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Development of benzalkonium chloride thin films for mucoadhesive buccal application

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Keywords: Thin films; Benzalkonium chloride; Mucoadhesive buccal; *Staphylococcus aureus*

Objectives: This study aims to develop thin film containing benzalkonium chloride (BzCl) for buccal adhesive applications.
Methods: Thin films were developed from various types and concentrations of polymers: hydroxypropyl methylcellulose (HPMC E15LVS) and polyvinylalcohol (PVA). The effects of other ingredients (glycerine and carbopol) on films properties were also studied. BzCl 0.1 and 1% w/w was added in the selected formulations as active ingredient. The films were evaluated for their physical appearance, strength, elasticity, mucoadhesiveness, powder X-ray diffraction, *in vitro* drug release and antibacterial test against *Staphylococcus aureus*.
Results: Films prepared from 5% HPMC and 8% PVA with 0.5% glycerine showed the suitable properties. HPMC films showed higher strength while PVA films showed higher elasticity, good mucoadhesion to porcine buccal mucosa was also observed *($p<0.05$)* in both films. Carbopol decreased the mucoadhesive property of the film *($p<0.05$).* There was no different in the amount of drug release from both films prepared from HPMC and PVA *($p>0.05$).* Films containing BzCl showed antibacterial activity against *S. aureus*.
Conclusion: Mucoadhesive buccal thin films containing BzCl were successfully developed. The films showed suitable mucoadhesive property and antibacterial activity.

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Introduction

Buccal drug delivery system is suitable for a local treatment on buccal mucosa and for avoiding the hepatic first pass effect and side effect of drugs.[1)] However, in application for local effect, the difficulty of applying due to high viscosity of semisolid preparations or the ease of removing due to low viscosity of solutions does affect the therapeutic efficacy.[2)] This research aimed to develop thin films for buccal adhesive application which can overcome the disadvantages of the conventional products and is convenient to use. [3-5)]

Materials and Methods

Hydroxypropylmethylcellulose E15LVS (HPMC, Rama Production Co.Ltd. Thailand), polyvinylalcohol (PVA, Sigma-Aldrich Co.Ltd, USA), glycerine (G, CP drugs Co.Ltd. Thailand), carbopol (C) (Ultrez-21®, CP drugs Co.Ltd. Thailand), benzalkonium chloride (BzCl, Acros organics, Denmark), were purchased from various suppliers and used as received. Other reagents were all analytical grade.

***Preparation of thin films*:**
Thin films were developed from HPMC and PVA solutions at various concentrations (5-10% w/w solutions). Thin films were prepared by solvent evaporation and casting method, the ease and wild spread technique involved in making films[6]. Five grams of each polymer solution was poured onto the glass plate (10 cm diameter) and dried at 50°C for 24 hr. The effect of glycerine and carbopol on films properties was also observed. BzCl (0.1 and 1% w/w) was added in the suitable formulations as active ingredient.

***Evaluations of thin films*:** The films were evaluated for their properties as follow:
Tensile property: The strength and elasticity of the films were measured through the stress and strain, using Texture Analyzer (TA. XT Plus Serial no. 10517).
Mucoadhesive property*:* The mucoadhesive force to porcine buccal mucosa of films and probe (control) was measured using Texture Analyzer. Porcine buccal mucosa was used within 24 hr after it was separated from the animal and kept in Krep's buffer at 10°C prior to use.
Powder x-ray diffraction (PXRD): PXRD of each excipient in powder form and dried films were performed using MiniFlex II; Desktop X-ray Diffractometer.

***In vitro* drug release:** The release of drug from the selected films containing BzCl (F2, F4) was performed at 37±2°C for 1 hr in artificial saliva. Thin films were placed in cellulose acetate membrane bag (Nominal MWCO 6,000-8,000), filled in close container and shaken in the shaking incubator at 150 rpm. The amount of BZCl was analyzed by UV spectrophotometric method (Perkin-Elmer lamda 2, Germany) at 257 nm.

Antibacterial activity of films: The antimicrobial activity of BzCl against *Staphylococcus aureus* (*S. aureus*) was tested.[7] The minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) values of BzCl were determined using a broth dilution technique. BzCl thin films were cut into a circle of 0.6 cm diameter and evaluated for antibacterial activity against *S. aureus* by agar diffusion method.

Results and Discussion

Transparent thin films (0.3-0.5 mm thickness) can be prepared from 5% HPMC or 8% PVA solutions. Glycerine, 0.5%, increased the strength of both films ($p<0.05$, data not shown). The influence of BzCl and C on properties of HPMC and PVA film was studied, the formulations were shown in Table 1. Carbopol 0.3% is the maximum amount added which can produce transparent films.

Table 1. Composition (% w/w) of selected polymer solutions for preparation of thin films.

	F1	F2	F3	F4	F5	F6	F7	F8
PVA	8	8	-	-	8	8	-	-
HPMC	-	-	5	5	-	-	5	5
Glycerine	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Carbopol	-	-	-	-	0.3	0.3	0.3	0.3
BzCl	0.1	1	0.1	1	0.1	1	0.1	1

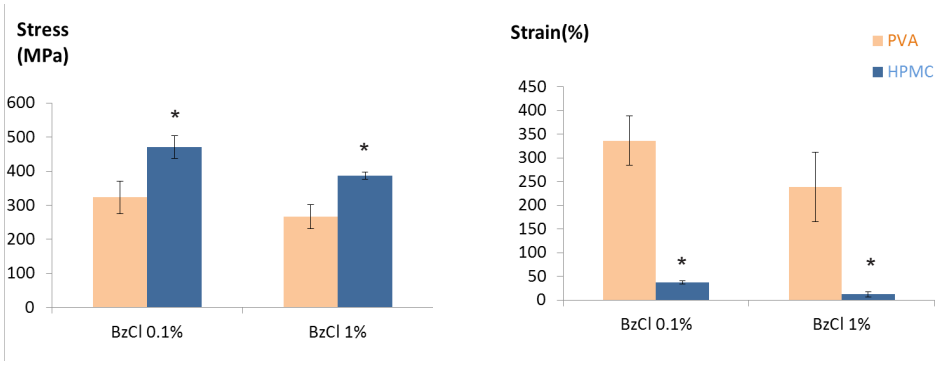

Figure 1. Effect of polymer and BzCl on tensile properties of films. (n ≥3, * = significant different at $p<0.05$)

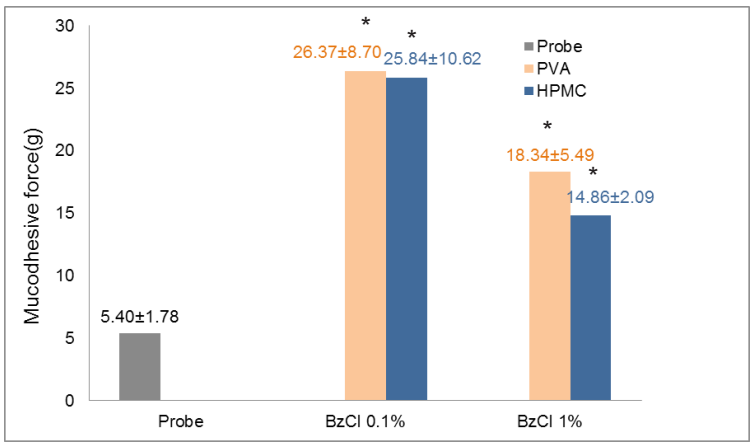

Figure 2. Effect of polymer and BzCl on mucoadhesive force of films (F1-F4). (n ≥3, * = significant different at $p<0.05$)

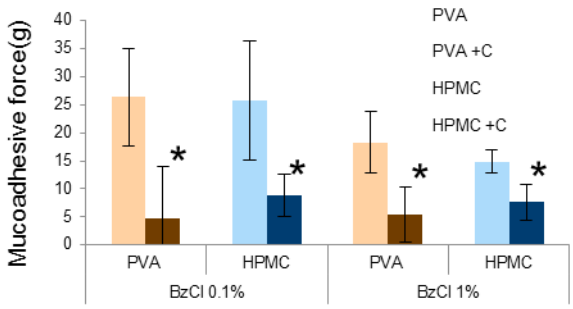

Figure 3. Effect of carbopol on mucoadhesive force of PVA and HPMC films. (n ≥3, * = significant different at *p<0.05*)

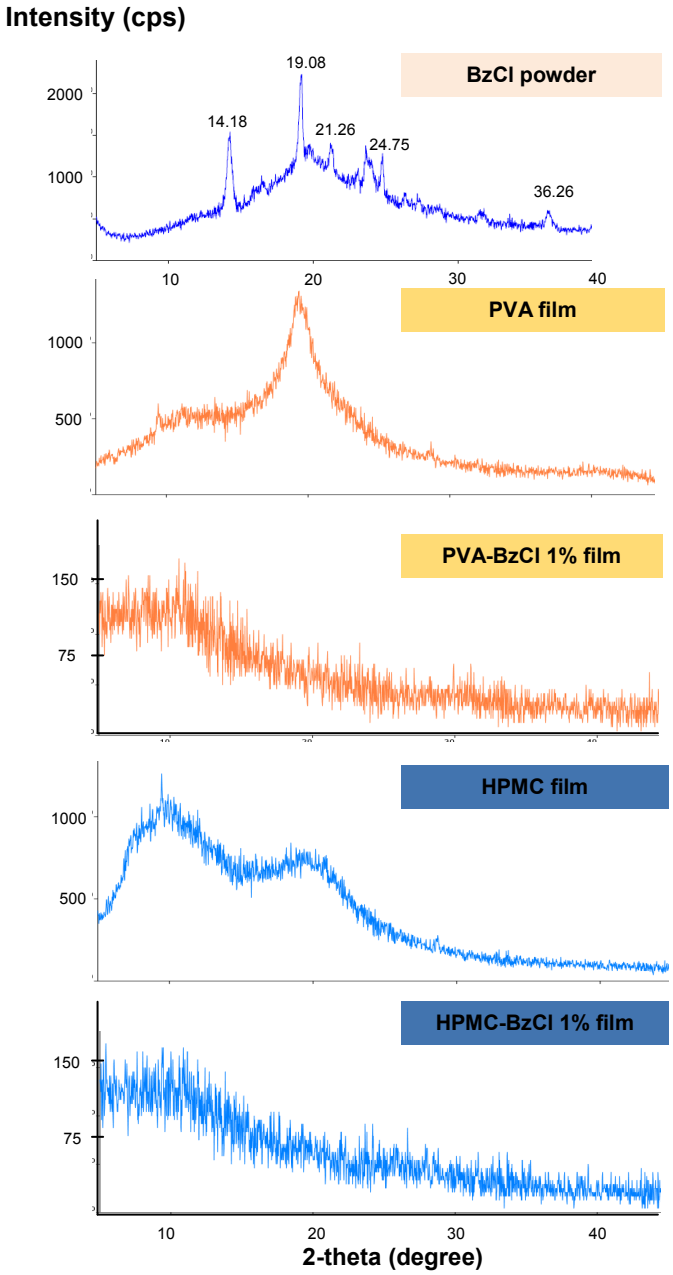

Figure 4. PXRD patterns of BzCl powder and films.

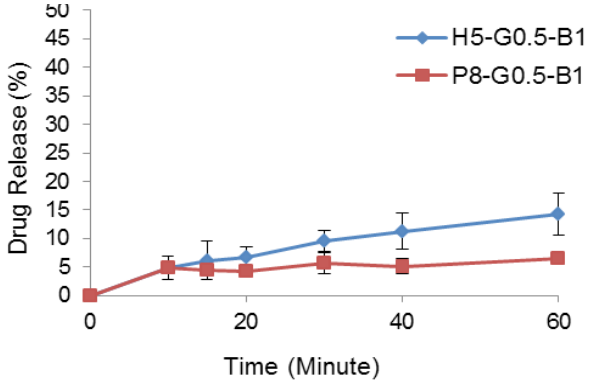

Figure 5. BzCl release from thin films containing PVA (F2) and HPMC (F4). (n≥3)

Table 2. Diameter (mm) of the clear zone of F1-F4 observed from agar diffusion method.

Control			Film formulations			
1% BzCl solution	PVA film	HPMC film	F1	F2	F3	F4
19±1	-	-	-	12±1	-	15.7±3.06

Tensile properties of films (F1-F4) was shown in Fig.1. PVA films showed higher elasticity while HPMC films showed higher strength. Different amount of BzCl loadings did no effect on strength and elasticity of films (p>0.05). Mucoadhesive data was shown in Fig. 2, mucoadhesive force of both PVA and HPMC films was higher than that of control (probe) (p<0.05). The effect of carbopol on mucoadhesive force of PVA and HPMC films containing 0.1 and 1% BzCl was shown in Fig. 3, the present of carbopol in films (F5-F8) decreased mucoadhesive properties (p<0.05). Though carbopol may be used as mucoadhesive polymers in oral preparations[6], the mucoadhesive properties was reported to be dependent on concentration of both carbopol[7] and film forming polymer such as poloxamer[9]. From PXRD pattern in Fig. 4, the characteristic peak of BzCl crystal was not observed in film containing drug. This can be both concluded that drug existed in films in amorphous form which is able to dissolve or existed in crystal form. The peak of drug in crystal form may not be able to observe because of the low amount of drug in film. In vitro drug release of formulation F2 and F4 was shown in Fig. 4. Both presented the same drug release of 6-14% (p>0.05) within 1 hour. Low amount of drug release might be from the viscosity of the dissolved film in the membrane bag which sustained the amount of drug release. The MIC and MBC value of BzCl were 2.5 and 5 μg/ml. The results in Table 2 revealed that both films prepared from solutions containing PVA and HPMC with1% BzCl (F2, F4) showed an antibacterial activity to *S. aureus*. Though the PXRD is a rapid analytical technique primarily used for identification of a crystalline drug study, the drug release study and antimicrobial activity test were also necessary to be done.

Conclusion

Mucoadhesive buccal thin films containing BzCl with appropriated properties can be formulated using HPMC or PVA and glycerine. Films prepared from polymer solutions containing 1% BzCl presented antimicrobial activity against *S. aureus*.

Acknowledgements

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