CHAPTER I

INTRODUCTION

In 1837, Mothes, a French scientist, invented the first gelatin capsule for pharmaceutical usage which gave an alternative for solid dosage form. After that capsule shells have been continually developed. There are two types of capsule shells in the market which are soft gelatin capsules and hard gelatin capsules but hard gelatin capsules have been found to be a favourite dosage form. However, hard capsules and soft capsules are still necessary to be produced from gelatin because of its excellent properties such as good film former, thermal reversible gel forming, and good dissolution in all biological fluids at body temperature. Eventhough, gelatin is a good material for capsule shell, it also has some disadvantages.

Few years ago, a serious epidemic Bovine Spongeform Encephalopathy (BES) or "Mad Cow Disease" was found in UK and other countries after that. This disease has stimulated people in concern about the safety of gelatin in foods, cosmetics and pharmaceutical products. Moreover, gelatin capsules containing active ingredients have been restricted for Islamic peoples around the world because gelatin is normally obtained from pig or cow's connective tissues.

Under tropical climate such as Thailand, high relative humidity (60-70% RH) can create a dissolution problem in human body for hard gelatin capsules (Jones, 1987: 31-48). Normally, gelatin capsule shells dissolve well at body temperature but if they are exposed to high moisture, the dissolution temperature of hard gelatin capsules is elevated to be higher than body temperature or 50°C. On the other hand, gelatin capsule shells can turn to be brittle if they were stored under low relative humidity. It can be concluded that gelatin is a sensitive material to moisture; therefore, conditions for manufacturing and storage should be carefully controlled. In addition, ingredients containing aldehyde groups can cause protein linkage between amine groups of gelatin and aldehyde groups of ingredients, which bring to dissolution problems of hard gelatin capsules. Therefore, many scientists around the world have been trying hard to find other materials to replace gelatin.

In 1998, Yamamoto et al. attained the patent on the capsule shell prepared by non-gelatin substances. The compositions of capsule shells are 79.6-98.7% of hydroxypropylmethyl cellulose (HPMC), 0.03-0.5% carrageenan, and 0.14-3.19% potassium or calcium ions which is known as "Vegetable capsule" by Capsugel (a division of Warner Lambert) afterwards.

Starches, such as potato starch, are also used as gelatin substitute for capsule shell preparation. Gelatin capsule shells are normally made by dipping mould method but starch capsule shells are produced by injection mould method which was developed by Capsugel (a division of Warner Lambert). There is only one product in the market which is manufactured under named "Capill®" by West Pharmaceutical Services (Vilivalum et al., 2000; Eith and Tomka, 1987). Since Capill® is made by injection mould method, therefore, its shape is different from regular gelatin capsules. Special semi-automatic filling machines such as Bosch™ (GKF) 400C are also needed.

Gelatin capsules have been used in the pharmaceutical industries for a long time. Therefore, replacement of gelatin with other materials for capsule shell preparation should not result in changing any current machines used for capsule production or capsule filling machine. The result of changing machine cause high costs around the world. It can be imagined how many machines have been using in Thailand and how many more in pharmaceutical industries around the world.

Generally, Thailand is an agricultural country which produces plenty of starches especially rice starch or glutinous rice starch. Starch is found to be in the top tens for Thai's exportation. However, the cost of starch is very cheap as compared to gelatin which is normally imported. After the market survey, starch costs 100 bahts per kilogram while gelatin costs 250 bahts per kilogram.

National Starch and Chemical Company has conducted a study on the cost effectiveness after the substitute of gelatin with starch for hard gelatin capsule shell production. It was found that the company can save up to 112,500 bahts for 5,000 kilogram batch size after substituting only 15% of modified starch, which is called Elastigel 1000J®

Moreover, starches show many advantage properties over other substances such as non-animal products, unnecessary to add preservative, excellent stability under

different conditions (especially moisture and temperature) and good for enteric delivery due to the fact that dissolution is pH-independent.

Thus, this study is not only to find out suitable starches that can substitute gelatin for hard capsule shell production but also to find out the maximum percentage of particular starches that can reduce the cost of the production. Eight different starches have been selected for this study as representatives for natural starch, pregelatinized starch and modified starch. The dipping moulding method is used to produce capsules for this study in order to use the existing machines which are normally used worldwide. The focus of the experiment would be the physical properties of the starch-gelatin mixture and the effects of plasticizers and surfactants on the properties of the mixture. Finally dissolution of drug release is used to compare the ability of starch substitute gelatin hard shell capsules as compared to commercial hard gelatin capsules.

Objectives:

1. To study suitable types and quantity of starch as substitutes for gelatin in hard shell capsules production by dipping method.
2. To study the effect of plasticizers and surfactants on films and hard shell capsules.
3. To compare the physical properties between the starch substitute gelatin hard shell capsules and the gelatin hard shell capsules.
4. To study the model drug release of starch substitute gelatin hard shell capsules as compared to gelatin capsules.
5. To study the stability and storage condition of starch substitute gelatin hard shell capsules as compared to commercial gelatin capsules.