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Research Article

FORMULATION AND *INVITRO* EVALUATION OF BUCCAL MUCOADHESIVE TABLETS OF CHLOROPHENERAMINE MALEATE

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ABSTRACT

Buccal drug delivery system is used to improve oral bioavailability by avoiding first pass metabolism. Chlorpheneramine maleate a Histamine H1 antagonist used in allergic reactions, hay fever, rhinitis, urticaria, and asthma. It is absorbed rapidly but incompletely when given orally and undergoes first pass metabolism resulting in a low absolute bioavailability .The objective of this study was to develop effective mucoadhesive buccal tablets of Chlorpheneramine maleate to improve its bioavailability. Buccal tablets of Chlorpheneramine maleate were prepared by direct compression method using bioadhesive polymers like Xanthan gum, HPMCK4M by taking polymers in different ratios with drug. Then these were evaluated for different parameters such as thickness, hardness, weight variation, content uniformity, swelling index, and surface pH, *ex vivo* bioadhesive strength, *in vitro* drug release, *ex vivo* drug permeation and *ex vivo* residence time. *In vitro* assembly was used to measure the bioadhesive strength of tablets with fresh porcine buccal mucosa as model tissue. The tablets were evaluated for *in vitro* release in pH 6.6phosphate buffer for 6 hrs in standard dissolution apparatus. In order to determine the mode of release, the data was subjected to Zero order, first order, Higuchi, Korsmeyer and Peppas diffusion model. The formulation Fa3 (HPMCK4M in 1:15 ratio with drug) followed First order and Korsmeyer and Peppas release kinetics governed by Non-Fickian mechanism, i.e. the drug release proceeded by both diffusion as well as erosion of the polymer. Therefore, the release of drug from the prepared tablets is controlled by the initial swelling of the polymer, followed by drug diffusion through the swollen polymer and slow erosion of the polymer.

Keywords: Buccal tablets, Mucoadhesive, Chlorpheneramine maleate.

INTRODUCTION

The concept of mucosal-adhesive or mucoadhesive was introduced into the controlled drug delivery in the early 1980's. Extensive efforts have been recently focused on targeting a drug or drug delivery system in a particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. Delivery of drugs via the absorptive mucosa in various easily accessible body cavities like the buccal, nasal, ocular, sublingual, rectal and vaginal mucosa offers distinct advantages over oral administration for systemic drug delivery. The main advantage of using these routes is that they avoid the first-pass effect of drug clearance. Drugs can be absorbed from the oral cavity through the oral mucosa either sublingually or buccally. Absorption of therapeutic agents from these routes overcomes premature drug degradation within the gastrointestinal tract as well as active drug loss due to first-pass hepatic metabolism that

may be associated with oral route of administration. Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration. On the other hand, the duration of buccal drug administration can be prolonged with saliva activated adhesive polymers without problems of sublingual administration[1, 5].

Chlorpheneramine maleate was selected as the model drug for the investigation because it has got certain characteristics that a drug should possess to get absorbed through the buccal route viz., high permeability and low molecular weight. Moreover it undergoes first-pass metabolism in the liver which is the reason for its lower bioavailability, so its bioavailability may be improved when delivered through buccal route. This molecule is satisfying general considerations for buccal drug delivery. Hence it is selected as drug candidate for bioadhesive buccal drug delivery.

MATERIALS AND METHODS

Materials

Chlorpheneramine maleate was purchased from Nice chemicals Ltd, Hyderabad, India. HPMCK4M, Xanthan gum, Mg. Stearate and talc was purchased from Qualikems Pvt Ltd, Hyderabad, India. Micro crystalline cellulose and Mannitol were purchased from Finar chemicals Ltd, Hyderabad, India.

Methods

PREFORMULATION STUDIES

Solubility Studies

The solubility of Chlorpheneramine maleate in phosphate buffer solution pH 6.6 and pH 7.4 was determined by phase equilibrium method. An excess amount of drug was taken into 20 mL vials containing 10 mL of phosphate buffers (pH 6.6, and pH 7.4). Vials were closed with rubber caps and constantly agitated at room temperature for 24 hr using rotary shaker. After 24 hr, the solution was filtered through 0.2µm Whatman's filter paper. The amount of drug Solubilized was then estimated by measuring the absorbance at 261 nm using a UV spectrophotometer[2].

Drug-excipients compatibility studies

A Fourier Transform – Infra Red spectrophotometer was used to study the non-thermal analysis of drug-excipients (Binary mixture of drug: excipient 1:1 ratio) compatibility. The spectrum of each sample was recorded over the 450-4000 $cm^{-1.}$ Pure drug of Chlorpheneramine maleate, Chlorpheneramine maleate with physical mixture (excipients) compatibility studies were performed[3].

Ex vivo permeation studies

Ex vivo permeation study was conducted for API and selected buccal formulations (Fa3, Fa4, Fb3 and Fc3) through the porcine buccal mucosa was performed using Franz diffusion cell and membrane assembly *(Vishnu et al., 2007),* at 37°C ± 0.2°C and 50 rpm. This temperature and rpm was maintained by magnetic stirrer. Porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hr of slaughter. The tissue was stored in Krebs buffer at 4°C upon collection. After the buccal membrane was equilibrated for 30 min with the buffer solution between both the chambers, the receiver chamber was filled with fresh buffer solution (pH 7.4), and the donor chamber was charged with 5mL (1mg/mL) of drug solution. Aliquots (3mL) were collected at predetermined time inter wells up to 8hr and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 226 nm using a UV spectrophotometer. The medium of the same volume (3mL), which was pre-warmed at 37°C, was then replaced into the receiver chamber[4, 6, 11].

The experiments were performed in triplicate (n = 3) and mean values were used to calculate flux (J) and permeability coefficient (P).

$$J = \frac{dQ/dt}{A} \qquad P = \frac{dQ/dt}{\Delta CA}$$

Where, J is Flux ($mg.hrs^{-1}cm^{-2}$), P is permeability coefficient (cm/h), dQ/dt is the slope obtained from the steady state portion of the curve, ΔC is the concentration difference across the mucosa and A the area of diffusion (cm^2).

Formulation and preparation of buccal tablets

Buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Xanthan gum, HPMCK4M are the mucoadhesive and biodegradable polymers used in this preparation of buccal mucoadhesive drug delivery systems.

Chlorpheneramine maleate was mixed manually with different ratios of Xanthan gum, HPMCK4M, Mannitol as sweetening agent/diluent and micro crystalline cellulose as binding agent/diluent added for 10 min. The blend was mixed with Talc and Magnesium Stearate for 3-5 min.

Then the powder blend was compressed into tablets by the direct compression method using

6mm flat faced punches. The tablets were compressed using a sixteen station CEMACH rotary tablet-punching machine. The composition of buccal formulations were given in table no.1.

Flow properties of Powder blend

The flow properties of powder blend were estimated by determining the angle of repose, Carr's index and Hausner's ratio. The angle of repose was measured by the fixed funnel method. The bulk density and tapped densities were determined for the calculation of Hausner's ratio and Carr's index[3].

In vitro Evaluation of buccal tablets of Chlorpheneramine Maleate

Physical Evaluation:

According to the methods mentioned in monograph of Chlorpheneramine Maleate in pharmacopeia, the Thickness, weight variation, hardness and friability of all formulations were studied using Digital Vernier caliper, electronic balance, Monsanto hardness tester and Roche friabilator respectively[7].

Content uniformity (Assay)

Six tablets of each formulation were taken and amount of drug present in each tablet was determined. Powder equivalent to one tablet was taken and added in 100ml of pH 6.6 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and the absorbance of resultant solution was measured by using UV-Visible spectrophotometer at 261 nm using pH6.6 phosphate buffer[7].

In vitro drug release of buccal tablets

The drug release rate from buccal tablets was studied using the USP type II dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed on the other side of the tablet. The tablet was further fixed to a 2x2 cm glass slide with a solution of cyanoacrylate adhesive. Then it was placed in the dissolution apparatus. The dissolution medium was 500 ml of pH 6.6 phosphate buffer at 50 rpm at a temperature of 37 ± 0.5 °C. Samples of 5 ml were collected at different time intervals up to 6 hrs and analyzed after appropriate dilution by using UV Spectrophotometer at 261nm.[8]

Swelling Index

Buccal tablets were weighed individually (designated as W_1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.6) solution. At regular intervals (0.5, 1, 2, 3, 4, 5 and 6hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W_2)[9, 10]. (This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following equation.

$$\text{Swelling index} = \frac{(W_2 - W_1)}{W_1} \times 100$$

Measurement of bioadhesion strength

A modified balance method was used for determining the mucoadhesive strength. An apparatus designed for determination of mucoadhesive bond strength was used. Bioadhesive strength expressed in Newton, required for detachment of the tablet from the mucosa was determined using the fresh pig buccal mucosa as mucosal substrate. The working of the fabricated bioadhesion test apparatus was based on the principle of double beam physical balance[9,10].

Moisture absorption study

Agar (5% w/v) was dissolved in hot water, transferred into Petri plates and allowed to solidify. Six buccal tablets from each formulation were placed in vaccum oven night prior to the study to remove moisture if any and laminated on one side with water impermeable backing membrane. They were taken placed on the surface of the agar and incubated at 37^{0}C for 4 hr. Then the tablets removed and weighed and the percentage moisture absorption was calculated[9, 10] using the following formula.

$$\text{\% Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Surface pH Study

Weighed tablets were placed in boiling tubes and allowed to swell in contact with pH 6.6phosphate buffer (12mL). Thereafter, surface pH measurements at predetermined intervals of 0.25, 0.5, 1, 2, 3, 4, 5, 6 and 6 h were recorded with the aid of a digital pH meter. These measurements were conducted by bringing a pH electrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the

readings[9, 10]. Experiments were performed in triplicate (n=3)

RESULTS AND DISCUSSION

Solubility studies

The solubility study was conducted in pH 6.6 and pH 7.4 phosphate buffers because these are average pH values of oral cavity and blood respectively. Solubility of Chlorpheneramine maleate in the pH 6.6 and pH 7.4 was found to be 9.38mg/ml, 10.97 mg/ml respectively.

Drug- excipients Compatibility studies

FTIR spectroscopic studies were conducted to determine possible drug polymer interactions. FTIR studies were conducted for pure drug and physical mixture.

Table 1: Composition of Chlorpheneramine Maleate buccal tablets

Formulation code	Fa1	Fa2	Fa3	Fa4	Fb1	Fb2	Fb3	Fb4	Fc1	Fc2	Fc3
Chlorpheneramine maleate	4	4	4	4	4	4	4	4	4	4	4
HPMCK4M	20	40	60	80	-	-	-	-	30	15	45
XANTHANGUM	-	-	-	-	20	40	60	80	30	45	15
MCC102	65	45	25	5	65	45	25	5	25	25	25
Mannitol	5	5	5	5	5	5	5	5	5	5	5
Mg.stearate	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4

Fa1-4: Indicates the formulation containing HPMCK4M in different ratios with drug (1:5, 1:10, 1:15, and 1:20).
Fb1-4: Indicates the formulation containing XANTHAN GUM in different ratios with drug (1:5, 1:10, 1:15, and 1:20).
Fc1-3: Indicates the formulation containing combination of HPMCK4M and XANTHAN GUM (1:1, 0.5, 1.5, 1.5:0.5).

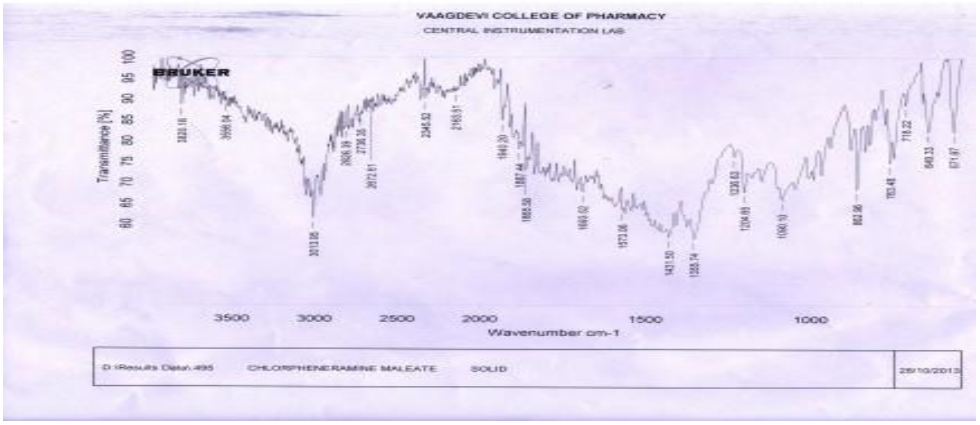

Fig. 1: FTIR studies of pure drug Chlorpheneramine maleate

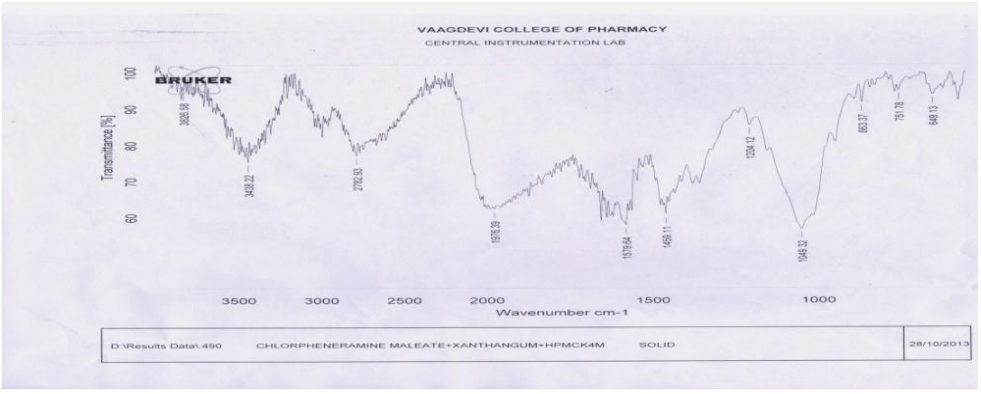

Fig. 4: FTIR studies of pure drug (Chlorpheneramine maleate) + HPMCK4M + Xanthan gum

IR spectra of pure drug (Chlorpheneramine maleate), Xanthan gum, HPMCK4M and physical mixture of Chlorpheneramine maleate with these polymers were obtained. The major peaks aromatic C=O peak at1583.06 cm^{-1}, C-C=C peak at 1573.06 cm^{-1}, N-CH_3 peak at 1553.06 cm^{-1} and O-H peak at 1654.78 cm^{-1} Which were present in pure drug (Chlorpheneramine maleate) are also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.
The results obtained by evaluating the powder blends of drug and excipients are shown in Table (2). Bulk density and tapped density were found in the range of 0.413-0.441 g/cc and 0.510-0.534 g/cc respectively. The value of Hausner's ratio was in between 1.20-1.23 (<1.25) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found to be in the range of 31.21 - 33.41 showing that blend of powder was free flowing and can be used for direct compression.

Physicochemical properties

The hardness of prepared buccal tablets was found to be in the range of 5.1±0.12 Kg/cm^2 to 5.71±0.27Kg/cm^2**.** The thickness was found to be 2.31±0.02 mm to2.39±0.03 mm. The friability of all tablets was less than 1% i.e., in the range of 0 .55 – 0.68 %. The percentage deviation from mean weights of all the formulations of tablets was found to be within the prescribed limits (table no.3).

Table 2: Preformulation characteristics (flow properties of powder blend)

Formulation code	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
Fa1	0.426±1.21	0.516±1.51	1.21±0.42	17.38±1.01	33.41±0.52
Fa2	0.413±1.42	0.518±1.61	1.21±0.74.	17.45±1.03	31.21±0.85
Fa3	0.441±1.43	0.510±1.70	1.23±0.67	18.33±1.01	31.34±0.76
Fa4	0.432±1.62	0.534±1.38	1.22±0.78	19.45±1.19	32.13±0.75
Fb1	0.419±1.31	0.511±1.51	1.22±0.91	17.76±1.18	33.17±0.54
Fb2	0.421±1.53	0.521±1.45	1.21±0.81	18.57±1.91	32.14±0.74
Fb3	0.440±1.18	0.527±1.36	1.23±0.84	18.96±1.72	31.56±0.86
Fb4	0.425±1.31	0.525±1.28	1.20±0.74	19.34±1.41	31.92±0.75
Fc1	0.415±1.19	0.521±1.52	1.21±0.92	17.75±1.51	31.95±0.21
Fc2	0.428±1.18	0.530±1.26	1.22±0.67	18.99±1.63	32.77±0.43
Fc3	0.423±1.61	0.510±1.29	1.21±0.91	17.31±1.53	31.78±0.19

Table 3: Physico-chemical parameters of Chlorpheneramine maleate buccal tablets

Formulation code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug content
Fa1	98±0.02	2.31±0.02	5.5±0.12	0.58±0.05	99.18±0.92
Fa2	99±0.5	2.36±0.01	5.4±0.14	0.64±0.13	99.53±1.00
Fa3	100±0.2	2.39±0.03	5.2±0.17	0.57±0.06	99.47±0.44
Fa4	99±0.3	2.33±0.01	5.1±0.12	0.68±0.12	99.12±0.92
Fb1	98±0.3	2.31±0.02	5.3±0.26	0.65±0.17	98.34±0.75
Fb2	99±0.1	2.30±0.02	5.3±0.32	0.55±0.11	98.72±0.72
Fb3	100±0.2	2.38±0.01	5.29±0.24	0.68±0.15	99.13±0.44
Fb4	99±0.31	2.32±0.03	5.56±0.29	0.58±0.07	98.71±0.92
Fc1	98±0.3	2.30±0.03	5.71±0.27	0.55±0.06	98.55±0.57
Fc2	100±0.4	2.32±0.02	5.6±0.21	0.67±0.03	99.78±0.39
Fc3	99±0.2	2.32±0.01	5.3±0.32	0.68±0.12	99.51±1.00

Each value represents the mean ±SD (*n* =3).

***In vitro* drug release of buccal tablets**

In-vitro drug release studies were conducted in phosphate buffer pH 6.6 and the studies revealed that the release of Chlorpheneramine maleate from different formulations varies with characteristics and composition of matrix forming polymers as shown in graph and the results were shown in table no. 4-5 and fig. 1-3.

Table 4: **Drug release from formulations containing single polymer with different ratios i.e. Fa1-4: HPMCK4M**

Time(hrs)	Fa1	Fa2	Fa3	Fa4
0.5	85.57±1.92	49.03±1.82	50.96±1.89	46.15±1.56
1	96.1±1.51	68.26±1.36	59.6±1.84	53.8±1.74
2	100±2.11	76.9±1.46	79.8±1.64	69.2±1.41
3	-	90.3±1.28	85.57±1.97	77.88±1.95
4	-	100.0±1.84	89.42±2.02	81.731±1.64
5	-	-	97.11±1.78	86.538±1.73
6	-	-	98.07±1.97	93.269±1.57

Each value represents the mean ± SD (n=3)

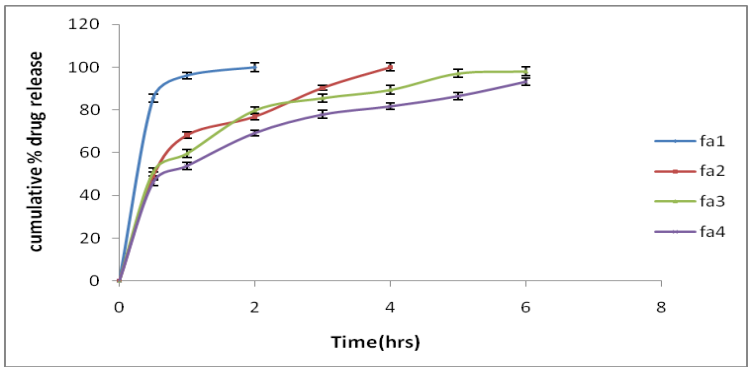

Fig. 1: ***In-vitro*** **cumulative %drug release of Chlorpheneramine maleate buccal tablets with HPMCK4M**

Table 5: Drug release from formulations containing single polymer with different ratios i.e.Fb1-4: XANTHAN GUM

Time(hrs)	Fb1	Fb2	Fb3	Fb4
0.5	89.42±1.82	58.65±1.64	50.0±1.89	43.26±1.36
1	90.38±1.98	72.11±1.83	69.23±2.73	63.46±1.82
2	98.07±1.54	81.73±2.11	75.96±1.53	69.23±1.46
3	100.0±2.46	95.19±2.73	78.84±2.08	81.73±1.28
4	-	99.03±1.54	84.61±1.84	85.57±1.84
5	-	-	89.42±1.64	86.53±1.67
6	-	-	95.19±1.97	90.38±1.54

Each value represents the mean ± SD (n=3)

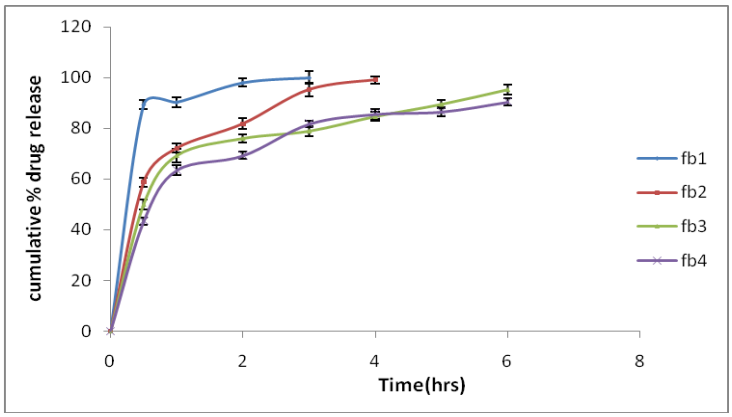

Fig. 2: ***In-vitro*** **cumulative %drug release of Chlorpheneramine maleate buccal tablets with XANTHAN GUM**

Table 6: **Drug release from formulations with combination of HPMCK4M and XANTHAN GUM in different ratios, i.e. Fc1 (1:1), Fc2 (0.5:1.5) and Fc3 (1.5:0.5)**

Time(hrs)	Fc1	Fc2	Fc3
0.5	45.19±1.72	34.61±1.75	43.26±1.63
1	59.61±1.63	52.88±1.47	52.88±1.76
2	75.00±1.51	60.57±1.38	69.23±1.95
3	87.50±1.88	75.96±1.63	72.11±1.43
4	95.19±2.11	80.76±1.93	78.84±1.84
5	100.0±1.74	87.50±2.85	81.73±1.94
6	-	90.38±1.75	93.34±1.75

Each value represents the mean ± SD (n=3)

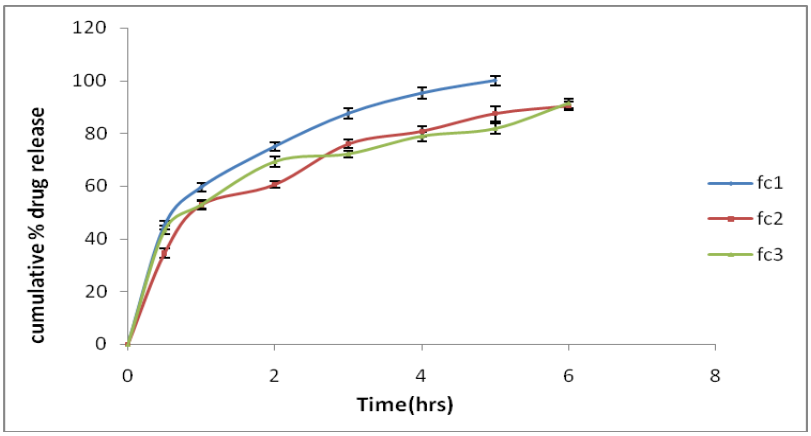

Fig. 3: ***In-vitro*** **cumulative % drug release of Chlorpheneramine maleate buccal tablets with Xanthan gum and HPMCK4M**

From the drug release studies, Fa3 formulation showed higher percentage of drug release, followed by Fb3, Fc3and Fa4. These formulations were considered as optimized formulations and evaluation tests (Swelling studies, Surface p^H study, moisture absorption study and exvivo residence study) were performed for these formulations to select the better formulation among these four formulations.

Swelling Studies of buccal tablets

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper bioadhesion (Peppas and Bury, 1985). The polymeric tablet formulations displayed an increase in weight due to water uptake. The % swelling index was found to be in the range of 186.95 at 7th hr for the formulation containing HPMCK4M and Xanthan gum; the formulation containing HPMCK4M showed 195.54 and the formulations containing HPMCK4M and Xanthan gum showed the swelling index in the range of 210.55 and 203.86 at 7th hr respectively. Formulations with the Xanthan gum showed higher swelling index values (higher water uptake) of all the formulations were given in Table 7.

Table 7: % swelling index profile of selected Chlorpheneramine Maleate formulations

Time (hrs)	% Swelling index			
	Fa3	Fc3	Fb3	Fa4
0.5	114.41±3.61	120.2±3.55	130.63±3.62	5.42±4.17
1	119.78±4.09	125.78±3.61	138.96±3.54	2.04±3.72
2	124.21±3.45	136.92±3.67	149.41±3.86	0.99±4.28
3	135.23±3.51	145.81±3.36	156.34±3.53	3.92±3.83
4	148.28±3.34	150.67±3.31	170.87±3.71	5.78±3.61
5	159.34±4.17	180.32±3.41	190.74±3.35	6.73±3.67
6	172.54±3.52	185.74±3.65	199.62±3.41	4.45±4.23
7	186.95±4.28	195.54±3.83	210.55±3.89	3.86±3.78

Each value represents the mean ± SD (n=3)

Surface pH study

The surface pH study of the buccal tablets was determined in order to investigate the possibility of any side effects. 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 surface pH of the selected formulations was found to be 6.88 ± 0.45 to 6.95 ± 0.63 and the pH was near to the neutral.

These results suggested that the polymeric blend identified was suitable for oral application and formulations were nonirritant to the buccal mucosa. Surface pH values for all the formulations shown in Table 8.

Moisture absorption test

The moisture absorption studies give an indication of the relative moisture absorption capacities of polymers and whether the formulations maintain their integrity after moisture absorption.

The comparative moisture absorption of various formulations was in order of Fb3 > Fa4 > Fc3 > Fa3.

Measurement of bioadhesion strength

This evaluation test was conducted for selected formulations (Fa3, Fa4, Fb3 and Fc3); there is a gradual increase in bioadhesion strength from Fa3 to Fc3. The maximum bioadhesion strength (54.54±0.52, 45.13±0.41) was found for formulations Fc3 and Fb3 and low bioadhesion strength was found for Fa3 and Fa4 (34.10±0.57, 34.92±0.21). The buccal tablets formulated with HMCK4M + Xanthan gum showed stronger mucoadhesion than HPMCK4M. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. Optimized tablet (Fa3) showed 34.10±0.57g of bioadhesion strength.

***Ex-vivo* residence time**

The *ex-vivo* residence time is one of the important physical parameter of buccal mucoadhesive tablets. The *ex-vivo* residence time was determined by using specially designed apparatus. As the concentration of mucoadhesive material increased, the residence time increased. This test reflects the adhesive capacity of polymers used in formulations. The results revealed that the formulations containing Xanthan gum showed better residence time than the other polymer formulations shown in Table 8.

Table 8: *Ex-vivo* residence time, Moisture absorption and Surface pH values of selected formulations

Formulation code	*Ex vivo* residence time(hrs)	Moisture absorbance	Surface pH	Mucoadhesive strength(gm)
Fc3	5.54	12.43±0.48	6.91±0.51	54.54±0.52
Fb3	6.65	15.12±0.31	6.88±0.45	45.13±0.41
Fa4	6.09	13.75±0.45	6.95±0.63	34.92±0.21
Fa3	5.04	11.91±0.32	6.89±0.67	34.10±0.57

Ex vivo permeation of buccal tablets

Table 9: Drug release of Chlorpheneramine maleate *ex vivo* permeated buccal tablet without permeation enhancer

Time (hrs)	Fa3	Fc3	Fa4	Fb3
0.5	9.18±0.61	10.43±0.55	8.53±0.62	7.27±0.17
1	12.02±0.09	15.12±0.61	11.43±0.54	9.78±0.71
2	16.26±0.45	17.92±0.67	14.82±0.86	12.99±0.28
3	22.86±0.51	20.14±0.36	20.99±0.53	18.26±0.83
4	31.72±0.34	28.62±0.31	27.51±0.71	26.63±0.61
5	40.56±0.17	39.97±0.41	35.96±0.35	34.71±0.67
6	51.13±0.52	47.21±0.65	46.25±0.41	43.18±0.23
Flux	0.164μghr^{-1}cm^{-2}	0.156μghr^{-1}cm^{-2}	0.147μghr^{-1}cm^{-2}	0.138μghr^{-1}cm^{-2}

Each value represents the mean ± SD (n=3)

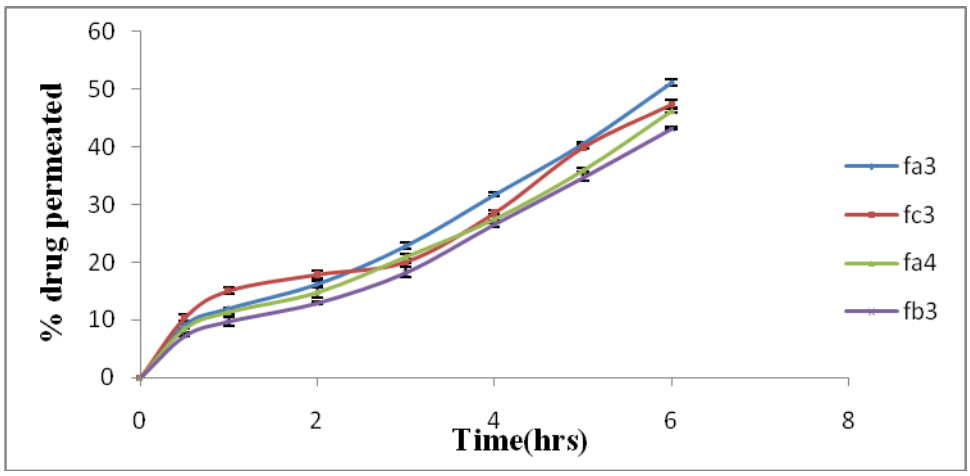

Fig. 4: *Ex vivo* permeation of Chlorpheneramine maleate from selected buccal formulations without permeation enhancer through porcine buccal mucosa

Table 10: Drug release of Chlorpheneramine maleate *ex vivo* permeated buccal tablet with permeation enhancer (1% Menthol)

Time (hrs)	Fa3
0.5	40.12±0.55
1	43.51±0.61
2	49.43±0.67
3	52.24±0.36
4	55.26±0.31
5	63.36±0.41
6	68.84±0.65
FLUX	0.475µg.hr^{-1}cm

Each value represents the mean ± SD (n=3)

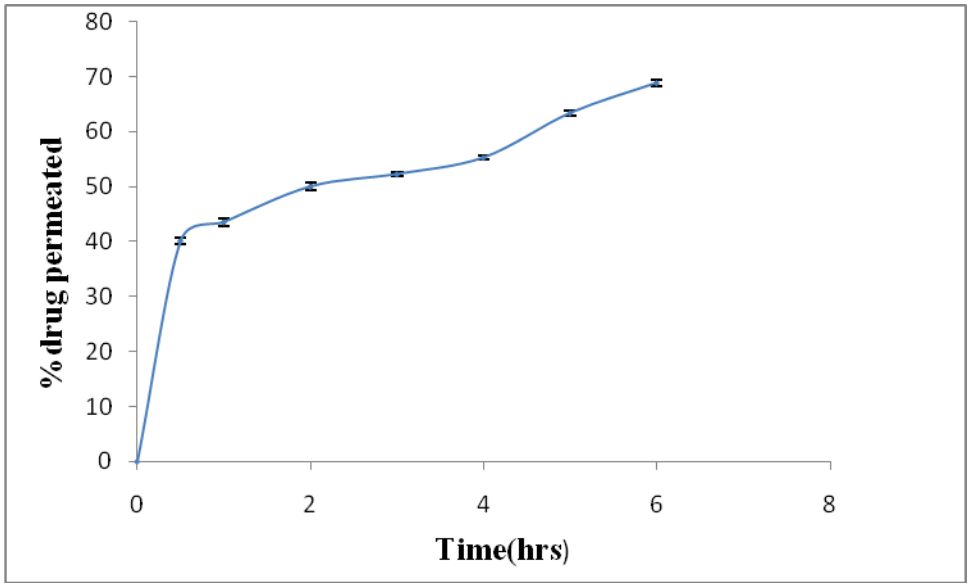

Fig. 5: *Ex vivo* permeation of optimized formulation (Fa3) from selected buccal formulations through porcine buccal mucosa with permeation enhancer

Table 11: Release kinetics and mechanism of diffusion of optimized formulations

Formulation code	Mathematical models (release kinetics)				
	Zero order	First order	Higuchi	Korsmeyer– Peppas	
	R^2	R^2	R^2	R^2	N
Fa3	0.937	0.974	0.986	0.993	0.817
Fa4	0.886	0.965	0.958	0.981	0.821
Fc3	0.925	0.944	0.965	0.985	0.813
Fb3	0.867	0.940	0.976	0.939	0.776

Each value represents the mean ± SD (n=3)

The formulations Fa4,Fb3and Fc3 followed first order release and Korsmeyer- Peppas order release kinetics governed by anomalous or non Fickian mechanism, i.e. the drug release proceeded by both diffusion as well as erosion of the polymer. Therefore, the release of drug from prepared tablets is controlled by the initial swelling of the polymer, followed by drug diffusion through the swollen polymer and slow erosion of the polymer. The drug release is depends up on the swelling behavior of the polymers, which produced by the slow dissolution of the systems. It was concluded that the release of drug from the tablets followed the diffusion controlled mechanism in all the formulations. The release kinetics and correlation coefficients were calculated for all the formulations and values were presented in the Table 11.

The optimized formulation (Fa3) showed first order drug release with R^2 value 0.986 and korsemeyers-peppas order release kinetics with R^2 value 0.993 governed by non- Fickian mechanism i.e. the drug release proceeded by both diffusion as well as erosion of the polymer.

CONCLUSION

From the above results, Fa3 composed of 1:15 (drug: HPMCK4M) formulation showed the complimentary physical properties with sustained buccal delivery of Chlorpheneramine maleate. When compared to all other formulations(Fa4, Fb3 and Fc3), from the in vitro drug release and bioadhesive strength point of view Fa3 formulation showed better results that meet all the criteria required for buccal formulation. The surface pH of the optimized formulation Fa3 was found to be 6.89±0.67. This pH is near to the neutral therefore, it was inferred that neutral pH of the formulation does not cause any irritation on the mucosa. From the exvivo permeation studies, optimized formulation (Fa3) shows improved permeation of drug with permeation enhancer. Therefore, Development of mucoadhesive buccal drug delivery of Chlorpheneramine maleate tablets with permeation enhancer (1% Menthol) is one of the alternative routes of administration to avoid first pass effect and provides prolonged release.

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