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DEVELOPMENT AND EVALVATION OF BUCCAL FILM OF KETOROLAC TROMETHAMINE

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ABSTRACT

The objective of the present study was to formulate Ketorolac Tromethamine buccal film and to evaluate the buccal film for its weight variation, thickness, drug content, percentage moisture absorption and percentage moisture loss. An in-vitro release study was designed using semipermeable membrane. Four formulations were prepared using 4% HPMC (KT_1), 6% HPMC (KT_2), 4%EC+0.05% PVP (KT_3 and 6%EC + 0.5% PVP (KT_4). The in-vitro release profile for the formulation KT_4 which contain 6%EC and 0.5%PVP and 8% EC showed sustain release up to 24 hours and obeyed first order kinetics.

Key words: Ketorolac tromethamine, buccal film, ethyl cellulose, polyvinyl pyrolidone, hydroxy propyl methyl cellulose.

INTRODUCTION

Buccal[1] cavity has wide varieties of functions and it acts as an excellent site for the absorption of drug. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agent in to the systemic circulation; there by avoiding the first pass hepatic[2] metabolism and gastro-intestinal degradation. However the buccal route of drug delivery has received much more attention because of its unique advantages over other trans mucosal routes. Various adhesive mucosal dosage[3] forms have been developed, which include adhesive tablets, gels, ointment, patches and more recently films.

Ketorolac is non-steroidal[4] anti-inflammatory drug (NSAID). Ketorolac inhibits the synthesis of prostaglandins[5] and may be considered a peripherally acting analgesics, it shows excellent binding with proteins and is largely metabolized in liver. Since the buccal route by passes the hepatic first[6] pass effect, the dose of Ketorolac could be reduced.

The physicochemical properties of Ketorolac Tromethamine[7], it suitable half life (2-3 hrs) and low mol. wt. 376.41 makes it suitable candidate for administration by buccal route.

MATERIALS AND METHODS

Ketorolac Tromethamine was a gift by Dr. Reddy's lab. Ltd. Hyderabad.

The polymers Hydroxypropyl methyl-cellulose (HPMC 15-cps), ethyl cellulose (EC 20 cps) and polyvinyl pyrolydone (PVP K-30) were obtained from Ozone pharmaceutical ltd. H.P. Other chemicals were of analytical grade.

Beer's Plot

Increasing concentration of Ketorolac Tromethamine was prepared in distilled water. The absorbance was determined in a spectro-photometer (Shimadzu) UV- VIS double beam at 324 nanometers. The absorbance values were plotted against the concentrations to yield the Beer's Plots.

Preparation of Reservoir Film

A number of buccal film containing 20 mg of Ketorolac Tromethamine in an area of 1 cm sq. were prepared by solvent casting[8] technique. PEG-600, glycerol in a concentration of 30% w/w of polymer was in corporated as plasticizer[9] in HPMC and EC film respectively. A film of 1 cm sq, area was cut from the total film area.

Rate Controlling Membrane

A rate controlling membrane was cast on a glass plate using ethyl cellulose (8% w/w) by incorporating glycerol (30% w/w of polymers) as plasticizer. Membrane of 1 cm sq in area was cut and both sides of drug reservoir[10] was sealed using this membrane to control the release[11] of drug.

Drug Content Determination

Buccal film of Ketorolac Tromethamine (1 cm sq) was prepared by different polymers like HPMC, EC. The size of film was 1 cm sq. The film of HPMC was dissolved in small amount of water shaken vigoursly for 5 minutes and then diluted with 10 ml of water. Buccal film of Ketorolac Tromethamine with EC was dissolved in small amount of chloroform shaken vigorously for 5 minutes and then diluted 10 ml with water. Both the solution were filtered trough whatmann[11] filter paper (no.42). The drug content was then determined after proper dilution and the absorbance was measured spectrophotometrically at 324 nm against a blank.

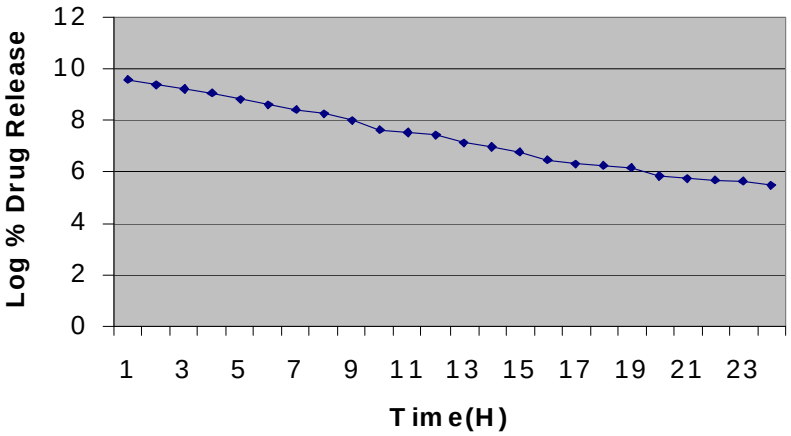


Fig. - 1: Release pattern of ketorolac tromethamine

***In-vitro* Release**

The *in-vitro* release study was carried out using semipermeable membrane. The membrane used was permeable to low molecular weight substance. The membrane was tied to one end of the open ended cylindrical tube[12], which acts as donor[13] compartment. A buccal film containing 20 mg of Ketorolac Tromethamine was placed inside the compartment.

This set up was placed over the beaker containing 100 ml distilled water, which acted as receptor compartment. The temperature was maintained at 37± 1°C and the continuous stirring was done. 5 ml of sample was withdrawn from receptor compartment at every one-hour time

Table - 1 : Formulation of buccal film of kt

S. No.	Batch code	Composition
1.	KT1	4% HPMC
2.	KT2	6% HPMC
3.	KT3	4% EC + 0.5% PVP
4.	KT4	6% EC + 0.5% PVP

Fig. - 2: Comparative *in vitro* release profile of ketorolac tromethamine formulations

(-♦-) Formulation KT_1 4% HPMC (- ■-) Formulation KT_2 6% HPMC (-▲-) Formulation KT_3 4% EC+0.5% PVP (-x-) Formulation KT_4 6% EC + 0.5% PVP. In all Formulations from KT_1 to KT_4 8% EC was used as the rate controlling membrane.

interval for 24 hours. The withdrawn quantity of sample was replaced with distilled water immediately. The collected samples were analyzed spectrophotometrically at 324 nm using water as blank. The experiment was performed for three times and the average values were reported.

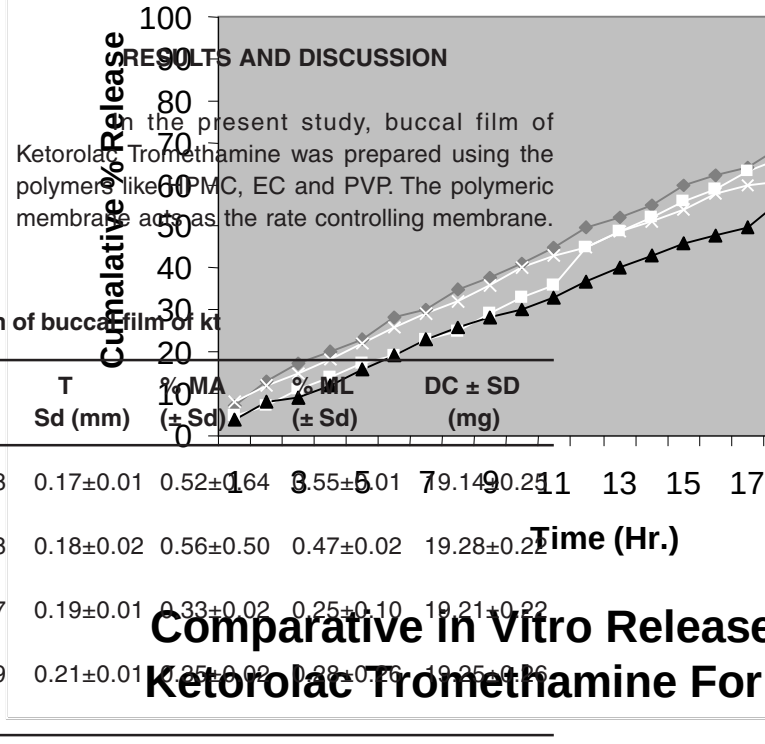
RESULTS AND DISCUSSION

In the present study, buccal film of Ketorolac Tromethamine was prepared using the polymers like HPMC, EC and PVP. The polymeric membrane acts as the rate controlling membrane.

Table - 2 : Evaluation of buccal film of kt

S. No.	Batch code	DRFC	PL % w/w	WV (mg)	T Sd (mm)	% MA (± Sd)	% ML (± Sd)	DC ± SD (mg)
1.	KT1	4% HPMC	PEG-600 (30%)	0.018	0.17±0.01	0.52±0.64	3.55±5.01	19.14±0.25
2.	KT2	6% HPMC	PEG-600 (30%)	0.018	0.18±0.02	0.56±0.50	0.47±0.02	19.28±0.22
3.	KT3	4% EC+ 0.5% PVP	Glycerol (30%)	0.017	0.19±0.01	0.33±0.02	0.25±0.10	19.21±0.22
4.	KT4	6% EC+ 0.5% PVP	Glycerol (30%)	0.019	0.21±0.01	0.25±0.02	0.28±0.26	19.25±0.26

DRFC: Drug Reservoir Film composition,PL:Plasticizer,%W/Wp: %W/W of Polymer,WV: Weight Variation, S.D:Standard deviation ,T:Thickness,%MA:Moisture absorption,%ML: Moisture loss, DC:Drug content.



Evaluation was done on the parameters like weight variation, thickness, moisture absorption; moisture loss and drug content (Table 2).

The thickness of film ranges from 0.17± 0.01 mm to 0.21± 0.01mm.The thinnest formulation was KT_1 and the thickest being KT_4. The usage of plasticizer in the formation of buccal films led to transparent, flexible films. Moreover the film was also checked for its cracks. This showed a uniform film formation. The weight of the film varied between 0.018 to 0.019mg(Table 2): moisture absorption of the films were also studied and it was shown that KT_2 showed highest moisture absorption and KT_3 showed minimum absorption: the % moisture loss was highest in KT_1 and minimum in KT_3. Drug content in the formulation was more or less same with a variation of 0.08% which is the indication for the formulation to be considered as a formulation having the drug uniformly dispersed in the film.

The *in-vitro* release study also showed good results. The increase in polymer concentration decreases the diffusion of the drug from the matrix. On comparison of the release results from the fourth formation KT_4 showed prolonged release of drug for a period of 24 hrs (fig-4). The formulation KT_4 showed first order release pattern shown in fig- 4. KT_4 was considered as the best formulation from the study for providing an extended release of the drug.

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