CHAPTER I

INTRODUCTION

Ranitidine is a histamine H_2-receptor antagonist. It completely inhibits the action of histamine on the H_2-receptors of parietal cells reducing gastric acid secretion and is used for the treatment of duodenal ulcer, gastric ulcer, and other associated symptoms (Mc Evoy, 1995). Unlike the other histamine H_2-receptor antagonists, ranitidine contains an aminoalkyl substituted furan ring while cimetidine contains an imidazole ring, famotidine and nizatidine contain a thiazolyl ring, and roxatidine contains a piperidine ring (Hohnjec et al. 1986; Budavari et al., 1996). The hydrochloride (HCl) salt of ranitidine is the most popular form because of its high water solubility that leads to the increment of its bioavailability (Teraoka, Otsuka, and Matsuda, 1993).

Ranitidine HCl can undergo several routes of chemical degradation. Hydrolytic degradative studies of ranitidine HCl have shown that two different pathways are operative under acid and alkaline conditions. At intermediate pH values both pathways are operative whilst at very low pH values ranitidine HCl is resistant to the hydrolytic cleavage (Haywood, Martin-Smith, and Cholerton, 1987).

The hydrochloride salt of ranitidine is highly hygroscopic powder. The critical relative humidity (CRH) of the ranitidine HCl bulk powder is about 67% relative humidity (RH) and around this relative humidity, ranitidine HCl is unstable (Teraoka et al., 1993).

Kanokwan Thiengthawat (1994) investigated chemical stability of ranitidine HCl in phosphate buffer solutions at 70°C. The pH-rate profile between pH 1 - 12 indicated that there were no specific acid-base catalyses but there was a general acid catalysis

by dihydrogenphosphate ion and there might be a general base catalysis by phosphate ion. Since the color of buffer solutions containing the drug had changed from clear-colorless to dark-red, an oxidative reaction might be one of the decomposition pathways of ranitidine HCl.

Patima Phuangchan (1997) studied the oxidative degradation kinetics of ranitidine HCl solutions by addition of various kinds of antioxidants in the presence of light and/or oxygen. She found that oxygen accelerated ranitidine HCl degradation more than light did. The differences in degradation rate constants were independent of mode of actions and concentrations of the antioxidants studied.

Cyclodextrins (CDs) are fascinating molecules and have become the subject of growing interest for several decades. This is not only the consequence of the ring shape of the natural CDs and of their ability to include, in their cavities, a wide variety of active molecules conferring on them new physicochemical properties, but also the consequence of the great number of derivatives and of the completely new applications offered by some of them. In the pharmaceutical field, CDs have been recognized as potent candidates to overcome the undesirable properties of drug molecules through the formation of inclusion complexes.

Cyclodextrins are well known for their capacities to stabilize many drug substances that are unstable in the presence of air, light or heat. In some cases, they can stabilize drug substances that are susceptible to hydrolysis or oxidation by including them into their molecular cavities (Duchêne and Wouessidjewe, 1990). For the moment, the only natural CDs (α -, β -, γ - CDs) that can be used industrially is β - CD, since it has been the most easily available, and it is therefore commonly employed. It also has a proper cavity size (with a diameter of about 6 Å) to include most of active molecules into their hydrophobic cavities. Unfortunately, compared with other CDs, β - CD is least water soluble (1.85 g/100mL at 25°C) and produces the greatest

nephrotoxicity after it has been administered intravenously (Duchêne and Wouessidjewe, 1996).

In recent years, a great number of CDs derivatives have been developed and studied in order to overcome the problems of water solubility and toxicity. 2-hydroxypropyl-beta-cyclodextrin (2HP-β -CD) is one of such derivatives possessing high water solubility (>50 g/100mL at 25°C) and low toxicity. In addition, it has been proved to be safe when it is administered via the parenteral route (Irie and Uekama, 1997). So in this study, 2HP-β -CD was chosen to investigate for its applicability in preparation of inclusion complexes with ranitidine HCl.

In order to overcome the aforementioned stability problems of ranitidine HCl, this research study is aimed to develop the preparation of inclusion complexes of ranitidine HCl using β -CD and 2HP-β -CD as complexing agents by co-grinding, freeze-drying, and kneading techniques.

Objectives

The objectives of this study are the following:

1. to study the stability of ranitidine HCl inclusion complexes.
2. to prepare ranitidine HCl inclusion complexes with CDs (β -CD and 2HP-β -CD) by co-grinding, freeze-drying, and kneading techniques.