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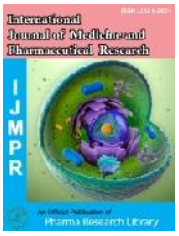

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Bilayered Buccal Tablets of Ondansetron Hydrochloride: II an *In-vitro* and Ex vivo Evaluation

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A B S T R A C T

Buccoadhesive tablets of Ondansetron hydrochloride (OH) were prepared using HPMC K4M and Carbopol 934 as mucoadhesive polymers and ethyl cellulose to act as an impermeable backing layer. Twelve formulations were developed with varying concentrations of polymers. The formulations were prepared by direct compression and characterized by different parameters such as weight uniformity, content uniformity, thickness, hardness, disintegration, swelling index, in vitro drug release studies, mucoadhesive strength, and ex vivo permeation study. The result of the in vitro release studies and permeation studies through bovine buccal mucosa revealed that complexed Ondansetron gave the maximum release and permeation. Optimized formulation characterized by FTIR, results showed no evidence of interaction between the drug and polymers.

Key words: Buccoadhesive tablet, mucoadhesion, Ondansetron hydrochloride, FTIR

A R T I C L E I N F O

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1. Introduction

Bioadhesive drug delivery necessitates the use of bioadhesive polymers as a means of prolonging the residence time of the dosage form on the absorbing membrane as well as localizing drugs in a particular region.

In this study a large variety of polymers in different combinations were used. The combinations of polymers were preferred because it could offer acceptable adhesion and biocompatibility properties. The selection of polymer and optimization of the formulation both from adhesion and controlled drug release point of view remain an important goal and challenge for development of a buccal dosage form [1]. Alternative routes of administration including intravenous, rectal, transdermal and nasal routes have been attempted to improve the systemic bioavailability of Ondansetron HCl, as these routes can allow the drug to reach the systemic circulation, bypassing the liver and escaping first-pass metabolism.The above advantage makes buccal drug delivery is an alternative route of administration for the drugs, which are undergoes first pass effect. Ondansetron HCl undergoes first-pass metabolism in the liver. This is the reason for lower bioavailability of Ondansetron HCl [2].

Odansetron is a selective 5-hydroxytryptamine type 3 (5-HT3) receptor antagonist used to treat chemotherapy- and radiotherapy-induced nausea and emesis The mean bioavailability of ondansetron in humans is about 60%. In general, emesis is preceded by nausea and in such a condition, ingestion of conventional dosage forms with water leads to vomiting and expulsion of a portion or the entire dose administered. Thus, it is beneficial to administer ondansetron as an oral drug therapy (ODT) dosage form [3].

Direct compression is simplest method of tablet manufacture as it required less equipments, has minimum processing steps, reduced labor cost. It is a dry process hence deterioration of active ingredient has been prevented. Further advantage of direct compression is that tablets disintegrate into their primary particles rather than granular aggregates. The resultant increase in surface area available for dissolution results in faster drug release. The direct-compression process is highly influenced by powder characteristics such as flowability, compressibility, and dilution potential. Difficulty in getting suitable excipients with high functionality creates opportunities for the formulation scientists to develop newer grades of existing excipients. Developing newer grades of existing excipients with varying physicochemical properties has been carried out by using techniques referred as “Coprocessing” or “Particle Engineering” of excipients. Co-processing is a novel phenomenon of developing a new single-bodied excipient by interacting two or more excipients at sub-particle level with an objective to provide a synergy of functionality improve [4].

Bioadhesive polymers such as Carbopol 934P, hydroxypropyl methylcellulose (HPMC K4M) are suitable for use in buccal adhesive preparations because when hydrated with water, they can adhere to the oral mucosa and withstand salivation, tongue movements and swallowing for a significant period of time. HPMC and Ethyl cellulose (EC) have been used as principal excipients to achieve adhesion to the oral mucous membrane and to control the drug release from the tablet. The main objective of the present study was to formulate a bilayered bioadhesive buccal tablet of Ondansetron HCl to prolong the residence time of the buccal tablet, which ensures satisfactory drug release in a unidirectional way to the mucosa, thus avoiding loss of drug due to wash out with saliva. The mucoadhesive buccal tablets were evaluated by weight uniformity, content uniformity, thickness, hardness, swelling index, in vitro drug release studies, mucoadhesive strength, and ex vivo permeation study. The mucoadhesive buccal tablet was compared for drug release and mucoadhesive study for both ondansetron hydrochloride with non-bitter taste base ondansetron and complexes of ondansetron.

2. Materials and Methods

Ondansetron HCl and Carbopol 934 P were gift samples from Zydus Cadila, Ahmedabad, India. Hydroxy propyl methyl cellulose K4 M obtained from AET laboratories, Hyderabad, India. Ethyl cellulose, Microcrystalline cellulose and Mannitol from Vilin Biomed Ltd, Roorkee, India. Spray dried lactose and Aspartame from Dr Reddy’s laboratories, Hyderabad, India.

Preparation of bilayered buccal tablets

Bilayered buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.40, except lubricant all the ingredients were thoroughly blended in a glass mortar with pestle for 15 min. After sufficient mixing lubricant was added and again mixed for additional 2-3 min. Preparation involves two steps, first the mixture is compressed using 8 mm flat faced punch on 16 stages rotary tablet compress machine. Then upper punch is raised and the backing layer of ethyl cellulose is placed on above compact then two layers are compressed again to get bilayered buccal tablet [5]. Composition of the prepared bioadhesive buccal tablet formulations of Ondansetron HCl were given in Table 1.

Evaluation of buccal tablets [6]

All prepared buccal tablets were evaluated for uniformity of weight and drug content, as per I.P. method. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness were measured by Vernier caliper.

Disintegration test :

The test was performed for buccal tablets which are not having backing; six tablets were taken randomly from each batch and placed in USP disintegration apparatus baskets. Apparatus was run for 4 hr and the basket was lift from the fluid, observe whether all of the tablets have disintegrated (USP NF, 2004).

Measurement of bioadhesion strength:

Bioadhesive strength of the tablets was measured on a modified physical balance [7].The apparatus consisted of a modified double beam physical balance in which a lighter pan had replaced the right pan and the left pan had been replaced by a glass slide (4 cm length and 2.5 cm width) with plastic hang suspended by Teflon rings and copper wire. The left-hand side of the balance was exactly 5 g heavier than the right side .The height of the total set up was adjusted to accommodate a glass container of 6.6cm height. All parts of modified physical balance were shown in Figure 1. In order to find out the bioadhesion strength first buccal tablet (n=3) was stacked to the glass slide with the help of knob, which was situated at the base of physical

balance. Now five grams weight from the right pan was then removed. This lowered the glass slide along with the tablet over the membrane with a weight of 5.0 g. This was kept undisturbed for 5 min. Then the weights on the right-hand side were slowly added in increments of 0.1 g till the tablet just separated from the membrane surface. The excess weight on the right pan, i.e. total weight minus 5g was taken as a measure of the bioadhesive strength.

Fig 1: Bioadhesion strength apparatus

Determination of the ex vivo residence time:

The ex vivo residence time was determined using a locally modified USP disintegration apparatus [8, 9] as shown in Figure 2. The disintegration medium was composed of 800 mL pH 6.6 phosphate buffer maintained at 37◦C. The porcine buccal tissue was glued to the surface of a glass slab, vertically attached to the apparatus. The buccal tablet was hydrated from one surface using 0.5 mL of pH 6.6 phosphate buffer and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to run in such a way that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the tablet from the mucosal surface was recorded. The experiments were performed in triplicate (n=3) and mean of triplicate was determined.

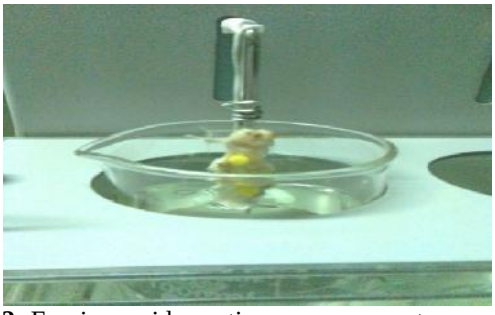

Fig 2: Ex vivo residence time measurement apparatus

Swelling Studies:

Buccal tablets were weighed individually [10] (designated as W1) and placed separately in Petri dishes containing 15 mL of phosphate buffer (pH 6.6) solution. At regular intervals (1, 2, 3, 4, 5, 6, 7 and 8 hr), 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 (W2). This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following equation

$$\text{Swelling index} = (W2-W1)/W1\times100$$

Surface pH Study:

The bioadhesive tablet was allowed to swell by keeping it in contact with 1 mL of distilled water for 2 hr at room temperature [11]. 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.

In vitro drug release of buccal tablets:

The United States Pharmacopeia (USP) XXIII rotating paddle method was used to study the drug release from the buccal tablets. The dissolution medium consisted of 200 mL of phosphate buffer pH 6.6. The release was performed at 37oC ± 0.5oC, with a rotation speed of 50 rpm [12]. The backing layer of buccal tablet was attached to the glass slide with instant adhesive (cyanoacrylate adhesive). The slide was placed in to the bottom of the dissolution vessel. Samples (5 mL) were withdrawn at predetermined time intervals and replaced with fresh medium. Dissolution for the conventional marketed product was conducted without glass slide. The samples were filtered through filter paper and analyzed after appropriate dilution by UV spectrophotometer at 310 nm.

Ex vivo permeation of buccal tablets:

Ex vivo permeation study of buccal tablets through the porcine buccal mucosa was performed using Franz-type diffusion cell at 37°C ± 0.2°C and 50rpm. This temperature and rpm was maintained by using 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. The epithelium was separated from underlying connective tissues with surgical scissors and clamped between donor and receiver chambers of the Franz-type diffusion cell. After the buccal membrane was equilibrated for 30 min with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh pH 7.4 buffer solution [13]. The buccal tablet was placed in donor chamber and 1mL of buffer solution (pH 6.6) was added [14]. Aliquots (5 mL) were collected at predetermined time intervals and filtered through a filter paper, and the amount of drug permeated through the buccal mucosa was then determined by measuring the absorbance at 310 nm using a UV spectrophotometer. The medium of the same volume (5 mL), which was prewarmed at 37°C, was then replaced into the receiver chamber. The experiments were performed in triplicate (n = 3) and mean value was used to calculate the flux, permeability coefficient.

Fourier transmitted infrared spectroscopy (FTIR) studies: The infrared absorption spectra of the samples were analyzed using an FTIR spectrophotometer pure drug and optimized tablets were prepared by compressing the samples with potassium bromide. The peak variation absorption between 400 and 4000cm-1 was detected and interpret the result.

3. Results and Discussion

All blend formulations were successfully compressed into tablets and all tablet formulations were within the

acceptable range of uniformity of weight, thickness, friability, content uniformity and hardness. The average weight of the tablet was found to be between 148.1 and 158.1 mg. Hardness of the tablets for all the formulations was found to be between 3.8 and 67.7 kg/cm^2. Percentage of drug content for all formulation was found to be between 98.75% and 101.10%. Surface pH of all the formulations was found to be between 5.99 and 7.18, which were within the acceptable salivary pH range (5.5–7.0). It was conducted that the tablets would produce no local irritation to the mucosal surface. All the results were shown in Table 2.

Measurement of bioadhesion strength

This evaluation test was conducted for all formulations; there is a gradual increase in bioadhesion strength from F1to F12. The maximum bioadhesion strength (35.9 g, 39 g) was found for formulations F20 and F16. Bioadhesion strength is depends on molecular weight and swelling behavior of the polymers, contact time with mucus [15]. The bilayered tablets containing higher proportions of carbopol showed good bioadhesion strength for 5min contact time. In all the formulations, as the polymer concentration increased, both the peak detachment force and work of adhesion increased, the reason for such findings might be ionization of CP at salivary pH, which leads to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region, while other polymers undergo superficial bioadhesion [16]. The optimized tablet (F20) showed 38.9±0.08 g of bioadhesion strength. Bioadhesion strength values of all the formulations represented in Table 3.

Ex vivo residence time

Ex vivo residence time for all the formulations varied from 3-11 hr. The optimized formulation (F20) showed 10.5±0.43 hr. The difference could be due to the combination of various amounts of polymers, which affects the mucoadhesion. In fact with bilayered tablets containing higher proportion of carbopol the mucoadhesion time was found to be increased. This is because of the high mucoadhesive nature of the carbopol and inter penetration of polymeric chains in to the mucus membrane. Ex vivo residence time and bioadhesion strength values were given in Table 3.

Swelling Studies of buccal tablets

Appropriate swelling property of a buccal device is essential for uniform and prolonged release of drug and proper mucoadhesion [17, 18]. In formulations containing HPMC K4M, (F16) shows swelling index of 3.25; within the formulations containing HPMC K4M, (F20) shows high swelling index of 3.02; The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. Results indicate that as the concentration of Carbopol 934P increases the swelling index increases. Swelling index values of all the formulations were given in Table 5. Swelling behavior of buccal tablets of all formulations as a function of time is shown in Figure 3a-3c.

In vitro drug release of buccal tablets

An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time [19]. In vitro drug release studies revealed that the release of ondansetron HCl from different formulations varies with characteristics and composition of matrix forming polymers as shown in graphs. The release rate of ondansetron HCl decreased with increasing concentration of HPMC K15M. These findings are in compliance with the ability of these cellulose derivatives to form complex matrix network which leads to delay in release of drug from the device. Carbopol is more hydrophilic, it can swell rapidly, and therefore decrease of carbopol content delays the drug release [20]. Formulations with spray dried lactose and mannitol showed higher percentage drug release values compared to MCC, this is because of the water soluble diluents (spray dried lactose and mannitol) can absorb more water and swell and then release the drug rapidly compared to that of water insoluble diluent (MCC) that retards the release. Data of the in vitro release was fit into different equations and kinetic models to explain the release kinetics of carvedilol from buccal tablets. The kinetic models used were zero-order equation, first-order equation, Higuchi and Korsemeyer-Peppas models. The results indicate that as the concentration of each polymer increases in the respective series, peppas mechanism turns to zero-order release profile. Drug release rate was increased with increasing amount of hydrophilic polymer.

The maximum cumulative percent release of ondansetron HCl (89.1±0.4%) from formulation F16 and F20 found to release (83.2±0.6%) could be attributed to ionization of carbopol at pH environment of the dissolution medium. Ionization of carbopol leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. This is because as the proportion of these polymers in the matrix increased, there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional pathlengths. When the thickness of the gelled layer and thus the diffusional pathlengths remain constant, zero-order release can be expected. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device. All the results were shown in the in the Table 4. The comparison of cumulative percent drug release of all formulations was shown in Figure 4a-4c.

Fourier transmitted infrared spectroscopic studies

FTIR study revealed that (Figure 5&6), in pure ondansetron HCl the keto group(1638 cm-1), tertiary amine (3411cm-1), C-C stretching (3175cm-1, 2909cm-1, 2721cm-1) gave peaks at respective wave numbers. In optimized formulation (F8) also same groups showed peaks very nearer to those wave numbers. From this it was concluded that there was no interaction between drug and excipients.

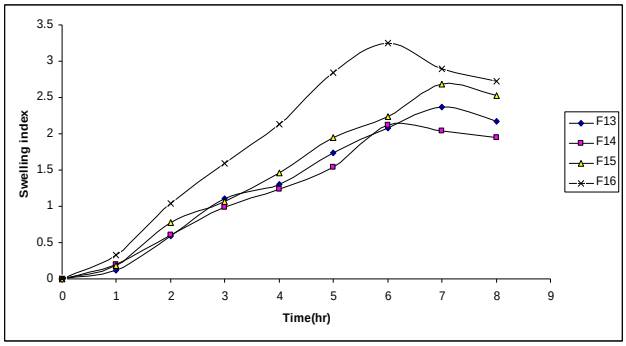

Fig 3a: Swelling index profile of Ondansetron HCl buccal tablets formulated with mannitol as diluents

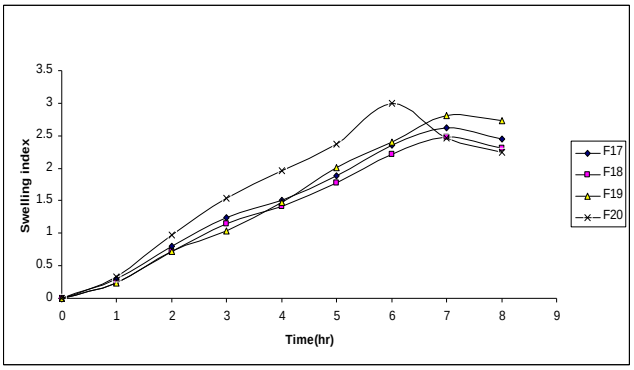

Fig 3b: Swelling index profile of Ondansetron HCl buccal tablets formulated with spray dried lactose as diluents

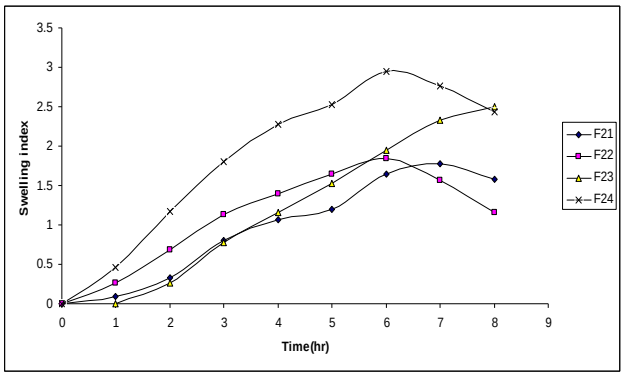

Fig 3c: Swelling index profile of Ondansetron HCl buccal tablets formulated with MCC as diluents

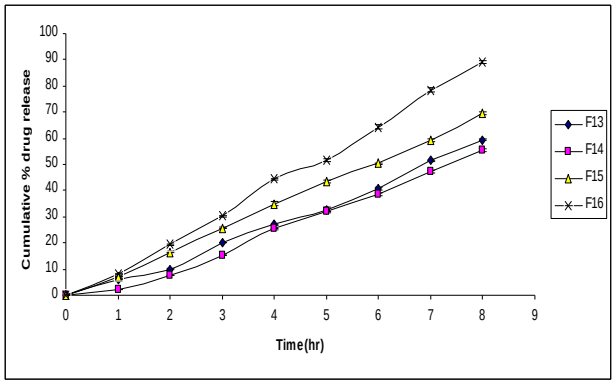

Fig 4a: In-vitro drug release profile plot of Ondansetron HCl buccal tablets formulated with mannitol as diluent
Acute toxicity study

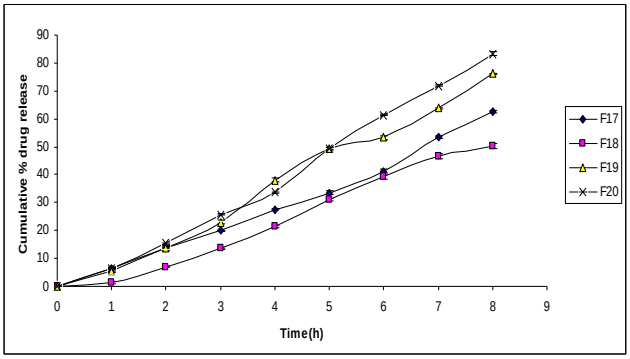

Fig 4b: In-vitro drug release profile plot of Ondansetron HCl buccal tablets formulated with spray dried lactose as diluents

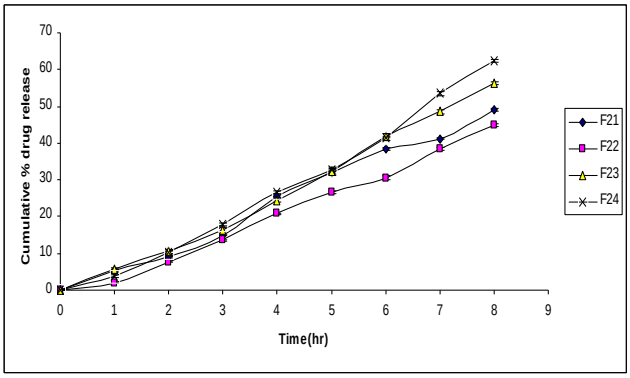

Fig 4c: In-vitro drug release profile plot of Ondansetron HCl buccal tablets formulated with MCC as diluents

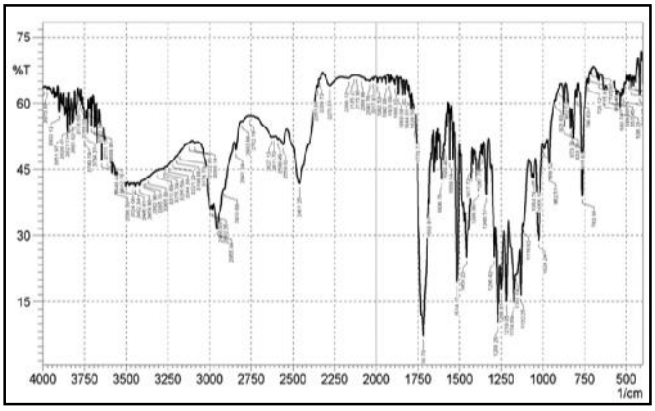

Fig 5:FTIR spectra of Ondansetron HCl

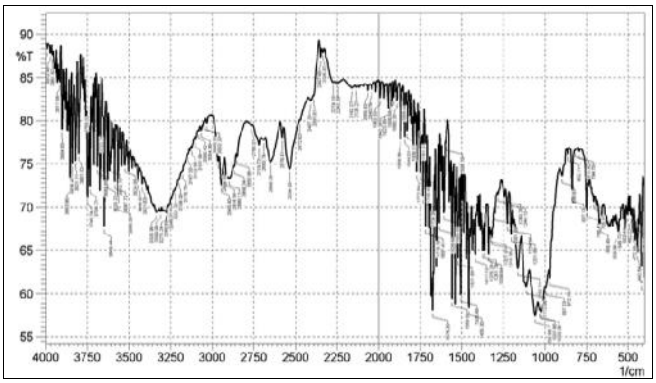

Fig 6: FTIR spectra of optimized formulation

Table1: Composition of formulations containing CP: HPMC K4M with different diluents

Ingredients(mg/tablet)	Formulation code											
	F13	**F14**	**F15**	**F16**	**F17**	**F18**	**F19**	**F20**	**F21**	**F22**	**F23**	**F24**
Ondansetron HCl	8	8	8	8	8	8	8	8	8	8	8	8
Carbopol-934	30	20	40	45	30	20	40	45	30	20	40	45
HPMC K4M	30	40	20	15	30	40	20	15	30	40	20	15
Mannitol	30	30	30	30	-	-	-	-	-	-	-	-
Spray dried lactose	-	-	-	-	30	30	30	30	-	-	-	-
MCC	-	-	-	-	-	-	-	-	30	30	30	30
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Ethyl cellulose(backing)	50	50	50	50	50	50	50	50	50	50	50	50
Total weight(mg)	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Table 2: Physical properties of the Ondansetron HCl buccal tablets formulated with HPMC K4M

Formulation code	Thickness (mm)	Weight Variation(mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug content	Surface pH
F13	2.64±0.024	158.1±0.50	0.12	5.0 ±0.05	100.94	6.81±0.050
F14	2.64±0.110	149.2±0.30	0.42	6.5±0.08	99.75	7.05±0.070
F15	2.69±0.020	150.0±0.35	0.08	6.4±0.12	99.66	6.33±0.050
F16	2.51±0.024	152.8±0.25	0.06	7.7±0.10	100.62	6.86±0.005
F17	2.61±0.032	151.8±0.55	0.12	3.8±0.08	98.75	6.84±0.020
F18	2.35±0.030	150.3±0.50	0.25	5.5±0.21	99.16	6.89±0.025
F19	2.54±0.005	157.3±0.30	0.31	4.7±0.04	98.98	7.18±0.085
F20	2.66±0.020	155.9±0.45	0.24	6.5±0.14	100.11	5.99±0.010
F21	2.69±0.015	149.2±0.55	0.28	5.1±10.12	99.63	6.66±0.095
F22	2.63±0.060	148.1±0.70	0.42	5.2±0.24	101.10	6.85±0.030
F23	2.74±0.025	159.9±0.80	0.18	6.4±0.07	99.55	6.82±0.070
F24	2.75±0.070	153.1±0.55	0.09	7.6±0.04	99.56	6.66±0.080

Table 3: Bioadhesive strength and ex vivo residence time of Ondansetron HCl buccal tablets with HPMC K4M

Formulation Code	Bio adhesion Strength (gm)	*Ex vivo* residence Time (hr)
F13	17.2±0.19	4.75±0.20
F14	18.2±0.09	4.25±0.30
F15	26.1±0.05	7.82±0.10
F16	38.0±0.14	8.75±0.20
F17	19.8±0.04	4.05±0.25
F18	19.1±0.13	4.12±0.15
F19	27.0±0.24	7.25±0.35
F20	35.9±0.08	10.5±0.43
F21	19.0±0.07	3.65±0.62
F22	20.6±0.34	4.85±0.16
F23	27.4±0.15	7.14±0.23
F24	37.0±0.18	8.72±0.42

Table 4: In-vitro dissolution kinetics parameters of Ondansetron HCl buccal tablets formulated with HPMC K4M

Formulation code	Correlation coefficient (R^2)				'n' value
	Zero order	First order	Higuchi	Peppas model	
F16	0.9547	0.8013	0.8565	0.9126	0.977
F20	0.9887	0.9203	0.8643	0.9856	1.124

Table 5: Swelling index profile of Ondansetron HCl buccal tablets containing CP:HPMC K4M

Time (hr)	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
0	0	0	0	0	0	0	0	0	0	0	0	0

1	0.12	0.19	0.18	0.33	0.29	0.24	0.23	0.33	0.09	0.26	0.26	0.46
2	0.59	0.61	0.77	1.03	0.79	0.72	0.71	0.98	0.32	0.68	0.77	1.16
3	1.10	0.98	1.06	1.59	1.23	1.14	1.03	1.53	0.80	1.12	1.15	1.79
4	1.29	1.24	1.46	2.13	1.50	1.40	1.46	1.96	1.07	1.39	1.53	2.28
5	1.73	1.53	1.94	2.84	1.88	1.77	2.00	2.36	1.19	1.64	1.94	2.52
6	2.08	2.11	2.24	3.25	2.35	2.21	2.39	3.02	1.64	1.83	2.33	2.95
7	2.37	2.04	2.68	2.90	2.62	2.47	2.80	2.46	1.77	1.56	2.52	2.76
8	2.17	1.95	2.52	2.73	2.45	2.31	2.72	2.23	1.58	1.16	2.25	2.43

4. Conclusion

HPMC K4M shows satisfactory buccoadhesive properties. Formulation F20 using this polymer in a drug: polymer: polymer (1:3:1) ratio showed significant bioadhesive properties with an optimum release profile and could be useful for buccal administration of ondansetron HCl. From the results, it was concluded that the in vitro drug release, bioadhesion strength, ex vivo residence time of the optimized formulation (F20) is suitable for buccal delivery. The release pattern followed non-fickian diffusion with Zero order release. FTIR studies concluded that there was no interaction between drug and excipients.

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