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FORMULATION AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILMS OF RANITIDINE HYDROCHLORIDE

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ABSTRACT

Delivery of the desired drug as mucoadhesives drug delivery systems has been subject of interest since last three decades. The various advantages associated with these systems made the buccal drug delivery as a novel route of drug administration. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver. The present investigation highlights the formulation and evaluation of mucoadhesive buccal films of Ranitidine Hydrochloride. The mucoadhesive buccal films of Ranitidine were prepared by solvent casting technique using polymers like hydroxyl propyl methyl cellulose E15 (HPMC E15) and carbopol 934P alone or in combination. The formulated films were evaluated for their physiochemical parameters like surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, water vapor transmission rate, thickness, weight of the films, folding endurance and drug content. In vitro release studies were performed with pH 6.8 phosphate buffer solution. The films exhibited controlled release more than 12 h. The best mucoadhesive performance and matrix controlled release was exhibited by the formulation A2 and A6. The formulation was found to be right and suitable candidate for the formulation of ranitidine buccal film for therapeutic use.

INTRODUCTION: Transmucosal route of drug delivery involves the delivery of the drug through the mucosal linings of the nasal, rectal, vaginal, ocular, and oral cavity. Amongst these oral cavity is a novel site for drug delivery. The oral mucosa has been investigated in several studies as a means to give both local and systemic amounts of drug. Drug delivery across the oral mucosa, can be divided into three different types sublingual delivery, buccal delivery, local delivery.

The buccal region offers an attractive route for systemic drug delivery for extended periods of time. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. Over the last two decades mucoadhesion becomes of interest for its potential to optimize localized drug delivery, by retaining a dosage form at the site of action or absorption site. Mucoadhesion may be defined as a state in which two materials, one of which mucus or a mucous membrane, is held together for extended period of time [1]. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses liver and avoids presystemic elimination in the gastro intestinal tract and liver [2].

These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. Ranitidine is a competitive inhibitor of histamine H2- receptors, drug of choice in the treatment of ulcer and Zollinger Ellision syndrome and readily absorbed from gastro intestinal tract [3].

The bioavailability of ranitidine following oral administration is about 50 % which might be due to colonic degradation by colonic bacteria [4].

The bioavailability of ranitidine is markedly lower from the human colon than the upper part of gastro intestinal tract. Various attempts have been made to develop the formulation of mucoadhesive buccal films of ranitidine for improving and enhancing bioavailability in a controlled release fashion. It may also be possible to avoid the first pass effect and presystemic elimination in the gastro intestinal tract and liver. The present investigation highlights the formulation and evaluation of mucoadhesive buccal films of Ranitidine Hydrochloride. The mucoadhesive buccal films of Ranitidine were prepared by solvent casting technique using polymers like hydroxy propyl methyl cellulose-E15 and carbopol-934P alone or in combination.

MATERIAL AND METHOD: Ranitidine hydrochloride was a gift sample from Ranbaxy Laboratories Ltd., Hyderabad, India. HPMC K15, Carbopol 934P, Propylene glycol and Ethanol were purchased from Loba chem Pvt. Ltd, Mumbai. All other ingredients used were of analytical grade.

Formulation of Ranitidine Hydrochloride Buccal Films: The films were prepared by the method of solvent casting Technique [5, 6]. Accurately weighed HPMC E15, and Carbopol 934P alone or in combination was added to magnetically stirred solvent system (ethanol) containing propylene glycol (which served the purpose of plasticizer as well as penetration enhancer) continuous stirring is necessary to prevent lump formation. Then drug was added to the above solution and stirred.

The solution was then transferred quantitatively to glass ring kept on the surface of mercury in petri-plates. The petri-plates were covered with inverted funnels to allow controlled evaporation of solvent. These were left undisturbed at room temperature (20-35^{o}C) for 1-2 days. The dried films were separated. Then the formulations were stored in desiccator until further use (**table 1**).

TABLE 1: FORMULA OF RANITIDINE HYDROCHLORIDE MUCOADHESIVE BUCCAL PATCHES

Formulation code	Drug	Carbopol934P	HPMC E15	Propylene glycol	Ethanol
A1	150 mg	75mg	----	0.5ml	12ml
A2	150mg	100mg	----	0.5ml	12ml
A3	150mg	----	75mg	0.5ml	12ml
A4	150mg	----	100mg	0.5ml	12ml
A5	150mg	100mg	100mg	0.5ml	12ml
A6	150mg	150mg	50mg	0.5ml	12ml
A7	150mg	50mg	150mg	0.5ml	12ml

Evaluation of Buccal Films (table 2):

Film weight: For evaluation of film weight three films of every formulation were taken and weighed individually on a digital balance. The average weights were calculated.

Thickness: The thickness of the buccal films was measured using a screw gauge micrometer with at least count of 0.01 mm at different spots of the films. The thickness was measured at five different spots of the film and average was taken.

Swelling index: The films were coated on the lower side with ethyl cellulose (to avoid sticking to the dish) then weighed and placed separately in petriplates containing 25 ml of distilled water. The dishes were stored at room temperature. An increase in the weight of the patch was noted in 15 min intervals for 60 min and the weight was calculated. The swelling percentage was calculated by using the following formula,

$$\text{Swelling index} = \frac{wt - w0}{w0} \times 100$$

Where, wt - the weight of swollen film after time t, w0 - weight of film at zero time zero.

Surface pH of films: Buccal patches were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed distilled water under stirring and then pouring the solution into a petri-plate till gelling at room temperature. The

surface pH was measured by means of a pH paper placed on the surface of the swollen patch.

Percentage Moisture Absorption: The percentage moisture absorption test was carried out to check the physical stability of the buccal films at high humid conditions. Three 1cm diameter films were cut out and weighed accurately then the films were placed in desiccator containing saturated solution of aluminium chloride, keeping the humidity inside the desiccator at 79.5 %. After 3 days the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found.

Percentage moisture absorption= $\frac{\text{final weight}-\text{initial weight}}{\text{initial weight}} \times 100$

Percentage moisture loss: Percentage moisture loss was also carried to check the integrity of films at dry condition. Three 1cm diameter films was cut out and weighed accurately and kept in desiccator containing fused anhydrous calcium chloride. After 3 days the films were removed, weighed. Average percentage moisture loss of three films was found out.

Percentage moisture loss= $\frac{\text{initial weight}-\text{final weight}}{\text{initial weight}} \times 100$

Folding Endurance: Folding endurance of the film was determined by repeatedly folding one patch at the same place till it broke or folded manually, which was considered satisfactory to reveal good film properties. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

Drug Content Uniformity: A film was cut into three pieces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, suitably diluted and analyzed at 313nm in a UV Spectrophotometer. The average of drug content of three films was taken as final reading.

TABLE 2: PHYSIOCHEMICAL EVALUATION OF BUCCAL FILMS

Evaluation parameters	FORMULATION CODE						
	A1	A2	A3	A4	A5	A6	A7
Weight variation (mg)	29.20±1.17	34.10± 1.31	32.10±1.13	32.15±1.17	24.91±1.16	26.21±1.14	31.01±1.14
Thickness of film (mm)	0.272±0.0037	0.284±0.0033	0.292±0.0024	0.232±0.0025	0.243±0.0027	0.292±0.0024	0.310±0.0033
Swelling index (%)	62.90±0.85	65.6±0.55	78.24±1.37	87.96±1.02	60.09±1.02	60.9±1.34	69.98±0.02
Surface pH	6.56±0.152	6.66±0.152	6.63±0.115	6.60±0.173	6.56±0.115	6.55±0.115	6.56±0.115
% Moisture absorbance	2.93±0.092	2.88±0.09	3.84±0.015	3.88±0.115	2.13±0.120	2.01±0.066	2.27±0.124
% Moisture loss	1.22±0.01	1.02±0.02	1.42±0.01	1.24±0.01	1.98±0.04	1.65±0.03	1.78±0.06
Folding endurance	94±12	96±13	102±25	108±12	99±12	95±13	98±11
Drug content (%)	98±1.0	98.9±0.291	99.92±0.11	99.16±0.291	99.50±0.50	99.96±0.057	99.6±0.08

Mucoadhesive strength [7]**:** Mucoadhesive strength of the patch was measured on a modified physical balance. The fresh sheep buccal mucosa was cut in to pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a glass vial, which was filled completely with phosphate buffer pH 6.8. The glass vial was placed and tightly fitted in the center of glass beaker. The phosphate buffer (pH 6.8, 37±10^{o}C) was filled in the glass beaker just touches the mucosal surface. The patch was stuck to the lower side of rubber stopper with cyanoacrylate adhesive. Two pans of the balance were balanced with 5 gm weight on the right hand side pan. A weight of 5 gm was removed from the right hand side pan, which lowered the pan along with the patch over the mucosa. The balance was kept in this position for 5 min. contact time. The water (equivalent to weight) was added slowly with infusion set (100 drops/min.) to the right-hand side pan until the patch detached from the mucosal surface. The weight in grams required to detach the patch from the mucosal surfaces gave the measure of mucoadhesive strength. Results are shown in **Table 3**.

TABLE 3: MUCOADHESIVE STRENGTH OF ALL FORMULATION

Formulation code	A1	A2	A3	A4	A5	A6	A7
Mucoadhesive strength	9±0.47	12±0.40	5±0.40	7±0.30	10±0.34	11±0.37	8±0.42

***In vitro* release study** [8]**:** The drug release studies were performed with USP dissolution test apparatus (Paddle method). The USP dissolution apparatus was thermostated at the temperature of 37±5°C and stirred at rate of 50 rpm. Film was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper face. Then the slide has immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution. The aliquots of 5 ml were withdrawn at the time interval of every hour and replaced with equal volume of dissolution medium. The sink condition was maintained throughout the study. The samples were analyzed at 313 nm in a UV-VISIBLE Spectrophotometer and cumulative amount of drug release at various time intervals was calculated.

Stability studies of Patches: The films (A2, A6) were kept at different temperatures (4°, 25°, and 40°) for two months. The samples were observed for physical appearance, weight variation, thickness, and drug content. The results of the stability studies are shown in **Table 4, 5 & 6**.

TABLE 4: STABILITY STUDIES OF FORMULATION AT 4°C

Formulations	A1				A6			
Period (days)	0	15	30	60	0	15	30	60
Physical appearance	TC	TC	TC	TC	TC	TC	TC	TC
Weight variation (mg)	34.10	34.08	34.06	34.06	26.21	26.21	26.21	26.20
Thickness (mm)	0.284±0.0033	0.284±0.0030	0.284±0.0028	0.284±0.0020	0.292±0.0024	0.292±0.0028	0.292±0.0028	0.292±0.0030
Drug content (%)	98.9±0.291	98.9±0.280	98.0±0.290	98.0±0.290	99.96±0.057	99.95±0.050	99.95±0.057	99.95±0.040

*TC- Transparent Colorless

TABLE 5: STABILITY STUDIES OF FORMULATION AT 25°C

Formulations	A1				A6			
Period (days)	0	15	30	60	0	15	30	60
Physical appearance	TC	TC	TC	TC	TC	TC	TC	TC
Weight variation (mg)	34.10	34.09	34.10	34.08	26.21	26.23	26.21	26.21
Thickness (mm)	0.284±0.0033	0.282±0.0028	0.280±0.0028	0.282±0.0020	0.292±0.0024	0.294±0.0020	0.291±0.0025	0.290±0.0030
Drug content (%)	98.9±0.291	98.0±0.280	97.0±0.292	96.0±0.290	99.96±0.057	99.82±0.040	98.90±0.067	98.65±0.020

*TC- Transparent Colorless

TABLE 6: STABILITY STUDIES OF FORMULATION AT 40°C

Formulations	A1				A6			
Period (days)	0	15	30	60	0	15	30	60
Physical appearance	TC	TC	TC	CO	TC	TC	CO	CO
Weight variation (mg)	34.10	34.10	34.11	34.12	26.21	26.21	26.21	26.21
Thickness (mm)	0.284±0.0033	0.275±0.0028	0.270±0.0022	0.268±0.0022	0.292±0.0024	0.294±0.0028	0.294±0.0028	0.294±0.0030
Drug content (%)	98.9±0.291	98.5±0.282	98.0±0.292	97.0±0.280	99.96±0.057	99.80±0.046	97.90±0.028	97.65±0.020

*TC- Transparent Colorless. *CO- Colorless to Opaque

RESULTS AND DISCUSSION: The mucoadhesive buccal films of Ranitidine hydrochloride were prepared by solvent casting technique using polymers like HPMC E15 and Carbopol 934P alone or in combination. Ethanol is used as the solvents. Propylene glycol was used as the plasticizer as well as penetration enhancer. The prepared Ranitidine hydrochloride buccal films were evaluated or characterized based upon their physicochemical characteristics like thickness, weight variation, swelling percentage, surface pH, folding endurance and drug content, percentage moisture

absorption, percentage moisture loss and in-vitro drug release.

All the patches have uniform thickness throughout. Average thickness was found to be in the range of 0.232 to 0.310 mm.

Drug loaded patches (1x1cm^2) were tested for uniformity of weight. The patches were found to be uniform. The average weight of the patch was found to be in the range of 24.91 to 34.10 mg.

The swelling of the patches were observed via agar plate method and shown in Table 2. These results were in agreement with the increase in area due to swelling. The swelling state of the polymer was reported to be crucial for its bioadhesive behavior. Swelling index was found to be proportional to HPMC E15 and inversely proportional to Carbopol 934P. Addition of certain amount of hydrophilic polymers increased surface wetability and consequently water penetration within the matrix. Patch A4 showed highest % swelling index (87.96%) due to higher amount of HPMC E15. Concentration of Carbopol 934P had positive effect on % swelling index, as the concentration of the Carbopol is increased in the case of patch A2, the % swelling index get increased.

Considering the fact that acidic or alkaline pH may affect or cause the irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films were determined by using suitable means. The all prepared formulation of ranitidine buccal film showing the pH range within the range of salivary pH i.e. 6.5 to 6.8. The observed surface pH of the formulation A1, A2, A3, A4, A5, A6, and A7 was 6.56, 6.66, 6.63, 6.60, 6.56, 6.55, and 6.56 respectively. The results are found that there is no significant difference of surface pH in all the formulation.

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for percentage moisture absorption (PMA) and percentage moisture loss (PML). The observed results of PMA and PML were shown in the Table 2. The observed PMA was in order of A4>A3>A7>A5>A6>A1>A2. Amongst all the formulation the high value of PMA can be observed in A4 and A3 this is due to the increasing swelling behavior of HPMC. PML was found in the order of A3>A4>A5>A7>A6>A1>A2 due to the high degree of hydration of mucoadhesive polymer like HPMC. So the formulation having only HPMC shows high PML than the formulation having HPMC and Carbopol.

The folding endurance was measured manually, by folding the film repeatedly at a point till they broke. The number of times of film could be folded at the same place without breaking gave the value of the folding endurance. Hence the breaking time was taken at the end point. The folding endurance was found to be highest for A4.

Mucoadhesive strength was found to be the best for formulation A2 containing Carbopol. Results indicated that the effect of Carbopol 934P is more significant than HPMC K15 and the higher concentration of Carbopol 934P had a positive effect on in vitro mucoadhesive strength.

In vitro drug release studies were performed for all the prepared formulation by using phosphate buffer pH 6.8 as dissolution medium and measuring drug concentration UV spectrophotometrically at 313nm. The studies were performed up to 12 h. The results of *in vitro* studies are shown in the **figure 1**. The graph was plotted by taking Cumulative percentage release Vs Time. It indicated that the drug release was higher in HPMC than HPMC-Carbopol combination at pH 6.8.

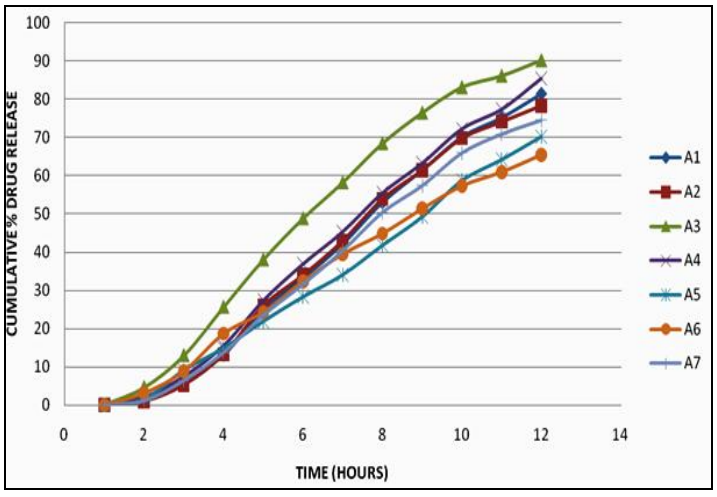

FIG. 1: *IN VITRO* DRUG RELEASE PROFILE OF ALL FORMULATION

An increase in the polymer (Carbopol 934P) content was associated with a corresponding decrease in the drug-release rate. The drug release was observed to be

sustaining with increasing the incorporation of higher amount of Carbopol 934P in patch A2. This could be due to the extensive swelling of the polymers, which created a thick gel barrier for drug diffusion. Formulation containing Carbopol and HPMC in combination shows better release profile then used alone.

Finally, mucoadhesive buccal films (A2, A7) were subjected to stability studies which were carried out in order to ascertain the chemical and physical stability of the formulations. No marked changes in the respective properties like physical appearance, weight variation, thickness and drug content of formulations were observed at storage temperature of 4°C, 25°C and 40°C.

CONCLUSION: The buccal films of Ranitidine hydrochloride were prepared by using Carbopol 934P and HPMC E15 alone or in combination and the buccal films were evaluated or characterized based upon their physicochemical characteristics like Surface pH, Percentage moisture absorbance, and Percentage moisture loss, swelling percentage, Thickness, Weight variation, Folding Endurance and drug content. Good results were obtained for both physicochemical characteristics and in vitro studies. So, it can be concluded that such mucoadhesive patches of HPMC K15 and Carbopol 934P could be a good carrier in buccal delivery of Ranitidine.

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