CHAPTER I

INTRODUCTION

The development of oral sustained release dosage forms has aimed to control the drug concentration and time release for improving therapeutic efficacy, safety and patient compliance. The oral sustained release dosage forms can be classified into two types as single unit and multiple units. Multiple-unit sustained release dosage forms such as pellets, microcapsules, microspheres and resin beads are contained in capsules or tablets in order to offer several advantages when compared to single unit dosage forms because they spread uniformly throughout the gastrointestinal tract (Bodmeier, 1997). Multiparticulates which have particle size smaller than 2 mm pass through the gut as if a solution, avoid the vagarious of gastric emptying and different transit rates. They spread over a large area of absorbing mucosa. It prevent gastric mucosa expose to high drug concentration, resulting in less variable bioavailability and reduced risk of local irritation. They also release drug in a more predictable manner (Clarke et al., 1995).

One of the methods for developing multiple-unit sustained release drug delivery systems is the ion exchange technique. The use of ion exchange resins occupies an important place in the development of sustained release preparations due to their controllable properties such as particle shape, size, internal pore structure and lack of toxicity. Moreover, the rate of release is regular, which has been attributed to the nearly constant ionic strength of the gastric and intestinal juices (Stippler et al., 2004), the rate constant for absorption being less variable for resinate compounds. The release profile of drug from drug-resin complexes, referred as "resinates", can be obtained by selecting suitable degree of crosslinkage and particle size of resin or by mixing uncoated resinates and semi-permeable coated resinates.

Pongjanyakul et al. (2005) evaluate the in vitro release kinetic of dextromethorphan hydrobromide resinates. The release of drug can be controlled by the particle diffusion controlled or in an adherent stagnant film (film diffusion

controlled), the same as previously reported by Bhaskar et al. (1986). Since particle diffusion and film diffusion are sequential step, the slower is rate-controlling.

Halder and Sa (2006) used ion exchange resins for preparing prolonged release of diltiazem hydrochloride. The drug was bound to Indion®254, a cation exchange resin, and the resinate was microencapsulated with polystyrene using an oil-in-water emulsion-solvent evaporation method.

Disintegrating tablets are advantageous to control drug release. Ideally, the compacted particles should disintegrate rapidly into individual particles in gastrointestinal fluids. The drug release should not be affected by the compaction process.

Prapaitrakul and Whitworth (1989, 1990) investigated the performance of three excipients in disintegrating tablet formulations which contained microcapsules. The phenylpropanolamine-resin complexes were microencapsulated with cellulose acetate butyrate by using emulsion-solvent evaporation technique. Microcapsules (125-250 micron) were compressed at compression pressure between 35 to 281 MPa with various diluents such as Emdex®, Fast Flo Lactose® and Avicel®. Tablets of acceptable physical properties only produced with Avicel®. When Emdex® or Fast Flo Lactose® was used, the tablet compressed at pressure below 176 MPa did not allow handling and at higher pressure unacceptably high tablet friability (above 50 %) was seen. Microcapsule compressed with Avicel® had the least deterioration in the release profile compared to Emdex® or Fast Flo Lactose®. Avicel® was able to accept larger quantities of microcapsules compared to Emdex® or Fast Flo Lactose® without similar increases in drug release rate.

Sriwongjanya and Bodmeier (1998) studied the drug release from hydroxypropyl methylcellulose (HPMC) matrix tablets containing propanolol hydrochloride-resin complexes. The release from drug-resin complexes tablets was significantly slower than from HPMC tablets containing drug without resin.

Pongjanyakul et al. (2005) investigated the effect of different polysulfonate resins and direct compression filters on physical properties of multiple-unit sustained

release dextromethorphan tablets. Dextromethorphan resinates were formed by a complexation with strong cation exchange resins, Dowex®50W (4 % crosslinkage 100-200 mesh) and Amberlite®IRP69 (8 % crosslinkage 100-140 mesh). A good performance of the tablets was obtained when microcrystalline cellulose (MCC) or spray dried rice starch (SDRS) was used. The plastic deformation of the fillers, such as MCC and SDRS, caused a little change in the release of dextromethorphan. MCC was more porous and underwent the plastic deformation, so it could absorb higher compression forces. SDRS had a good protective effect on the resinates under compression pressure. Small particles of this filler could cover the surface and prevent the fracture of the microparticles in the tablets. A higher release rate constant was found in the tablets containing dicalcium phosphate dehydrate (DCP), indicating the fracture of the resinates under compression, which was attributable to the fragmentation of DCP. The high degree of crosslinking of polystyrene was more resistant to deformation.

This study investigate the use of ion exchange resin for sustained release diltiazem hydrochloride, a highly water soluble drug. The strong acid ion exchange resins, like sulfonic acid, are very suitable for designing a preparation with prolonged action, since they provide a more moderate release than the carboxylic acid resins (Deasy, 1984).

The objectives of this study are to develop multiple-unit sustained release tablets of film-coated diltiazem hydrochloride resinates, which covered the following aspects

- The method for preparing diltiazem hydrochloride resinates.
- Drug release profile from diltiazem hydrochloride resinates.
- Coating resinates with acrylate polymer by fluidized bed technique to modify diltiazem hydrochloride release.
- Tableting of film-coated resinates for developed multiple-unit sustained release tablets.