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ORIGINAL RESEARCH ARTICLE

Formulation and Evaluation of Olibanum Gum Based Rabeprazole Buccal Tablets as Permeation Enhancing System

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ABSTRACT

Buccoadhesive tablet of Rabeprazole sodium was developed to prolong its release and improve bioavailability by avoidance of hepatic first pass metabolism. The bilayered buccoadhesive tablets were prepared by direct compression technology, using different mucoadhesive polymers such as carbopol-934 as primary, xanthum gum & olibanum gum as secondary polymer, sodium deoxycholate as permeation enhancer. The tablets were evaluated for Physical characterization, assay, swelling index, bioadhesion study, *in-vitro* residence time, microenvironment pH, in-vitro drug release and in vitro permeation. Bioadhesive strength tends to quite linear with increasing amount of each polymer. Percentage release of drug tented to very non-linear with polymer amount. The formulation (F13) with CP and OG containing 1:1 ratio including sodium deoxycholate was considered as an optimized formulation. The drug release of this formulation was found to be non-Fickian and approaching zero order kinetics. The optimized formulation was carried out for stability studies; the result indicated that no significant change with respect to adhesive strength, in vitro residence time, in vitro drug release and in vitro permeation study

Key words: First Pass Metabolism, Swelling Index, *In-Vitro* residence time, Buccoadhesive Strength

INTRODUCTION

Oral drug administration has been one of the most suitable and widely accepted by the patients for the delivery of most therapeutically active drugs. Various dosage forms like tablets, capsules and liquid preparations have been administered by oral route. But, due to some unsuitable physiological conditions of the gastro-intestinal tract like relatively poor absorption, presence of various digestive enzymes of the gastrointestinal lumen and epithelium, poor absorption efflux (i.e. by P-glycoprotein, etc.) and first pass metabolism by hepatic enzymes, the administration of some drugs is affected. Mucoadhesive formulations have been researched for delivery to the buccal cavity, generally with the addition of permeation enhancers. Also, it may be necessary to hide the taste of drugs or excipients by the incorporation of taste masking agents [1]. Bioadhesive buccal delivery of drugs is one of the alternatives to the oral route of drug administration, particularly to those drugs that undergo first-pass effect. The stratified squamous epithelium supported by a connective tissue lamina propria, which is present in buccal mucosa, was targeted as a site for drug delivery several years ago. Problems accompanied with oral route of administration such as extensive metabolism by liver, drug degradation in gastrointestinal tract due to harsh environment, and invasiveness of parenteral administration can be solved by administering the drug through the buccal route [2,3]. Moreover buccal drug delivery offers a safer method of drug utilization, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity[4]. Buccoadhesive delivery systems make use of polymers that are highly bioadhesive and do not dissolve before releasing the incorporated drug, rather drug leaches out of the physiologically inert matrix on absorption of minimum amount of aqueous fluid [5]. The objective of present study is to design buccoadhesive bilayered tablets which will release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first pass metabolism for improvement in bioavailability, to reduce dosing frequency and to improve patient compliance. Rabeprazole sodium (RBEs), a proton -pump inhibitor used in treatment of Gastric ulcer, Peptic ulcer, Duodenal Ulcers, Erosive or Ulcerative GERD (Gastro Esophageal reflux Disease), Symptomatic GERD, Pathological Hypersecretory conditions (Zollinger

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- Ellison). RBE sodium is very soluble in water and in alkaline media. The stability of RBEs is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The degradation is catalyzed by acidic reacting compounds and PPIs are usually stabilized in mixtures with alkaline reacting compounds. Therefore exposure of RBEs to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability. Delayed release dosage form is best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation are absorbed preferentially in the intestine [6]. All these factor can be circumvented by buccal route. Short half -life (1-2 hr) and low bioavailability make it suitable candidate for buccal drug delivery

MATERIALS AND METHOD

Rabeprazole sodium was a gift sample of zydus cadila Ltd. Mumbai, xanthum gum was a gift sample of Mulberry chemicals pvt ltd, Mumbai, olibanum gum obtained from S.R. International Mumbai, carbopol 934 (CP), ethyl cellulose (EC), polyvinyl pyrrolidone K-30 (PVP), mannitol, sodium deoxycholate, talc, D-mannitol were obtained as gift samples from Central Drug House, India.

EXPERIMENTAL

Preparation of Buccal Tablets

Bi-layer buccal tablets were prepared by a direct compression method using two steps. Various batches were prepared by varying the ratio of different polymers either alone or in combinations with varying ratios as summarized in (**Table 1**) to identify the most effective formulation. The mucoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then removed and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force.

Table 1: Composition of buccal mucoadhesive tablets

Formulation Code	Rabeprazole Sodium	Carbopol 934	Xanthum Gum	Olibanum Gum	Sodium deoxycholate
F1	20	100%	-	-	-
F2	20	97%	-	-	3%
F3	20	25%	75%	-	-
F4	20	50%	50%	-	-
F5	20	75%	25%	-	-
F6	20	23.875%	71.625%	-	3%
F7	20	48.50%	48.50%	-	3%
F8	20	71.625%	23.875%	-	3%
F9	20	25%	-	75%	-
F10	20	50%	-	50%	-
F11	20	75%	-	25%	-
F12	20	23.875%	-	71.625%	3%
F13	20	48.50%	-	48.50%	3%
F14	20	71.625%	-	23.875%	3%

Evaluation of Buccoadhesive Bilayer Tablets:

All the tablet of formulations was evaluated for uniformity of weight, drug content and content uniformity as per IP method. Friability was determined using Roche friabilator while hardness was measured by Pfizer hardness tester.

Surface pH

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the oral cavity. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence attempt is made to keep the surface pH close to the neutral pH. The buccal mucoadhesive tablets (n=3) were made in contact with 1 ml of distilled water and allowed to swell for 2 hours at room temperature. The pH was measured by bringing the pH meter electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 min [7].

In-Vitro Bio-Adhesion Studies

Bioadhesive strength of the tablets was measured using modified physical balance. Bioadhesion studies were performed in triplicate and average bioadhesive strength was determined. From the bioadhesive strength, force of adhesion was calculated [8].

Force of adhesion (N) = (Bioadhesive strength/1000) X 9.81

In-Vitro Mucoadhesion/Retention Time Determination

The in vitro retention time is one of the important physical parameter of buccal mucoadhesive tablet. The adhesive tablet was pressed over excised goat mucosa for 30 sec after previously being secured on glass slab and was immersed in a basket of the dissolution apparatus containing around 750 ml of

phosphate buffer, pH 6.8, at 37°C. The paddle of the dissolution apparatus as adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The time for complete erosion or detachment from the mucosa was recorded [9, 10].

In-Vitro Swelling Studies

The swelling rate of buccoadhesive tablets was evaluated using 1% w/v agar gel plate. For each formulation 3 tablets were weighed and average weight of each 3 tablets was calculated (W_1). The tablets were placed with the core facing the gel surface in 5 Petri dishes (each containing 3 tablets) which were placed in an incubator at 37±0.1°C. Three tablets were removed at time intervals of 0.5, 1, 2, and 4 and 6 hours, excess water on the surface was removed carefully using filter paper and swollen tablets were weighed [11], the average weight (W_2) was determined and then swelling index was calculated using the formula:

% Swelling index = $[(W_2-W_1)/W_1]$ X 100

Moisture absorption

Moisture absorption study: Agar (5%, m/V) was dissolved in hot water. It was transferred into petri dishes and allowed to solidify. Six buccal tablets from each formulation were placed in a vacuum oven overnight prior to the study to remove moisture, if any, and laminated on one side with a water impermeable backing membrane. They were then placed on the surface on the surface of the agar and incubated at 37 ºC for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated [12].

Stability Studies of Rabeprazole Sodium Buccoadhesive Tablets in Human Saliva

The human saliva was collected and filtered. The tablets from each batch were immersed in 5 ml of human saliva and placed in a temperature-controlled oven at 37ºC ± 0.2ºC for 6 hours. At regular time intervals (0, 1, 2, 3, and 6hours), the stability of the RBEs buccoadhesive tablet was then evaluated by its appearance, such as color and shape, and RBEs content [13].

In-Vitro Drug Release Studies

USP type II rotating paddle method was used to study the drug release from the bi-layer tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release study was performed at 37 ± 0.5°C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The glass slide was placed at the bottom of the dissolution vessel. 10 ml samples were withdrawn at predetermined time intervals (1 hour) and replaced with fresh medium. The samples were filtered through Whattman filter paper no.42 and analyzed after appropriate dilution by UV Double beam spectrophotometer at 280 nm [14].

In- Vitro Permeation Test

This test was carried out in the Franz diffusion cell, where the lower compartment was filled with artificial saliva, while the upper compartment was filled with 1ml of a pH 7.4 phosphate buffer. The amount of drug permeated through goat buccal mucosa was determined by extracting the whole solution of the upper compartment. The samples transferred into volumetric flasks were stored in a refrigerator until they were analyzed [15].

Table 2: Observed physical parameters of buccoadhesive tablet

Formulation Code	Weight Uniformity (mg) (n=20)	Thickness(mm) (n=10)	Hardness (Kg/cm^2) (n=3)	% Friability (n=3)	% Drug Content (n=3)
F1	197±1.2	3.7±0.1	4.75±0.23	0.56±0.08	98.55±0.2
F2	199±1.4	3.6±0.2	4.60±0.56	0.55±0.06	99.12±0.9
F3	202±0.6	3.8±0.1	6.20±0.24	0.32±0.03	97.56±0.6
F4	196±1.3	3.7±0.2	5.32±0.30	0.36±0.04	101.5±0.4
F5	199±0.8	3.7±0.1	4.40±0.15	0.44±0.05	99.22±0.8
F6	199±1.2	3.7±0.1	6.50±0.22	0.32±0.08	98.6±0.9
F7	198±2.2	3.6±0.1	5.30±0.30	0.35±0.06	100.5±0.3
F8	202±1.4	3.7±0.1	6.55±0.74	0.46±0.03	97.5±0.4
F9	202±0.2	3.8±0.2	7.65±0.56	0.22±0.04	97.8±0.2
F10	198±1.9	3.6±0.3	7.54±0.65	0.21±0.05	99.8±0.6
F11	201±0.1	3.6±0.2	6.70±0.24	0.23±0.08	102.7±0.5
F12	199±1.4	3.7±0.4	7.55±0.32	0.22.±0.06	98.8±0.3
F13	199±1.3	3.8±0.1	7.65±0.56	0.23±0.08	100.2±0.2
F14	197±1.2	3.7±0.2	6.71±0.65	0.21±0.06	97.6±0.4

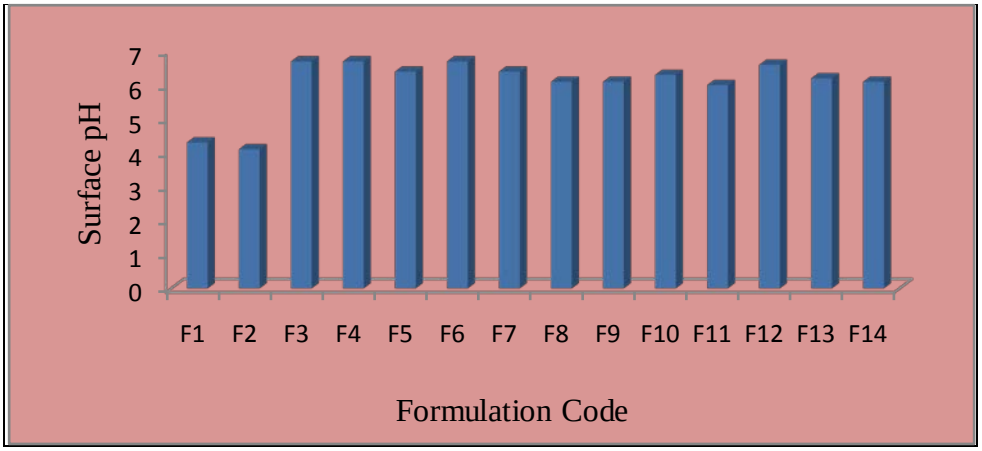
RESULTS AND DISCUSSION

The average weight of tablet was found to be between 196.0 mm to 202.0 mm and maximum % deviation was found to be ±1.2 from all formulations. The thickness of all the tablets was found to be between 3.6 mm to 3.8 mm and % deviation in thickness was found to be 0.02 to 0.18. Percent drug content was found to be between 102.7% and 97.5%. Thus all tablets comply with I.P. standard.

Surface pH

The surface pH of all formulations was found in between 6.0 to 6.7 except F1 and F2 which were showing pH less than 5 because of carbopol and hence even it has bioadhesive property it cannot be used alone in buccal mucoadhesive formulations. These results reveal that formulations provide an acceptable pH in the range of salivary pH (5.5-7.0) cannot produce irritation to the buccal mucosa. Tablets containing Olibanum Gum show more hardness in comparison to Xanthum Gum & Carbopol alone. The hardness of tablets increased with increase in percentage of Olibanum Gum. It is well known that a high concentration of a plasto-elastic binding agent leads to an increase in plastic deformation of the formulation and subsequently to the formation of more solid bonds, resulting in tablets with more resistance to fracture and abrasion [16]. Results are shown in (**Fig.1**).

Fig 1: Graphical representation of surface pH of mucoadhesive formulation F1-F14



Bioadhesive strength

Bioadhesive performance & in vitro retention time is one of the important physical parameter of buccal mucoadhesive tablet. The results shows that F3, F4, F5 tablets shows lower in vitro retention time of 3 hours, while the Olibanum Gum tablets show the longer retention time of greater than 8 hours. The Bioadhesive Strength of tablet was dependent on the property of the bioadhesive polymers, which on hydration adhere to the mucosal surface & also on the concentration of polymer used. For In-vitro Retention time, the results shows that F3, F4, F5 tablets shows lower in vitro retention time due to erosion and faster fragmentation within 3 hours.

The highest adhesion force i.e. highest strength of the mucoadhesive bond was observed with the formulation F1 & F2 containing only carbopol , this followed by F11,F14 & F10,F13 formulations containing CP:OG (3:1) & CP:OG (1:1) alone & with permeation enhancer (Sodium deoxycholate) respectively.

The reason for such findings might be ionization of Carbopol at salivary pH which leads to improved attachment of the device to mucosal surface. Adhesion force decreased as another polymer is mixed with Carbopol. Results are shown in (**Fig.2**).

Fig 2: Graphical representation of bioadhesive strength of mucoadhesive formulation F1-F14

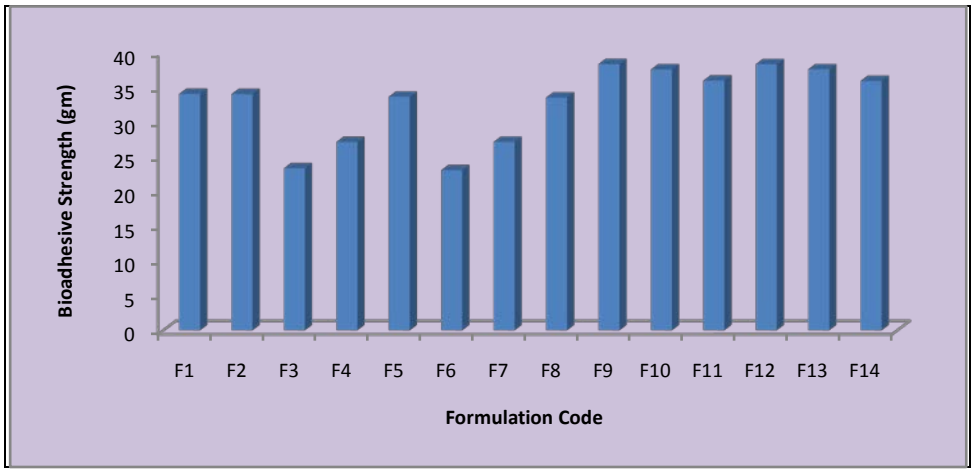
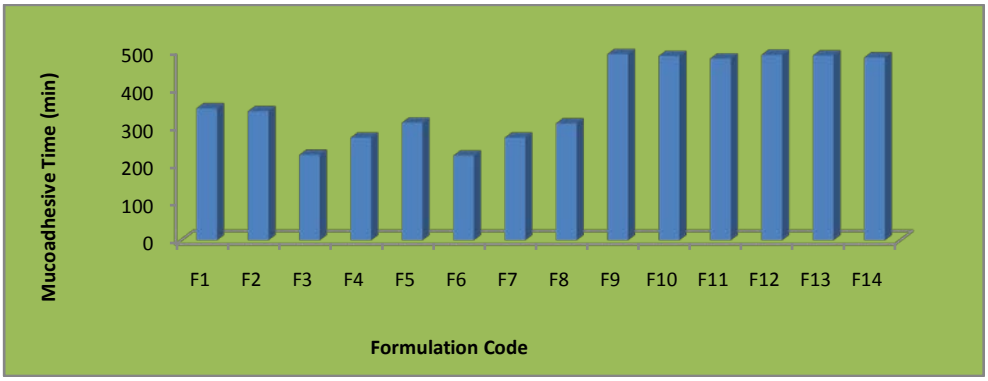


Fig. 3: Graphical representation of bioadhesive strength of mucoadhesive formulation F1-F14



Swelling index

Swelling Index was calculated with respect to time. The Swelling Index increased as the weight gain by the tablets increased proportionally with rate of hydration. Swelling Index measurement could be done upto 3 hours with formulations containing Xanthum Gum, because it loses its shape and size at the end of 3 hours. The F3, F4, F5 were shown the % swelling index in the range of 48-53% in 4 hours. This is because Xanthum Gum dissolves in water & thereby gets eroded to greater extent. Swelling Index of Olibanum Gum was less than that of Carbopol & Xanthum Gum; suggesting its moderate swellability. CP & XG at the ratio 1:3 exhibited the highest swelling index (53%). The optimized bilayered tablets (F13) had a 45.5% Swelling Index after 4 hours. Swelling is one of the primary characteristics for a polymer to be bioadhesive. However, excessive swelling due to over hydration always leads to the formation of a slippery surface. Hence retention of dosage forms at the site of application is practically impossible. Results are shown in (**Table 3**).

Moisture absorption

Formulation containing carbopol alone absorbed more moisture in comparison to other formulation. Order of increasing moisture absorption was Olibanum gum < Xanthum gum < Carbopol (**Table 3**). This may be due to more hydrophilic nature of Carbopol. Results are shown in (**Table 3**).

Table 3: % Swelling index of formulations F1-F14

Formulation Code	% swelling Index			Moisture absorbed (%)
	1h	2h	4h	
F1	169.54	223.54	307.54	18.25
F2	169.49	222.86	306.25	18.08
F3	64.97	193.64	109.57	12.83
F4	123.5	98.49	54.97	13.61
F5	152.53	113.78	49.04	15.31
F6	64.55	192.14	109.51	12.09
F7	123.10	99.21	54.86	13.52
F8	151.56	113.70	48.52	15.17
F9	158.42	212.19	298.78	9.85
F10	141.47	206.75	256.73	10.73
F11	139.92	197.25	244.17	12.60
F12	158.56	212.76	298.89	9.69
F13	140.97	206.02	257.22	11.02
F14	140.52	197.98	244.42	12.79

Stability study

All of the tablets were acceptable with respect to color and RBEs concentration shown in (**Table 4**).

Table 4: ***Stability data of buccoadhesive tablets in normal human saliva***

Sampling Time (hours)	Color Change	Thickness (mm)	Change in Shape Diameter (mm)	Drug Recovered (%)
0	No	3.8	9.00	98.37
1	No	3.9	9.17	98.51
2	No	4.0	9.75	97.47
3	No	4.2	10.43	97.54
6	No	4.5	11.21	98.34

In-vitro drug release

Drug release rate was increased with increasing amount of hydrophilic polymer (**Fig. 4, 5, 6 & 7**) reveal that the maximum cumulative % release of RBE from formulation F1 & F2 could be attributed to ionization of CP at pH environment

of the dissolution medium. Ionization of CP leads to the development of negative charge along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counterion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the high water uptake. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate. Formulations F3, F4, F6 and F7 showed relatively high rate of release of RBE which is due to rapid swelling & erosion of Xanthum Gum. Further the increase in rate of drug release could be explained by the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release of the highly soluble drug. Moreover, the hydrophilic polymers would leach out & hence, create more pores & channels for the drug to diffuse out of the device. Thus higher concentration of Xanthum Gum cannot be incorporated into such formulations for sustaining the release.

The release of RBE was decreased with increasing concentration of Olibanum Gum. The possible reason for observed reduction in total drug release may be the interaction between two oppositely charged bioadhesive polymer i.e. OG & CP. It may be expected that interpolymer complex between carboxylic group of CP & hydroxyl group of OG will be formed & complex formation may retard the dissolution rate. C-934 is highly cross-linked polymers that swell in water & do not disintegrate upon 24 hours.

To examine further the release mechanism of RBE from buccoadhesive tablets, the result were analyzed according to the equation [17].

$$\frac{Mt}{M\infty} = Kt$$

The obtained value of n lie between 0.5 and 1.0 in all formulations for the release of RBE sodium, indicating non- Fickian release kinetics, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation.

Fig. 4: In vitro drug release study of RBEs formulations (F1-F4)

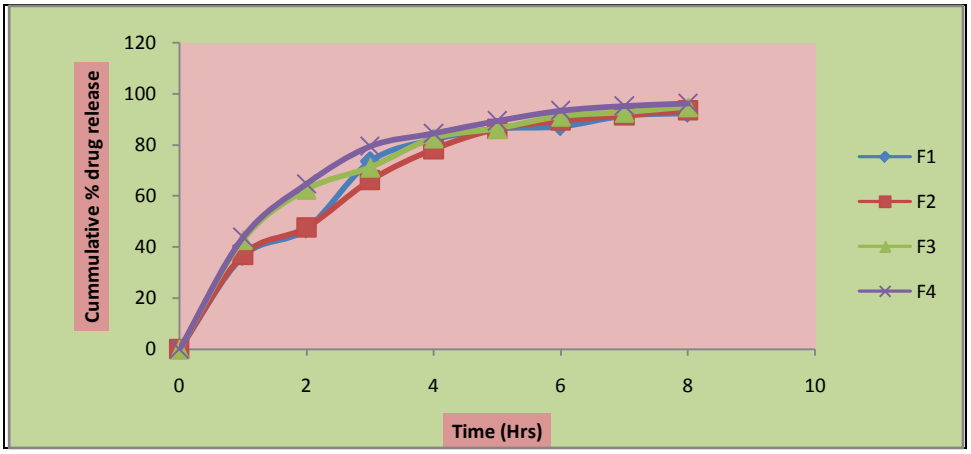


Fig 5: In vitro drug release study of RBEs formulations (F5–F8)

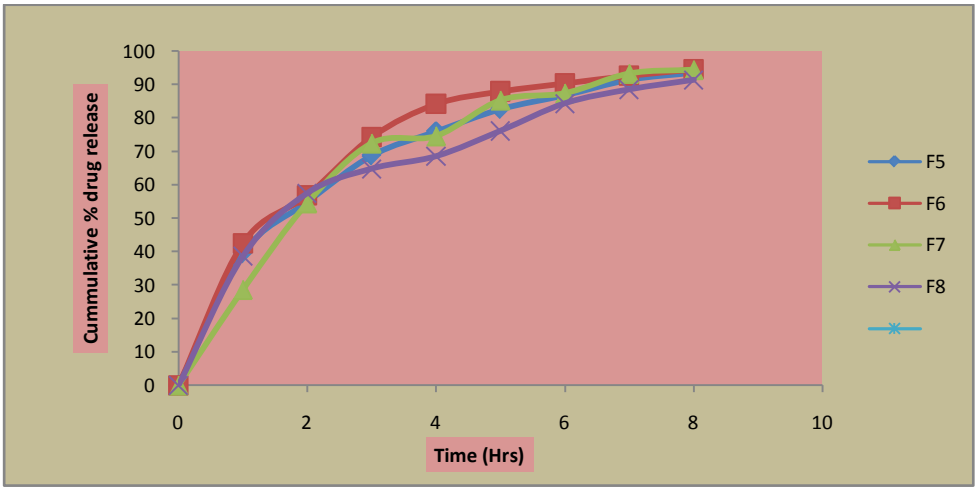


Fig 6: In vitro drug release study of RBEs formulations (F9-F12)

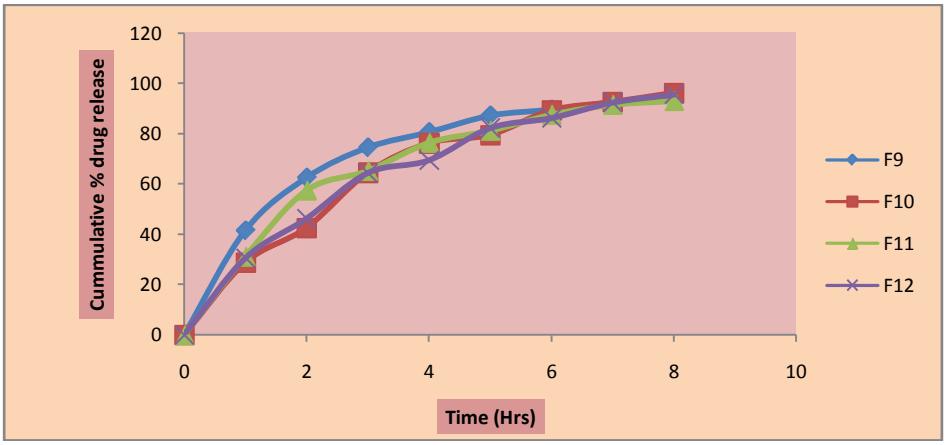
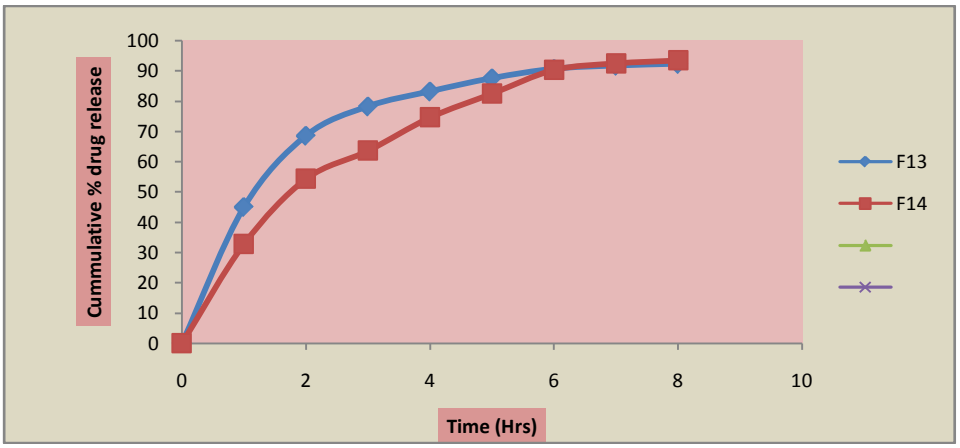


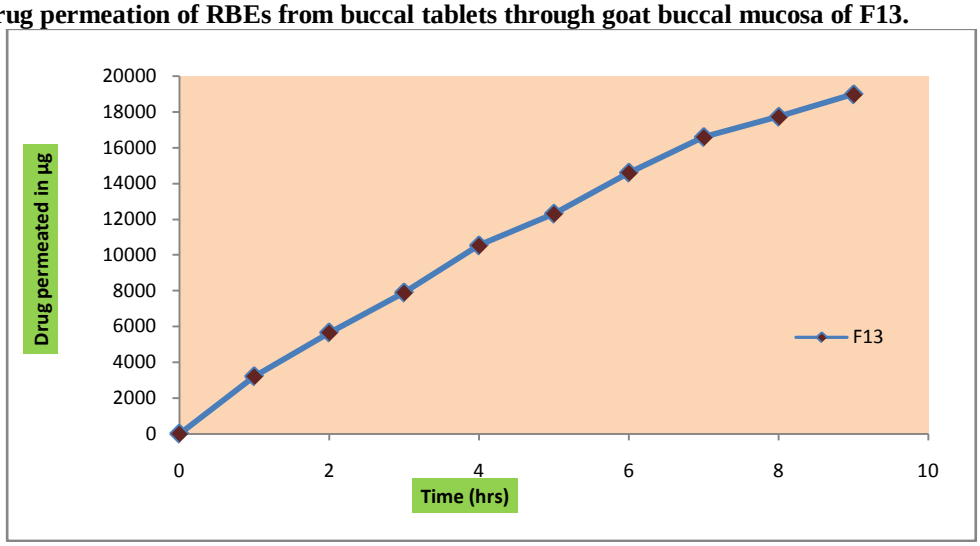
Fig 7: In vitro drug release study of RBEs formulations (F13-F14)



In vitro permeation study

The result of in vitro permeation study (**Fig 8**) shows that the formulation F13 having a polymer combination of Carbopol-934: Olibanum Gum (1:1) has higher permeation flux (7.93 ± 0.26 µg h^{-1} cm^{-2}) and permeation coefficient (1.84 ± 0.07) than the other formulation.

Fig 8: In vitro drug permeation of RBEs from buccal tablets through goat buccal mucosa of F13.



CONCLUSION

Buccoadhesive system for the controlled release of RBEs was developed by using CP, XG and OG in different ratios. The formulation F13 containing CP & OG 1:1 in combination with Sodium deoxycholate showed suitable release kinetics and properties for adhesion to the buccal mucosa and was free of any interaction between polymers and drug.

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