CHAPTER I

GENERAL BACKGROUND

Introduction

Several drug delivery technologies are used to achieve the required drug levels at the site of action as a result of attaining adequate blood levels in the general circulation. There are numerous dosage forms that are designed for administration by all possible delivery routes to maximize therapeutic response. Rectal route is one of drug transportation used in the present because of many advantages both on patients and drug properties. For example, when patient is vomiting or unconscious or convulsion, they cannot get any medicine per oral. Suppository is usually first considered and it is also suitable for young children. For drug that can be destroyed by gastric juice or first-pass elimination, rectal dosage of medicaments was proved to enhance drug bioavailability because they can be absorbed directly to circulation (Angel. 1995; Coden and Liebermann, 1986).

This route of delivery is used in many different therapies, intended either for local or for systemic effect. Local effect is mostly desired to act directly at the target organ especially in the case of pain and itching due to the occurrence of hemorrhoids or used as laxative. Systemic effect can be used to relieve fever, nausea or analgesic action and this route are becoming increasingly important for systemic drug delivery as well (Marion et al., 1996). Especially prospected for protein and peptide drug delivery instead of injection because of rapid onset in this area. In addition many researchers studied about sustain release action for chronic disease such as hypertension or diabetes mellitus. (Hermann, 1995; Banga and Chien, 1985)

However, suppositories have many limitations particularly in storage condition. Because they melt at the room temperature so it is necessary to keep them in the refrigerator. In Thailand, which is the tropical country, using or carrying and storage of suppositories became trouble to patient. Besides during transportation, it may be melted although, they can recover when keeping in the cool place but drug distribution in the

suppository has been changed. Moreover, Suppository preparations required the specific equipment for industrial production.

Many researchers found the way to overcome these problems and one of that is rectal capsule. Rectal capsule (also known as shell suppository) is generally similar to soft capsule except they may have lubricant coating to aid gliding during administration. Its shape is elongated like suppositories but can keep in the tropical climate without special packaging (Kirt and Nem-Allachwill, 1969; Hanff and Rutten, 1996; Yamazaki et al., 1993). The drug was dissolved or suspended in liquid vehicle and filled in the same way of common soft capsule. Although the soft gelatin capsule can be used as rectal capsule but many researchers interested in using hard gelatin capsule due to the advantages of thinner of capsule shell and ease of preparation (Cade et al., 1986; Tillotts Pharma, 1992). Many publishers showed the satisfactory result such as the investigation of hard gelatin capsule as a rectal dosage form, it was found that ibuprofen capsule could provided adequate drug in blood level via rectal route (Marvola et al., 1996,1997). Storey and Trumble (1992) changed the route of administration of doxepin and carbamazepine from per oral to rectal route and the patients, who take the medicine, gave good response to the drug.

Liquid filling in hard gelatin capsule has recently developed while many technologies are provided to prevent liquid leakage. The special design of capsule, gelatin banding and specific formulation such as thixotropic or matrix-base formula were widely used to get the desired effect and it make hard gelatin capsule properties familiar to soft capsule. In addition, coated hard gelatin capsule was also used by administration into body for gliding and protective effect (Widmann and Scherer, 1969; Bener and Allachwill, 1969; Hagenlocher et al., 1986; Hannula et al., 1988). The capsule shell will be dissolved by rectal fluid and drug spreaded over mucous layers and then acted as same as mould suppositories. Hardy et al. (1987) utilized gamma scintigraphy to evaluate the spreading of suppository bases filling in hard gelatin capsules when administered by rectal route of human subjected. The result showed that spreading of base occurred within one hour after administration.

In the present study, Dimenhydrinate was selected as a model drug for development of rectal capsule dosage form. The drug is an antihistamine and antiemetic agent, when prepared into this dosage form, should be rapid onset of action and shows the systemic effect. Hence, the preparation must be designed to obtain the rapid dissolving similar to marketed product, Gravol®. Dimenhydrinate was incorporated to thixotropic liquid base and the dispersion was kept flowable state by stirring then filled into hard capsules. This technique was chosen due to convenience of flow property of mass during filling process into capsules, good drug homogeneity and no crystal structure changes during storage/temperature cycling. Additionally, it was appropriate for heat-labile material because it can be prepared without heat (Baykara and Yuksel, 1992; Shah et al., 1996; Walter et al., 1992). The liquid filled capsules were coated, with perforated pan coater or fluid-bed coater, by using cellulose and polyacrylate as coating agent.

Objectives of this study

1. To prepare liquid formulation for filling into hard gelatin capsule which has both good physical appearances and desired release characteristic.
2. To compare the coating quality of perforated pan coater and fluid-bed coater when applied for liquid filled capsule coating.
3. To study the effect of type coating polymers, cellulose and polyacrylate polymer, types and amounts of plasticizers on film properties, especially drug release from coated hard gelatin capsule.
4. To investigate the aging effects on the drug content and the release profiles of rectal capsule after storage at 35 ^{o}C, 45 ^{o}C and room temperature for 4 months.