CHAPTER IV

DISCUSSION AND CONCLUSIONS

Polysaccharide gel (PG) extracted from dried fruit-hulls of durian was a natural water soluble polymer which found to be useful for preparation a mucoadhesive film for oral mucosal administration such as triamcinolone acetonide and miconazole nitrate mucoadhesive films as an alternative dosage forms for local oral wound healing and antifungal. The mucoadhesive films were prepared by casting/solvent evaporation method. Due to the pale brown color of PG, therefore all the film products were pale brown films.

The pH of PG solution at 2% concentration was about 2.4, and a taste was sour. Increasing pH of PG solution resulted in decreasing viscosity. Above pH 5, PG solution have changed in physical appearance such as color and air bubbles, the color of PG solution turned into brown color with a lot of air bubbles trapped in the solution. In this study, 2% PG solution was adjust to pH 3.7 with 0.1M $NaHCO_3$, increasing of pH resulted in decreasing sour tastes.

An ideal mucoadhesive films were the films with good adhesive strength, free of any air bubble, uniform thickness, easy to peel off from glass plate after drying with characteristics of flexibility and did not have any crack or fracture. In this study, the physical characteristics of the products of the mucoadhesive film formulations was depended on the nature of polysaccharide gel (PG). PG film without plasticizer was pale brown in color, transparent, brittle and hard to peel off from glass plate. PG film with plasticizers using sorbitol, polyethylene glycol 400 (PEG 400) and polyethylene glycol 6000 (PEG 6000) showed increased in flexibility and easy to peel from glass plate, while PG film product with hydroxypropylmethylcellulose (HPMC E15) showed not very different from PG film product without plasticizer except that the film product with HPMC E15 was a translucent film. The characteristics of PG film was depended on types of plasticizer and their concentrations.

The physical appearance of PG film with drug using triamcinolone acetonide and miconazole nitrate was not different from PG film base. Because of the good mucoadhesive property of PG film, 3 layer films were produced. HPMC E15 was a water soluble polymer which the mucoadhesive property was poorer than PG film, then HPMC E15 was used as backing layer. The 3 layer film was poured on ground glass, the bottom layer, the rough side, was HPMC and the top layer, the smooth side, was PG and resulting product of the translucent film was obtained.

According to the results of physical appearance, the PG film with plasticizer was easier to peel off from glass plate and flexible than the PG film without plasticizer. Plasticization generally prevented close compaction of the polymer macromolecules by reducing the relative number of polymer intermolecular attractions and then increasing the polymer's free volume. Thus polymer molecules could freely move to cause an increase in their flexibility (Gutierrez-Rocca and McGinity, 1994). These results were in agreement with the mechanical property study that plasticized PG film had lower Young's modulus and stress at break, and higher %strain at break and toughness than those of PG film. These values indicated that PG film with plasticizer was softer and tougher than PG film without plasticizer, the results were similar to the previous reported by Gerddit (2002) and Nakchat (2002). Increasing the plasticizer concentration increased the % strain at break, toughness and film thickness. The value of % Strain at break or elongation which defined as the distance at break related to original distance of free film were increased with respected to the increasing of plasticizer concentration, except the formula that plasticized with PEG 6000 and HPMC E15. Moreover, the very low value of % strain at break and toughness of the film plasticized with PEG and HPMC indicated that the film was brittle (Table 5). Young's modulus that indicated the hardness or stiffness of the product was decreased as the level of plasticizer increased, except the formulation that plasticized with PEG 6000. Therefore, the S30PG formula was chosen as a PG film base, the appropriate values of tensile study and physical characteristics of satisfactory product were obtained. In comparison of the mechanical properties between PG film with drugs and PG film base showed the same property as well as the PG film with plasticizer, soft and tough films were obtained. In addition, the 1 layer film with drugs provided soft and tough product while the 3 layer film with drugs provided soft and weak product.

The Infrared spectra in this study was to characterized the changes in the functional groups of the PG film, drug and dressing film with drug. Because of the ratio of drug to PG was very low, 0.1:100 in Triamcinolone-PG film and 2:100 in Miconazole-PG film, then both of the drug-loaded film showed the spectrum similarly to that of PG film base. From the previous study by Gerddit (2002) found that films of polysaccharide gel with plasticizers did not initiate new product, these results also showed that no peak of new products appeared.

The moisture sorption of film preparation of PG film base and 3 layer PG film comparison with HPMC film was investigated by exposing the films to moisture at 75% relative humidity. The results showed that the moisture sorption of 1 layer and 3 layer films were not different. HPMC film could absorb moisture less than PG film plasticized with 30% sorbitol (w/w base on PG). Plasticizers or low-molecular-weight diluents are added to polymers to modify their physical properties and to improve their film forming characteristics (Rowe and Forse, 1981). Plasticizers can change the viscoelastic behavior of polymers significantly. In particular, plasticizers can turn a hard, brittle polymer into a softer, more pliable material, and possibly make it more resistant to mechanical stress. These changes in the mechanical properties also affect the permeabilities of polymer films (Porter and Ridgway, 1982). This experiment was in agreement with Gerddit (2002), moisture sorption of PG film was increased with respect to increasing the interstices plasticized PG polymer.

The in vitro release of triamcinolone acetonide from PG films were studied. The profile of drug release showed that triamcinolone acetonide rapidly penetrated through cellulose acetate membrane into pH 7.4 phosphate buffer. The results were possible that PG was a water soluble polymer with 1.5 fold of swelling property (Nakchat, 2002), when the polymer swelled the void spaces increased with the polymer unfolded and the coils hydrated. The drug substantially diffused through these voids. The release characteristics of topical products can be assessed for quality assurance by using membranes other than skin (Guy and Hadgraft, 1990). All diffusion experiments were done by adding 1% w/v polyoxyethylene-20-cetyl ether as a solubilizer into phosphate buffer to overcome the low solubility of drugs in buffer solutions. The use of this solubilizer is well documented in the literature for *in vitro* diffusion studies. There was no significant affect on the permeation of caffeine

between phosphate buffer without solubilizer and phosphate buffer with solubilizer (Asbill, et al., 2000).

Dias, et al (1999) studied the permeation of caffeine through human skin, cellulose acetate and silicone membranes. It was found that the diffusion through epidermal tissue is significantly slower than through the synthetic membranes. Penetration of the caffeine through the cellulose acetate membrane showed the fastest. This synthetic membrane cannot be used predictively to estimate the efficiency of formulations on skin. In this experiments, the release profile of PG film base of triamcinolone acetonide was also studied. The results showed that PG film base interfered with the same absorbance wavelength of triamcinolone acetonide. These results indicated that the extraction of triamcinolone acetonide from the buffer solution should be further studied.

The in vitro releases of miconazole nitrate from PG film through cellulose acetate membrane was slower than triamcinolone acetonide. It was possible that the drug was entrapped in PEG 6000. Therefore the release of drug was reduced. The release profile of PG film base of miconazole nitrate was also studied. The release of drug depended not only on the nature of the matrix but it also dependent on the solubility of the drug. The rates of release of drugs from the matrices are in decreasing order as the solubility parameters (Sumathi and Ray, 2002).

The 3 layer PG film base was produced for the sensory analysis of taste, ease of application, adhesiveness, non-irritation, no-residue, non-annoyance, product appearance satisfaction and overall satisfaction after use in volunteers. This study was a preliminary in vivo investigation of some characteristics and property of the film before being further studied in clinical trial. The highest scores was adhesiveness, present that PG was a good mucoadhesive film. The values of ease of application and no-residue also showed high scores, indicated that PG film was comfortable to use and completely soluble. In addition, the scores of overall satisfaction after use was higher than product appearance satisfaction. However, about the taste, they have many suggest that the flavors of the film should be adjusted such as cool feeling and sweetening. The modification of taste should be considered in further investigation.

Conclusions

The intraoral mucoadhesive films of polysaccharide gel extracted from durian fruit-hulls was pale brown in color, transparent but very brittle. Variation in type and ratio of plasticizer affected the chemical structure of the film, thereby influencing the physical characteristics, water sorption, mechanical properties, thickness of film, and finally the permeation of drug.

The incorporation of plasticizers into PG film generally increased film flexibility and water sorption ability. The tensile properties of the films were evaluated. Young's modulus and stress at break were decreased with increasing plasticizer concentration, whereas increasing %strain at break and toughness. Regarding all of the properties evaluated, sorbitol was found to be the most suitable plasticizer to achieve the aim of this study.

Addition of drugs to polysaccharide gel did not change the physical appearances and did not form a new product. The in vitro drugs release profile of Triamcinolone-PG film was faster than Miconazole-PG film. However, the release rate of both drugs were very fast. The consumer test which used 3 layer film showed that PG film was a good mucoadhesive film with their adhesive property, facilitation and less of residue.

From this study, it was concluded that PG was a new natural water soluble polymer for application as a mucoadhesive film preparation in pharmaceuticals. The previous studies found that PG has antibacterial activity and wound healing property. It was interesting to apply PG for the treatment of wound in oral cavity. Therefore, further in vitro and clinical studies of this film preparation should be carried on.