7	0.043	0.888	0.0888	7.99	0.3025	8.29	86.26
8	0.045	0.938	0.0938	8.44	0.3913	8.83	90.80

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 17: *In Vitro* Dissolution Profile of Formulation F11 (Drug+ Hpmc K4m In 1:5 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.016	0.213	0.0213	1.91	0	1.91	20.10
2	0.021	0.338	0.0338	3.04	0.0213	3.06	31.12
3	0.026	0.463	0.0463	4.16	0.0550	4.22	42.90
4	0.032	0.613	0.0613	5.51	0.1013	5.61	57.11
5	0.037	0.738	0.0738	6.64	0.1625	6.80	69.18
6	0.040	0.813	0.0813	7.31	0.2363	7.55	76.79
7	0.042	0.863	0.0863	7.76	0.3175	8.08	82.20
8	0.044	0.913	0.0913	8.21	0.4038	8.62	87.65

Averages of triplicate were reported (n=3) CLA- Cumulative loss added
CDR- Cumulative drug release

Table 18: *In Vitro* Dissolution Profile of Formulation F12 (Drug+ Hpmc K4m In 1:6 Ratio)

Time (hrs.)	Absorbance at 323nm	Conc. of drug (µg/ml)	Amount of drug in 10ml (mg)	Amount of drug in900ml (mg)	CLA	CDR	Cumulative % drug released
0	0	0	0	0	0	0	0
1	0.015	0.188	0.0188	1.69	0	1.69	17.05
2	0.019	0.288	0.0288	2.59	0.0188	2.61	26.30
3	0.021	0.338	0.0338	3.04	0.0475	3.09	31.13
4	0.026	0.463	0.0463	4.16	0.0813	4.24	42.82
5	0.029	0.538	0.0538	4.84	0.1275	4.97	50.10
6	0.035	0.688	0.0688	6.19	0.1813	6.37	64.27
7	0.039	0.788	0.0788	7.09	0.2500	7.34	74.04
8	0.043	0.888	0.0888	7.99	0.3288	8.32	83.92

Averages of triplicate were reported (n=3)
CLA- Cumulative loss added
CDR- Cumulative drug release

Parameters	0 days	30 days	60 days
Drug content	98.62±1.99	98.44±1.24	98.43±1.02
Surface Ph	6.32±0.03	6.33±0.04	6.35±0.03
Mucoadhesive strength (g)	24±0.35	24±0.30	23±0.25
Swelling index (%)	93.83±2.52	93.32±2.33	92.30±1.59

Averages of triplicate were reported (n=3) **(MEAN ±SD)**

Table 19: *In Vitro* Dissolution Profile of Optimized Formulation F7 (Drug+ Hpmc K15m In 1:5) Stored At 40±2^{0}c And 75±5% Rh For 60 Days

	Cumulative % drug released		
Time (hrs.)	0 days	30 days	60 days
0	0	0	0
1	8.01	8.00	7.91
2	14.92	14.88	14.68
3	24.21	24.20	23.41
4	35.89	35.85	34.89
5	49.97	49.94	48.37
6	64.21	64.19	63.51
7	74.04	73.90	73.22
8	90.81	90.78	89.81

DISCUSSION:

In the current study a successful attempt was made to formulate Mucoadhesive buccal tablets of Ketorolac Tromethamine by direct compression method using mucoadhesive polymers Carbopol 934, HPMC K15M, and HPMC K4M in different ratios and ethyl cellulose as backing layer with Tartrazine as colouring agent.

IR spectra of pure drug and with the polymers showed no significant shift in functional peaks and do not show any incompatibility, thus the polymers are compatible with thedrug.

The formulated tablets were satisfactory in terms of physical parameters (hardness, thickness and weight variation), drug content, surface pH, swelling index, mucoadhesive strength, *in vitro* drug release, *in vitro*

permeation studies. The surface pH of all the formulated tablets was in the range of salivary pH. Mucoadhesive strength which is the major criteria along with *in vitro* drug release in selection of optimized formulation is optimum for F7formulation. Although all buccal tablets exhibited satisfactory drug release, the best results were obtained with F5, F7 (HPMC K15M), F9 (HPMC K4M) formulations. Since mucoadhesive strength is also important for buccal tablets, it is optimum for F7 formulation, so F7 is selected as optimized formulation. *In vitro* dissolution studies of optimized formulation indicated drug release followed Korsmeyer-Peppas model.

The release of the Ketorolac Tromethamine from buccal tablets followed non- fickian release kinetics which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. The release of the drug from the prepared tablets is controlled by swelling of the polymer, followed by drug diffusion through swelled polymer, slow erosion of polymer.

The above study demonstrated the possibility of making buccal tablets for Ketorolac Tromethamine with reduced dose and controlled release will be more efficacious and acceptable than the conventional and intramuscular drug delivery systems to avoid frequent dosing in treating of short-term management of post-operative and moderate to severe pain.

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