

# Preparation and Evaluation of a Novel Buccal Adhesive System

Submitted: February 3, 2004; Accepted: April 29, 2004.

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## ABSTRACT

The aim of the present study was to prepare and evaluate a novel buccal adhesive system (NBAS) containing propranolol hydrochloride (PH). A special punch was fabricated and used while preparing an NBAS. Solubility of PH in phosphate buffer solution (pH 6.6), partition coefficient between phosphate buffer (pH 6.6) and 1-octanol, and permeability coefficient through the porcine buccal mucosa were performed and found to be 74.66 mg/mL, 5.17, and 5.6, respectively. Stability of NBAS was determined in natural human saliva, and it was found that both PH and device are stable in human saliva. NBAS was evaluated by weight uniformity, thickness, hardness, friability, swelling, mucoadhesive strength, in vitro drug release, and in vivo human acceptability studies. Swelling index was higher (4.4) for formulations containing hydroxyl propyl methyl cellulose (HPMC) K4M alone, and it decreases with its decreasing concentration in the NBAS. Mucoadhesive strength (MS) was measured by using a modified apparatus. All NBASs showed higher MS with porcine buccal mucosa when compared with that of rabbit buccal mucosa. NBASs containing carbopol (CP) 934P and HPMC K4M at the ratio of 1:1 showed higher MS (44.76 g) with porcine buccal mucosa when compared with 1:2 (39.76 g), 0:1 (23.29 g), and 1:0 (22.22 g) ratios, respectively. The mechanism of PH release was found to be by non-Fickian diffusion (value of "n" between 0.5 and 1.0) and followed first order kinetics. In vivo human acceptability study showed that the newly prepared NBAS was comfortable in the human buccal cavity. It can be concluded that NBAS is a superior, novel system that overcomes the drawback associated with the conventional buccal adhesive tablet.

**KEYWORDS:** buccal delivery, carbopol 934P, HPMC K4M, propranolol hydrochloride, mucoadhesion.

## INTRODUCTION

In recent years, delivery of therapeutic agents through various transmucosal routes has gained significant attention owing to their presystemic metabolism or instability in the acidic environment associated with oral administration.<sup>1-5</sup> The oral mucosa can be categorized into sublingual, gingival, and buccal mucosa through which oral transmucosal delivery can be achieved. Absorption of therapeutic agents from the oral cavity provides a direct entry of such agents into the systemic circulation, thereby avoiding the first-pass hepatic metabolism and gastrointestinal degradation.<sup>6-8</sup> However, the buccal route of drug delivery has received much more attention because of its unique advantages over other oral transmucosal routes.<sup>7,9-10</sup>

Delivery of various therapeutic agents via the buccal route using conventional matrix tablets, films, bilayered systems, and hydrogel systems has been studied and reported by several research groups.<sup>11-16</sup> A number of formulation and processing factors can influence properties and release properties of the buccal adhesive system. The conventional buccal adhesive tablets have some limitations: (1) conventional tablets may not have a uniform adhesive layer, leading to weak adhesion; and (2) because of nonuniform adhesive and backing layers, the release of drug may not be unidirectional.<sup>17</sup> Technically, an ideal buccal adhesive system must have the following 3 properties: (1) maintains its position in the mouth for a few hours, (2) releases the drug in a controlled fashion, and (3) provides drug release in a unidirectional way toward the mucosa.<sup>7,17</sup> In regard to the first requirement, strong adhesive contact of the system with buccal mucosa can be established if a system having a uniform adhesive surface is prepared using appropriate combinations of the mucoadhesive polymers. Furthermore, by using similar polymers at appropriate ratios, the second requirement can also be achieved. The third requirement can be fulfilled by preparing a system having uniform adhesive and backing layers.<sup>7,17</sup> Various buccal adhesive dosage forms, such as discs, microspheres, and bilayered tablets, have been thoroughly prepared and reported by several research groups.<sup>11-17</sup> However, limited studies exist on novel devices that are superior to those of conventional buccal adhesive systems for the delivery of therapeutic agents through buccal mucosa.

This study reports a novel system for buccal drug delivery. The principal aim was to prepare and evaluate a NBAS. The

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study mainly focuses on the preparation of the system using a special punch and in vitro evaluation parameters. The effect of loading dose along with sustained release dose on the controlled release behavior of the drug has been also examined using sustained release tablets. PH is a nonselective beta-adrenergic blocking agent used in the treatment of hypertension, angina pectoris, and many other cardiovascular disorders. PH is subjected to an extensive and highly variable hepatic first-pass metabolism following oral administration, with a reported systemic bioavailability of between 15% and 23%.<sup>18-19</sup> Therefore, it was chosen as a model drug candidate.

## MATERIALS AND METHODS

### Materials

PH (99% purity) was received as a gift sample from Sigma Laboratories (Mumbai, India). CP 934P and HPMC K 4M were also received as a gift samples from BPRL (Bangalore, India). All other chemicals were either reagents or analytical grade and were used as received. Double-distilled water was used throughout, and its purity was checked by comparing its density and conductivity with the literature values, which agreed well.

### Methods

#### *Solubility Studies*

The solubility of PH in phosphate buffer solution (pH 6.6, an average pH of oral cavity) was determined at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ . Briefly, an excess amount of PH was added into 20-mL screw-cap tubes containing 10 mL of phosphate buffer (pH 6.6). Tubes were constantly agitated under 150 rpm speed at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$  for 24 hours using an automatic shaking water bath (Jeiotech, Kyunggi-do, Republic of Korea). After 24 hours, the solution was passed through a 0.2- $\mu$  filter, and the amount of PH was solubilized was then estimated by measuring the absorbance at 290 nm using a UV spectrophotometer (Shimadzu 1601PC, Kyoto, Japan). The standard curve for PH was established in phosphate buffer (pH 6.6) and from the slope of the straight line the solubility of PH was calculated.<sup>20</sup> The studies were repeated in triplicate ( $n = 3$ ), and mean was calculated.

#### *Partition Coefficient Studies*

The partition coefficient of PH between phosphate buffer solution (pH 6.6) and 1-octanol was determined at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ . Briefly, an excess amount of PH was added into the 100-mL volumetric flask containing 50 mL of equivalent mixture of phosphate buffer solution (pH 6.6) and 1-octanol and placed in an automatic shaking water bath for 24 hours. Then, both phases were separated and filtered through a

0.2- $\mu$  filter, and the amount of PH solubilized in each phase was determined by measuring the absorbance at 290 nm using a UV spectrophotometer. The partition coefficient PH was calculated from the ratio between the concentration of PH in organic and aqueous phases.<sup>21</sup>

#### *In Vitro Permeation Through Porcine Buccal Mucosa*

In vitro permeation studies of PH through the porcine buccal mucosa was performed using Franz-type diffusion cells at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ . Porcine buccal mucosa was obtained from a local slaughterhouse and used within 3 hours of slaughter. The tissue was stored in Krebs buffer at  $4^{\circ}\text{C}$  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. The temperature was maintained at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$  by a jacket surrounding the receiver chamber that was stirred with a magnetic bead. After the buccal membrane was equilibrated with Krebs buffer solution between both the chambers, the receiver chamber was filled with fresh Krebs buffer solution (pH 6.6), and the donor chamber was charged with a known volume of PH solution, 4.5 mg/mL. Aliquots (5 mL) were collected at a preset time (every hour for 6 hours) and filtered through a 0.2- $\mu$  filter, and the amount of PH permeated through the buccal mucosa was then determined by measuring the absorbance at 290 nm using a UV spectrophotometer. The dissolution medium of the same volume (5 mL), which was prewarmed at  $37^{\circ}\text{C}$ , was then replaced into the diffusion cell.<sup>22</sup> The experiments were performed in triplicate ( $n = 3$ ) and mean value was used to calculate the permeability coefficient.

#### *Design and Fabrication of a Special Punch*

A new punch (11 mm) was fabricated by making a 2-mm protrusion in available 11-mm flat-faced punch as shown in Figure 1. However, the lower punch (11 mm) remained flat faced.

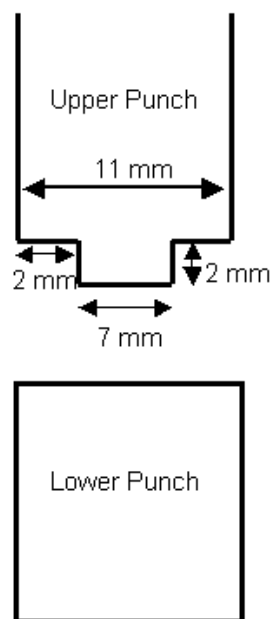
#### *Preparation of NBAS*

The preparation process of NBAS is shown by schematic representation (see Figure 2). The new method mainly involves 3 steps: (1) formation of core, (2) formation of buccal adhesive cup, and (3) formation of NBAS. The composition of core (fast and sustained release layers) and adhesive cups along with polymer ratios are presented in Table 1. All ingredients were passed through American Society for Testing Materials (ASTM) sieve no. 100 and blended separately in a mortar. The core (fast and sustained release layers) was prepared using an electrically operated Cadmach single-station punching machine (Cadmach, Ahmedabad, India).

**Table 1.** Composition of Core Layer and Buccal Adhesive Cup Along With Their Formulation Code\*

Ingredients (mg)	Formulation Code			
	F1	F2	F3	F4
Fast release layer				
Propranolol hydrochloride	2	2	2	2
D-mannitol	30	30	30	30
Lactose	18	18	18	18
Sustained release layer				
Propranolol hydrochloride	8	8	8	8
CP 934P	30	15	10	-
HPMC K4M	-	15	20	30
Lactose	12	12	12	12
Adhesive cup layer				
CP 934P	155.5	72.5	51.83	-
HPMC K4M	-	72.5	103.66	155.5
Magnesium stearate (3% wt/wt)	4.5	4.5	4.5	4.5
CP 934P:HPMC K4M ratio	1:0	1:1	1:2	0:1

\*CP 934P indicates carbopol 934P; and HPMC K4M, hydroxyl propyl methyl cellulose.



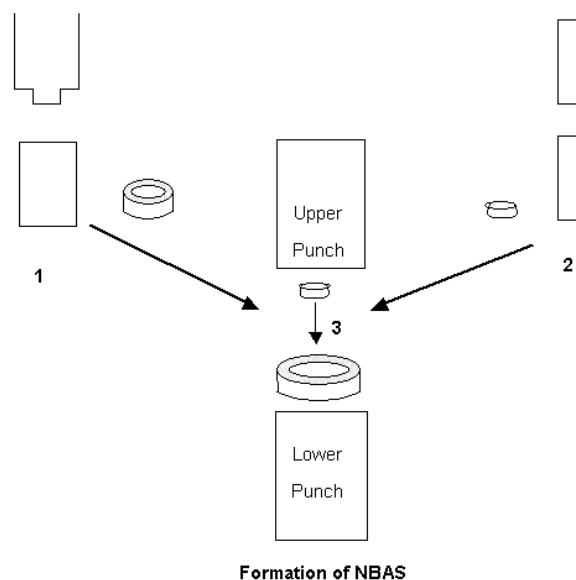
**Figure 1.** Cross-sectional view of the special punch.

The punching machine, equipped with 7-mm flat-faced punches and dies, was used for preparing the core. Then, buccal adhesive cups were prepared by using the same punching machine equipped with special punch and flat-faced punch as upper and lower punches, respectively (see Figure 3). Finally, buccal adhesive cups were placed in an 11-mm die cavity and core was inserted into the cup and then compressed using 11-mm flat-faced upper and lower punches to obtain NBAS. The cross-sectional view of an NBAS is shown in Figure 4. In addition, sustained release buccal adhesive tablets of PH (10 mg of PH mixed with CP 934P and HPMC K4M at similar ratios as shown in Table 1) were prepared in a similar manner to compare the release behavior of PH with that of NBAS. Various formulations were pre-

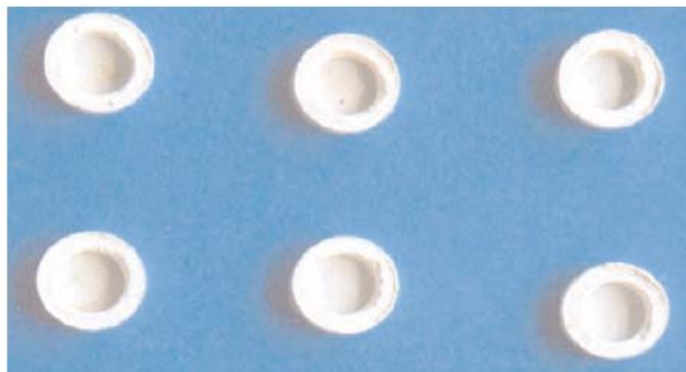
pared by varying the ratio of CP 934P and HPMC K4M to choose the effective formulation.

#### Evaluation of Physical Properties of NBAS

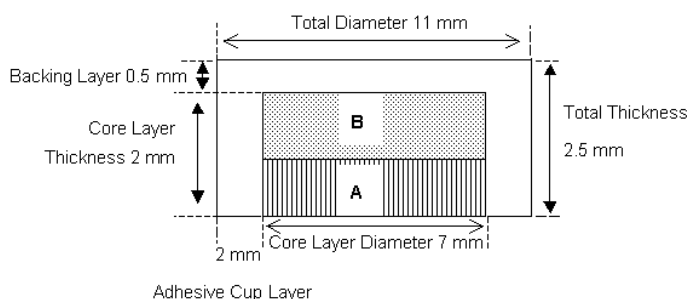
NBASs were examined for weight uniformity, thickness uniformity, hardness, and friability in a similar manner as stated for conventional oral tablets. The obtained values of these properties were then compared with the values of limit stated in the *Indian Pharmacopoeia* for conventional oral tablets.



**Figure 2.** Schematic representation of preparation of an NBAS: (1) preparation of buccal adhesive cups using an 11-mm special punch, (2) preparation of core layer using 7-mm flat-faced punches, and (3) insertion of core into the cup and compression using 11-mm flat-faced punches to obtain NBAS.



**Figure 3.** Novel buccal adhesive cups prepared using a special punch.



**Figure 4.** Cross-sectional diagram of an NBAS consisting of fast (A) and sustained (B) release layers.

#### Swelling Studies

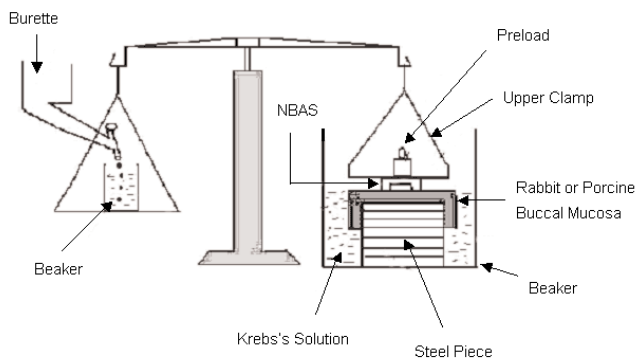
NBASs (n=3) were weighed individually (designated as  $W_1$ ) and placed separately in petri dishes containing 4 mL of phosphate buffer (pH 6.6) solution. At regular intervals (0.5, 1, 2, 3, 4, 5, and 6 hours), the NBASs were removed from the petri dishes and excess surface water was removed carefully using the filter paper. The swollen NBASs were then reweighed ( $W_2$ ), and swelling index (SI) was calculated using the following formula.

$$SI = \frac{(W_2 - W_1)}{W_1} \quad (1)$$

#### In Vitro MS Measurement

MS of NBAS with porcine and rabbit buccal mucosa was measured using a modified 2-arm balance. The design of apparatus used while measuring the mucoadhesive strength is shown in Figure 5.<sup>23</sup> Porcine buccal mucosa as well as rabbit buccal mucosa were obtained from a local slaughterhouse and stored in Krebs buffer at 4°C upon collection. The experiments were performed within 3 hours of procurement of both the mucosa. The porcine or rabbit buccal mucosa was fixed to the stainless steel piece with cyanoacrylate adhesive and then placed in a beaker. Krebs solution was added into

the beaker up to the upper surface of the buccal mucosa to maintain buccal mucosal viability during the experiments. The NBAS was attached to the upper clamp of the apparatus and then the beaker was raised slowly until contact between porcine or rabbit buccal mucosa and NBAS was established. A preload of 50 g was placed on the clamp for 5 minutes (preload time) to establish adhesion bonding between NBAS and porcine or rabbit buccal mucosa. The preload and preload time were kept constant for all the formulations. After completion of the preload time, preload was removed from the clamp, and water was then added into the beaker from the burette at a constant rate of 100 drops per minute. The addition of water was stopped when NBAS was detached from either porcine or rabbit buccal mucosa. The weight of water required to detach an NBAS from buccal mucosa was noted as MS, and these experiments were repeated with fresh mucosa in an identical manner (n = 3).



**Figure 5.** Mucoadhesive strength measurement device.

#### In Vitro Drug Release

In vitro release studies of PH were performed in phosphate buffer solution (pH 6.6, 150 mL) at 37°C using a modified dissolution apparatus.<sup>24</sup> The modified dissolution apparatus consisted of a 250-mL beaker as a receptor compartment and a glass rod attached with a grounded glass disk (2-cm diameter) as a donor tube. The back surface of NBAS or sustained release buccal tablet was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The donor tube was then dipped into the receptor compartment containing dissolution medium, which was maintained at 37°C ± 0.2°C, and stirred at a constant speed using a magnetic bead. Aliquots (5 mL each) were withdrawn at preset times (0.08, 0.16, 1, 2, 3, 4, 5, and 6 hours), filtered through a 0.2-μ filter, and then the amount of PH released was estimated by measuring the absorbance at 290 nm using a UV spectrophotometer (n = 3). The dissolution medium of same volume (5 mL) prewarmed at 37°C ± 0.2°C was replaced to maintain its constant volume and sink condition. The cumulative amount of drug release was calculated and used while plotting the release and release kinetics curves.

### Stability of NBASs

Stability studies of NBAS were performed in normal human saliva using the optimized formulation (F2) selected based on the results of swelling, release, and mucoadhesion strength studies. Briefly, the human saliva was collected from humans (aged 18-55) and filtered. NBASs were placed in separate petri dishes containing ~5 mL of human saliva and placed in a temperature-controlled oven (Jeio Tech) for 6 hours at  $37^{\circ}\text{C} \pm 0.2^{\circ}\text{C}$ . At regular time intervals (0, 1, 2, 3, and 6 hours), the NBAS was examined for change in color and shape, collapse of the NBAS, and PH content. The experiments were repeated in triplicate ( $n = 3$ ) in a similar manner.

### In Vivo Human Acceptability Study

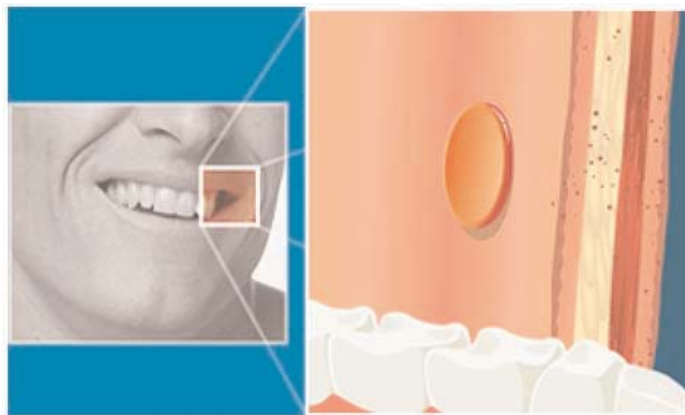
A clearance was obtained from the institutional human experimentation committee and then informed consent was obtained from all the volunteers before conducting the study. This study was conducted according to the guidelines given by the committee under the supervision of the registered medical practitioner. The study was conducted on 20 healthy human male volunteers (aged 18-55 years) using placebo NBAS. Food was prohibited from 0.5 hours before the study until its conclusion, and water was provided as needed. Volunteers were given placebo NBAS along with an instruction sheet and were instructed to press the placebo NBAS against the buccal mucosa for about 1 minute. The attachment site of NBAS to all the volunteers' buccal mucosa was as shown in Figure 6. Volunteers were then asked to record the time of insertion and time and circumstances of end of the adhesion (erosion or dislodgment of systems). After completion of the study, a questionnaire was given to volunteers to score the parameters such as irritancy, comfort, taste, dry mouth, salivation, dislodgment of the system during the study, and heaviness of the system at the place of attachment.

## RESULTS AND DISCUSSION

Solubility behavior of drugs in solution whose pH is an average pH value of the oral cavity (ie, pH 6.6), partition coefficient, and permeation through model buccal mucosa, as well as drug stability, will provide useful information before a buccal adhesive system can be developed. Solubility of PH in phosphate buffer solution (pH 6.6) and its partition coefficient between phosphate buffer solution (pH 6.6) and 1-octanol were  $74.6 \pm 2.15$  mg/mL and  $5.17 \pm 0.40$ , respectively. In vitro permeation studies of PH through porcine buccal mucosa were performed to compare the permeability coefficient with its partition coefficient. The permeability coefficient (P) of PH was calculated using Equation 2:

$$P = \frac{(dQ/dt)}{(\Delta C A)} \quad (2)$$

where  $dQ/dt$  is the cumulative amount of drug permeated per unit time;  $\Delta C$  is the concentration difference between the donor and receiver chambers; and  $A$  is surface area of buccal mucosa available for diffusion. The obtained values of flux and P of PH were  $4.23 \pm 1.2$  and  $5.60 \pm 2.1$ , respectively. The values of partition coefficient and P were almost similar. In earlier studies, Schoenwald and Hung<sup>25</sup> studied the corneal permeation of beta blocking agents through porcine buccal mucosa. In these experiments, a plateau was found for lipophilic drugs at log distribution coefficient. It is likely that there will be a plateau for drugs with a higher lipophilicity. The important role of the lipophilicity was also shown by the amount of drug remaining in the tissue after experiments, which is probably due to binding of drug in lipophilic parts of the epithelium. Since our experiments also showed good correlation between the values of partition coefficient and P, and PH is a highly lipophilic drug,<sup>18,25</sup> it can be assumed that PH absorbs through buccal mucosa by passive diffusion.



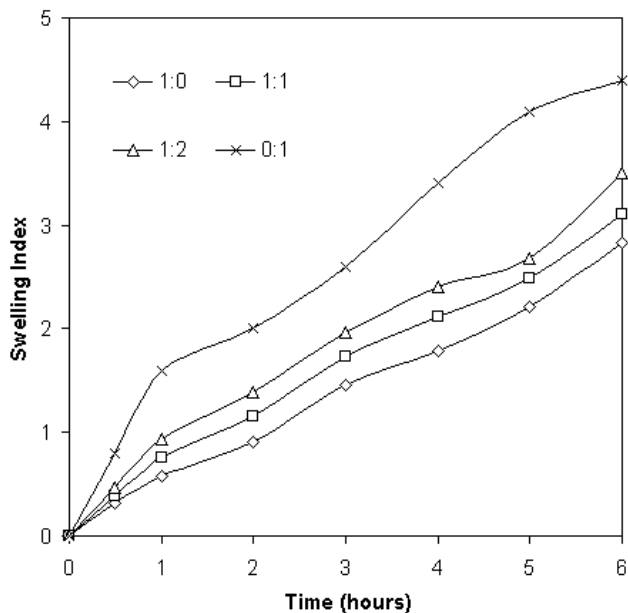
**Figure 6.** View of attachment site of NBAS in the oral cavity.

The values of variation in weight and friability were found to be within the limits of conventional oral tablets stated in the *Indian Pharmacopoeia*. Thickness of NBAS varied from 1.93 mm to 2.06 mm and complied with the theoretical value of the system as shown in Figure 4. Hardness of NBAS varied with the ratio of CP 934P and HPMC K4M and was less for formulations containing CP 934P alone. This finding may be because of the fluffy nature of CP 934P. On the other hand, formulations containing CP 934P and HPMC K4M at the ratio of 1:1 and 1:2, respectively, exhibited increased strength.

Swelling behavior of NBASs as a function of time is shown in Figure 7. Symbols represent only mean values; SD values were removed for visual clarity. Appropriate swelling behavior of a buccal adhesive system is an essential property for uniform and prolonged release of drug and effective mucoadhesion. The rate and extent of swelling increased with an

increasing concentration of HPMC K4M in the systems. Formulations containing CP 934P and HPMC K4M at the ratio of 0:1 exhibited highest SI followed by 1:2, 1:1, and 1:0 ratios, respectively. Maximum swelling was attained at the fifth hour, after which polymer started eroding slowly in the swelling medium. High amount of water uptake by HPMC K4M at a faster rate might have resulted in higher rate and extent of swelling. In earlier studies, Mahaguna et al<sup>26</sup> showed that the hydration of HPMC K4M is dependent on water-absorbing capacity and molecular weight, and that hydration increases with an increasing concentration of HPMC K4M in the buccal adhesive tablets.

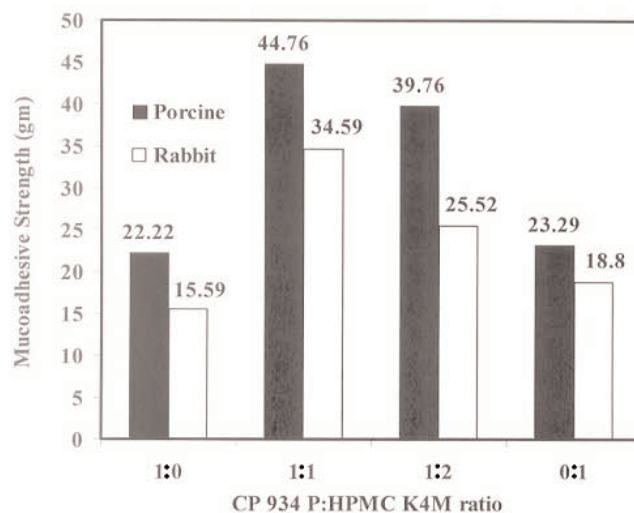
MS of NBASs with porcine and rabbit buccal mucosa as a function of CP 934P and HPMC K4M ratio is shown in Figure 8. The figure shows only the mean values of MS for clear visibility. Mucoadhesion may be defined as the adhesion between a polymer and mucus. In general, mucoadhesion is considered to occur in 3 major stages: wetting, interpenetration, and mechanical interlocking between mucus and polymer. The strength of mucoadhesion is affected by various factors such as molecular weight of the polymers, contact time with mucus, swelling rate of the polymer, and biological membranes used in the study.<sup>27</sup> In this study, porcine and rabbit buccal mucosa were used as biological membranes to investigate the effect of different biological membranes on MS. NBASs containing CP 934P and HPMC K4M at the ratio of 1:1 (F2) exhibited highest MS with both the buccal mucosa when compared with 1:2 (F3), 0:1 (F4), and 1:0 (F1) ratios, respectively. However, all the formulations exhibited higher MS with porcine buccal mucosa than with rabbit buccal mucosa. This finding can be attributed to the low amount of keratin present in the porcine buccal mucosa



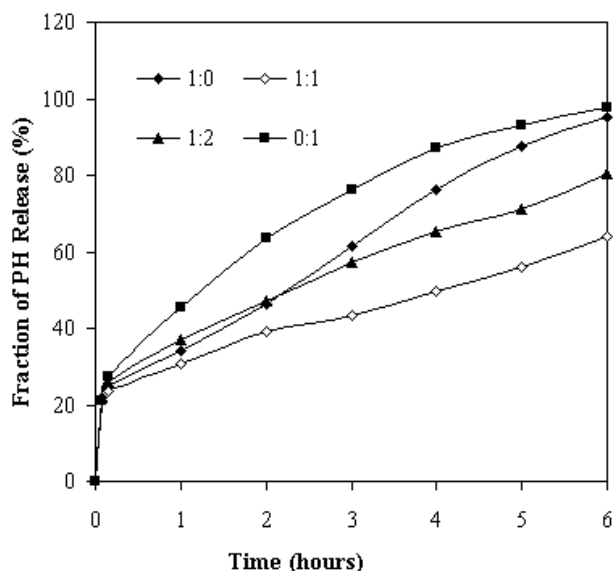
**Figure 7.** Swelling index of NBASs containing CP 934P: HPMC K4M at different ratios.

compared with rabbit buccal mucosa.<sup>27</sup> Since the MS of CP is dependent on the pH of surrounding medium, NBASs containing CP 934P alone (F1) exhibited weak MS. This finding may be owing to a loss of hydrogen bonding with the mucus. The pH of the buffer solution used in the present study was 6.6, which presumably could have decreased the MS because of the change in the ionization property of carboxylic groups present in the CP.<sup>27,28</sup> On the contrary, many researchers have reported maximum MS for tablets containing CP alone. However, they have used different grades of CP, contact time, and pH.<sup>29</sup>

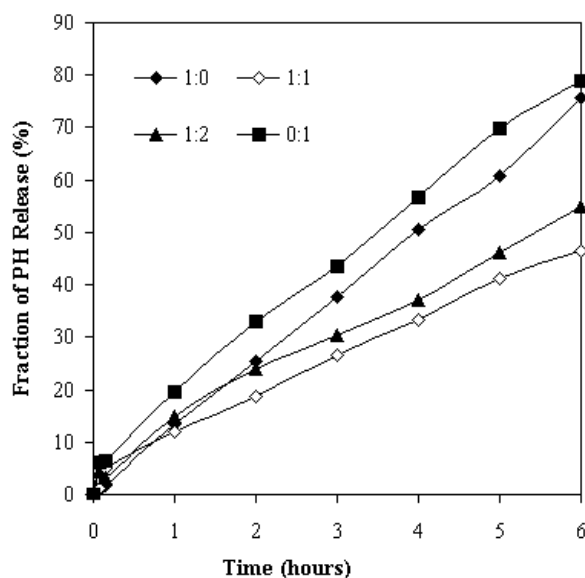
An ideal controlled release system should be able to release the drug immediately to attain the therapeutic level at a faster rate and maintain this drug level for a prolonged period of time.<sup>17</sup> In addition, controlled release formulations reduce the need for frequent administrations and enhance patient compliance by maintaining in vivo drug levels in the therapeutic range.<sup>30</sup> Since extensive research work has been undertaken on only sustained release buccal adhesive tablets (matrix tablets), NBAS was prepared by incorporating both the fast and sustained release dose to modulate the controlled release behavior. In vitro release behavior of PH from NBASs is shown in Figure 9. Formulations containing HPMC K4 M alone (F4) exhibited higher cumulative amount of drug release when compared with other formulations (F1, F2, and F3), which could be attributed to its high rate and extent of swelling. This finding was also supported by the results of swelling studies where the highest SI was also exhibited by a formulation containing HPMC K4M alone (see Figure 7). In theory, the higher the uptake of water by the polymer, the more the amount of drug diffused out from the polymer matrix. Thus, this high amount of water uptake by HPMC K4M may lead to considerable swelling of the polymer matrix, allowing drug to diffuse



**Figure 8.** Mucoadhesive strength of NBASs containing CP 934P: HPMC K4M at different ratios measured by using the porcine and rabbit buccal mucosa.



**Figure 9.** Cumulative release profile (%) of PH from NBASs containing CP 934P: HPMC K4M at different ratios.



**Figure 10.** Cumulative release profile (%) of PH from sustained release buccal adhesive tablets (matrix systems) containing CP 934P: HPMC K4M at different ratios.

out at a faster rate.<sup>29</sup> On the other hand, among the formulations F1, F2, and F3, the formulation F1 (CP 934P alone) exhibited higher cumulative amount of drug release. This may be due to the ionization of CP 934P at pH 6.6, a pH environment higher than its ionization constant ( $pK_a$ ) 6. Ionization of CP leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure, leading to slightly higher uptake of water that might have contributed to higher drug release from the polymer matrix systems.<sup>29</sup> The release behavior of PH from formulations containing CP 934P and HPMC

K4 at the ratio of 1:1 and 1:2 was impressive since these formulations showed effective controlled release pattern. Furthermore, in order to compare the release behavior of PH between NBAS (containing both fast and sustained release layers) and sustained release buccal tablets (matrix system), in vitro release studies were performed separately in an identical manner, and the results are shown in Figures 9 and 10, respectively. Incorporation of loading dose (2 mg) along with sustained release dose into the NBAS resulted in faster release (~2 mg within 10 minutes) at the initial period and controlled release pattern in the later period (see Figure 9). All the formulations of sustained release buccal tablets exhibited a poor release pattern in which the time taken by those formulations to release 2 mg of PH was more than an hour (see Figure 10), which justifies the importance of loading dose in the controlled release systems. The release mechanism of PH from NBAS was studied by using the following well-known equation:

$$\frac{M_t}{M_\infty} = Kt^n \quad (3)$$

where  $M_t/M_\infty$  is fractional release of the drug,  $t$  denotes the release time,  $K$  represents a constant, incorporating structural and geometrical characteristics of the device, and  $n$  is the diffusional exponent and characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of  $n$  falls between 0.5 and 1.0; while in case of Fickian diffusion,  $n = 0.5$ ; for zero-order release (case II transport),  $n = 1$ ; and for supercase II transport,  $n > 1$ .<sup>29</sup> The obtained values of  $K$  (kinetic constant),  $n$  (diffusional exponent), and  $r^2$  (correlation coefficient) are presented in Table 2. The values of  $n$  were estimated by linear regression of  $\log(M_t/M_\infty)$  vs  $\log(t)$ , and these values were between 0.5 and 1.0, indicating that the release of PH was found to be by non-Fickian diffusion. In the kinetics study, the order of drug release from all the formulations was studied by plotting the log percentage cumulative retained vs time curve, and it followed first-order kinetics.

Usually the stability studies are performed in phosphate buffer solutions whose pH pertains to buccal cavity. But, the information obtained from stability studies performed in normal human saliva would be more accurate to mimic the stability of

**Table 2.** Estimated Values of  $n$  (Diffusional Exponent),  $K$  (Kinetic Constant), and  $r^2$  (Correlation Coefficient) Following Linear Regression of  $\log(M_t/M_\infty)$  Versus  $\log(t)$  for NBASs\*

Formulation Code	$n$	$K$	$r^2$
F1	0.601	1.53	0.9932
F2	0.553	1.45	0.9869
F3	0.756	1.56	0.9943
F4	0.804	1.65	0.9971

\*NBAS indicates novel buccal adhesive system.

**Table 3.** Stability Data of NBASs in Normal Human Saliva\*

Sampling Time (hours)	Color Change <sup>†</sup>	Thickness (mm) <sup>‡</sup>	Change in Shape		
			Diameter (mm) <sup>‡</sup>	Collapsing <sup>†</sup>	PH Recovered (%) <sup>‡</sup>
0	No	2.03	11.02	-	99.86
1	No	2.09	11.14	No	99.48
2	No	2.16	11.45	No	99.65
3	No	2.50	11.77	No	99.29
6	No	2.61	12.14	No	99.37

\*NBAS indicates novel buccal adhesive system.

<sup>†</sup>Visual observation

<sup>‡</sup>Mean of 3 readings

drug and device in the oral cavity in vivo. Therefore, the stability of NBAS was examined in natural human saliva. Based on the results of mucoadhesion and in vitro release experiments, formulation F2 was found to be a better formulation among other formulations because it exhibited higher MS and prolonged release of drug. Hence, the stability studies were performed only on the optimized formulation (F2), and obtained data are presented in Table 3. NBAS did not exhibit change in color or shape, suggesting the satisfactory stability of the drug and device in the human saliva. In theory, if the drug is instable in human saliva, its color would change.<sup>21</sup> Choi and Kim<sup>21</sup> reported that color of the omeprazole changed to yellow after being placed in human saliva. Physical properties of the NBAS such as thickness and diameter increased slightly owing to swelling of the system in human saliva. But NBAS did not collapse in the human saliva until the end of the study, confirming the sufficient strength of the device.

Comfortability of the buccal adhesive system in the oral cavity is an important concern in buccal drug delivery. Hence, this study also documented the response of human volunteers to some of the parameters associated with the comfort of the NBAS in the oral cavity. Since the model drug used in the present study was an antihypertensive agent, placebo NBAS containing CP 934P and HPMC K4M at the ratio of 1:1 was used to conduct the in vivo acceptability study on healthy human male volunteers. The response of healthy human male volunteers to each subjective parameter was calculated, and obtained results are presented in Table 4. Based on these results, it can be concluded that the NBAS would be comfortably placed in the human oral cavity.

## CONCLUSION

NBAS, with uniform adhesive layer, has overcome the drawback associated with conventional buccal adhesive tablets. With the NBAS, which consists of fast and sustained release layers, PH can be released and permeated through buccal mucosa rapidly at first and then continuously for a prolonged period. This design is superior and novel to those of conventional dosage forms in tablet or lozenge formulations, which only provide a short duration of continuous drug administra-

**Table 4.** Response of Healthy Human Male Volunteers to Various Parameters\*

SI No.	Criteria	Volunteers Response (%)
1.	Irritation	
	e) None	100
	f) Slight	-
	g) Moderate	-
2.	Taste	
	f) Normal	90
	g) Slightly unpleasant	10
	h) Very unpleasant	-
	i) Pleasant	-
	j) Very pleasant	-
3.	Comfort	
	f) Very comfortable	-
	g) Comfortable	50
	h) Slightly uncomfortable	50
	i) Moderately uncomfortable	-
4.	Dryness of mouth	
	e) None	90
	f) Slight	10
	g) Moderate	-
5.	Salivary secretion	
	e) None	20
	f) Slight	60
	g) Moderate	20
	h) Severe	-
6.	Heaviness of NBAS at the place of attachment	
	e) None	90
	f) Slight	10
	g) Moderate	-
7.	Dislodgement of the system during study	
	c) No	100
	d) Yes	-

\*NBAS indicates novel buccal adhesive system. Twenty volunteers participated in the study.

tion. Moreover, this design also excels above the sustained release preparations currently available, which are capable of achieving sustained release of drug but often have delayed onset time. Our studies suggest that the NBAS is an appropriate device for delivering various therapeutic agents through buccal mucosa as this system has shown effective mucoadhesion, satisfactory stability, and last but not least comfortability in the oral cavity.

## ACKNOWLEDGEMENTS

The authors wish to thank the J.S.S. Mahavidyapeetha, Mysore, India and Dr. B. G. Nagavi, Principal, J.S.S College of Pharmacy, Mysore, India for providing the necessary facilities to complete this work.

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