CHAPTER I

INTRODUCTION

Cimetidine is an H_2-receptor antagonist which is used to antagonize the effects of histamine on the acid secretory cells in the gastric mucosa. Clinical uses of cimetidine is obviously to inhibit the secretion of gastric acid in the hypersecretion state such as duodenal and peptic ulceration, and treatment of pathological hypersecretory condition of Zollinger-Ellison syndromes (1-5).

It was reported that cimetidine has different crystalline forms (polymorphism) when crystallized under various conditions. Prodic-Kojic, B. et al (7) and Shibata, M. et al (8) found the four crystalline forms of cimetidine, three anhydrous (forms A, B, and D) and a monohydrate form (form C). The difference crystal forms were obtained by varying the kinds of solvents and solvent/solute ratios. The dissolution rate constant of polymorph C in deionized water was greater than those polymorphs A, D, and B 1.29, 1.70 and 1.90 times respectively. Cimetidine polymorph C was significantly more pharmacologically effective to prevent the stress ulceration in rat than polymorphs A, B, and D (8) but its stability was lower than those of the others. The structural conversion of polymorph C into polymorph A on dehydration was also reported (8).

Since the bioavailability of pharmacologically active compounds is generally dependent on their crystalline forms (9). The present of less active cimetidine crystalline form would render the drug less effective in clinical use. The bioavailability of cimetidine depends on the conformation of the molecule because of the necessary for effective binding to the histamine H_2-receptor. The previous studies (8, 15) revealed that the molecular conformation of polymorphs A or C would probably bind effectively to the histamine H_2-receptor. It was stated (7) that the infrared spectra of the two polymorphs, cimetidine A and cimetidine B, may be used for their identification and determination of polymorph B when present in polymorph A.

The purposes of this study were to prepare the crystalline forms of cimetidine polymorphs A and B and to determine the content of polymorph B in its mixture with polymorph A both in raw material and in its formulated tablet by the IR spectrophotometry. The experiment for polymorphs C and D was omitted because polymorph C was unstable and the preparation of crystalline form D was very difficult (8).