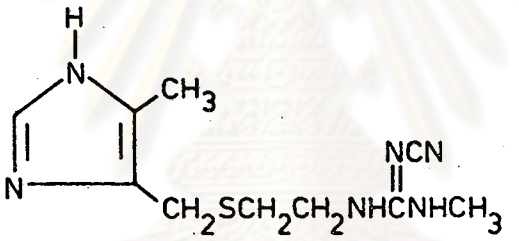
CHAPTER II

BACKGROUND

Chemistry of Cimetidine

1. Chemical name The chemical name of cimetidine is Guanidine, N"-cyano-N- methyl -N'-[2- [[(5-methyl-1H-imidazol-4-yl) methyl]thio]ethyl] - It has the following structure.



$C_{10}H_{16}N_6S$, Molecular weight 252.34

2. Description : White to off-white, crystalline powder, unpleasant odor, melting range 141-145°c (5).

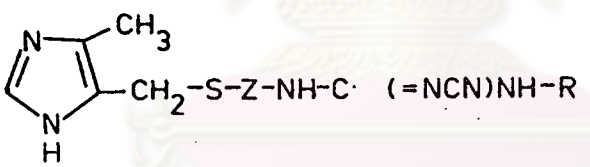
3. Solubility : 1 part soluble in 200 part of water, in 18 part of alcohol, in 1000 part of chloroform, and insoluble in ether (5).

4. Preparation

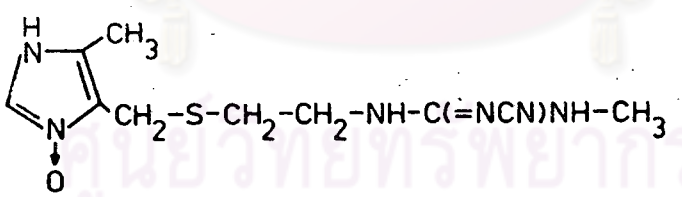
4.1 A solution of 4-[(2-aminoethyl) thiomethyl] -5-methyl imidazole (34.0 g) and N-cyano-N', S-dimethylisothiourea (22.4 g) in acetonitrile (1 l) was heated under reflux for 48 hours. The product obtained was recrystallized from acetonitrile to yield cimetidine (13).

4.2 4-[(2-Aminoethyl) thiomethyl] -5-methylimidazole (23.4 g) in ethanol (200 ml) was slowly added with stirring to a solution of dimethylcyanodithioimidocarbonate (20 g) in ethanol at room temperature. The mixture was set aside overnight and filter to afford N-cyano-N'-[2-(5-methylimidazol-4-yl) methyl thioethyl] -S-methylisothiourea in two crops. A solution of methylamine in ethanol (33 %, 75 ml) was added to a solution of the isothiourea (10.1 g) in ethanol (30 ml) and the mixture was set aside at room temperature for 2.5 hours. Concentration and recrystallization afforded cimetidine (13).

4.3 Imidazolylmethyl sulfides (I) (Z=alkene, R = C_{1-4} alkyl) was prepared.



(I)



(II)

Thus 2-cyano-1-methyl-3[[3-hydroxy imino-2-oxo-butyl]thio]ethyl, guanidine, MeC(:NOH)COCH$_2$SCH$_2$SCH$_2$CH$_2$NHC(:NCN)NHMe, was stirred with ammonium acatate and formaldehyde in acetic acid at 65°C.

to yield imidazole N-oxide derivative (II), then was treated with N,N-dimethyl, methanesulfonamide to give cimetidine (14).

Polymorphism

A polymorphism is a solid crystalline phase of a compound resulting from the possibility of at least two different arrangements of the molecules of the compound in the solid state. In general, two polymorphs are different in the crystal structure but identical in the liquid or vapour states. Different polymorphs are different in structural orientation, physicochemical properties; such as solubility, crystal shape, melting point, density, hardness, optical and electrical properties, vapour pressure, stability, and also the pharmacological activities (6.9).

Polymorphs can be classified into two types: 1. Enantiotropic polymorph: one polymorphic form can be reversibly changed into the another form by varying temperature or pressure, 2. Monotropic polymorph: one polymorphic form is unstable at all temperatures and pressures. At a specified temperature and pressure the only one polymorphic form will be thermodynamically stable (6).

After it has been determined that a drug substance does exist in more than one crystalline form, the conditions under which each can be produced should be established. In this manner, proper crystallizing conditions can be maintained from batch to batch to ensure a uniform and acceptable raw material. Recrystallization technique, kinds of solvent, rate of crystallization and other

factors may cause one crystal form dominate. If there are many polymorphic forms in the drug, it should be determined which one would alter their pharmaceutical or biological beheavior (6).

Cimetidine has four crystalline forms (polymorphs), three forms (polymorphs A, B, and D) are anhydrous and one form is monohydrate (polymorph C). The different forms are obtained from various crystallized conditions. Each polymorphic form has different pharmacological activity because the binding to H_2-receptor site is not the same. And the most active form is closely related to the receptor on specific steriochemistry.

Lemont B. Kier (15) proposed that the characteristic of the H_2-receptor activity of histamine are

a) distance between the nitrogen atom of the imidazole ring and the nitrogen atom of the side chain is near 3.6 Å

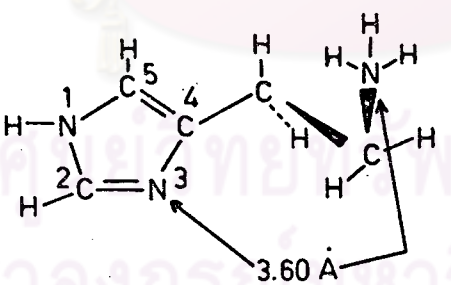


Fig. 1 The molecular conformation of histamine H_2-receptor

b) the orientation of the nitrogen atoms with respect to the imidazole ring is *gauche*.

Four crystalline forms of cimetidine

The intramolecular distances between the N(2) atom of the imidazole ring and the N(3), N(4), or N(5) atom of the cyanoguanidine group and the orientation between the two moieties in the cimetidine molecules of polymorph A, B and C are listed in the table 1(8). The *gauche* orientation of the guanidine group with respect to the imidazole ring is observed in polymorphs A and C, their intramolecular N-N distances are in the range of 2.881-5.061 Å for polymorph A and 3.836-4.416 Å for polymorph C(8). According to the proposal of Lemont B. Kier (15), the molecular conformation of polymorphs A and C would probably be the conformation necessary for effective binding to the histamine H_2-receptor.

Cimetidine polymorph A

It is an anhydrous and platelet crystal; its melting point is 141.5-143.0°C. The conformation of polymorph A (Fig. 2) is characterized by an intramolecular H-bonding at N to H-N group in the

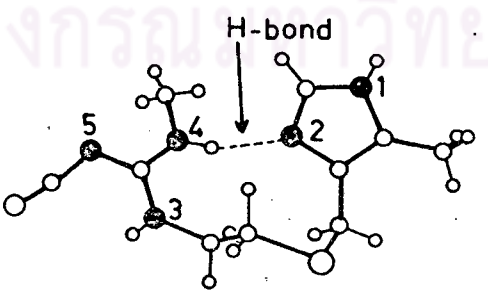


Fig. 2 The Molecular conformation of cimetidine polymorph A

●; N atom.

imidazole and in the guanidine residue, forming a stable ten-membered ring system (8, 16). This conformation makes polymorph A to be thermodynamically more stable than the others.

The solubility of crystalline form A in gastric juice was 5.4 g/liter and its dissolution rate constants in deionized water measured by disk and particle methods were 0.81 $mg/cm^2/min$ and $1.16x10^{-2}$ $mg^{\frac{1}{3}}/min$, respectively (8).

Cimetidine polymorph B

It is an anhydrous and needle crystal; its melting point is 142-145°C. The conformation of polymorph B has not been reported, but the pharmacological activity for H_2-receptor antagonist in rat was done. At low dose (12.5 mg/kg) which corresponds to that used clinically, its efficacy in preventing stress ulceration in rat was lower than polymorphs A and C (8).

Its solubility in gastric juice was 4.7 g/liter and the dissolution rate constants in deionized water measured by disk and particle methods were 0.74 $mg/cm^2/min$ and $0.79x10^{-2}$ $mg^{\frac{1}{3}}/min$, respectively (8).

Cimetidine polymorph C

It is a monohydrate and pyramidal crystal. The melting point of form C is between 70-80°C, which is lower than those of the other forms, suggesting the presence of water of crystallization. The conformations of form C presented in Fig. 3 and Table 1, shows the intramolecular N-N distance of approximately 3.6 Å and *gauche* orientation. These characteristics appear to be the optimal

binding to the active site of the histamine H_2-receptors (8).

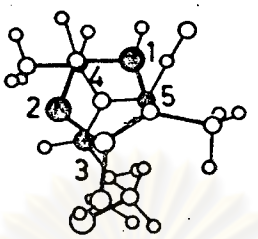


Fig. 3 The Molecular conformation of cimetidine polymorph C, ●; N atom

The molecular conformation of polymorph C was characterized by the folded form resulting from the weak stacking interaction between the imidazole and guanidine moieties; so it was stabilized by double hydrogen bond forming with neighboring molecules and *via* molecule of water crystallization (8).

Its solubility in gastric juice was 5.8 g/liter and the dissolution rate constants in deionized water measured by disk and particle methods were 1.24 $mg/cm^2/min$ and 1.50×10^{-2} $mg^{\frac{1}{3}}/min$, respectively (8).

Cimetidine polymorph D

It is an anhydrous and cubic crystal. Its melting point is 145-146° C. The conformation of polymorph D (Fig. 4) is spirally curled conformation; it is linked in a head-to-tail arrangement with the neighboring molecules *via* intermolecular hydrogen bonds between the imidazole nitrogen and guanidine nitrogen atoms. It is trans orientation; the intramolecular N-N distances is

in the range of 5.584-7.378 Å (8). According to the proposal of Lemont B. Kier (15), the molecular conformation of polymorph D will not have an activity on the histamine H_2-receptor.

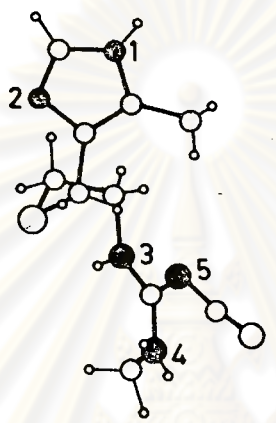


Fig. 4 The Molecular conformation of cimetidine polymorph D
●; N atom

Its solubility in gastric juice was 5.0 g/liter and the dissolution rate constant in deionized water measured by particle method was 0.88×10^{-2} $mg^{\frac{1}{3}}$/min (8).

Selected portions of the "X-ray Structure Studies and Physicochemical Properties of Cimetidine Polymorphism" reported by Shibata at al (8) are presented in Table 1, Table 2 and Figure 5.

Table 1 Intramolecular Distances (Å) between the N(2) Atom of the Imidazole Ring and the Nitrogen Atom of the Cyanoguanidine Group of Cimetidine

Nitrogen atom of the cyanoguanidine group	Intramolecular distances (Å)		
	Form A	Form C	Form D
N(3)	4.090	3.914	5.584
N(4)	2.881	3.836	7.378
N(5)	5.061	4.416	5.737
Orientation between the imidazole ring and the cyanoguanidine group	*gauche*	*gauche*	*trans*

Table 2 The Solubilities and the Dissolution Rate Constants of the Four Crystalline Forms, of Cimetidine

Crystalline form of Cimetidine	Solubility in gastric fluid g/l	Dissolution rate constants in deionized water	
		Disk method $mg/cm^2/min$	Particle method $mg^{\frac{1}{3}}/min$
A	5.4	0.81	1.16×10^{-2}
B	4.7	0.74	0.79×10^{-2}
C	5.8	1.24	1.50×10^{-2}
D	5.0	_a	0.88×10^{-2}

_a The experiment for form D was omitted because of the difficulty in preparing its crystalline form.

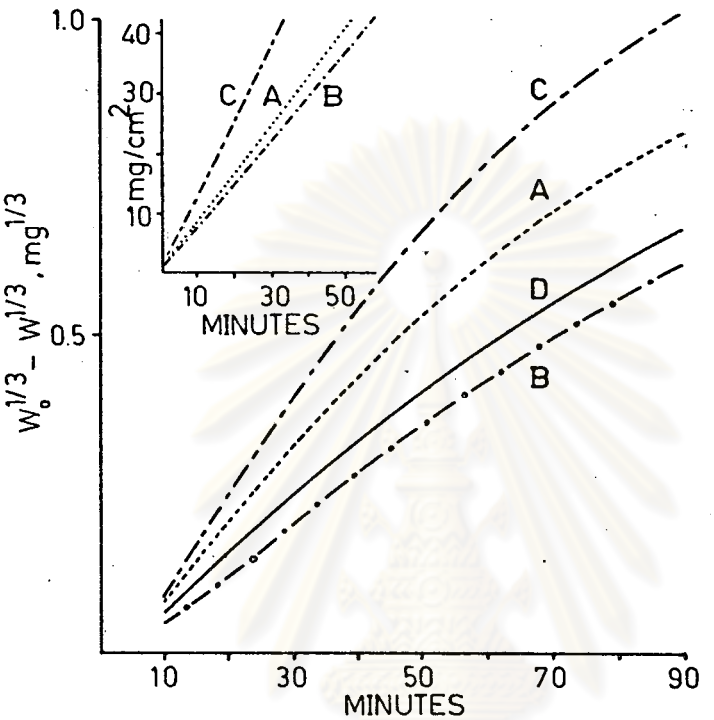


Fig. 5 Dissolution profiles of the four crystalline forms of cimetidine in particle systems and those of the three crystalline forms in disk systems.

Polymorphism Identification

1. Differential Thermal Analysis

Differential Thermal Analysis (DTA) has been used extensively to identify the various types of polymorphs. In this method, the heat loss and gain, resulting from physical or chemical changes occurring in a sample, is recorded as a function of temperature as the substance is heated at a uniform rate. Enthalpic changes, both

endothermic and exothermic, are caused by phase transitions. For example, fusion, sublimation, solid-solid transition, and water loss generally produces endothermic effects while crystallization produces exothermic effects (6, 17).

2. Infrared Spectroscopy

The Infrared spectrum is said to be one of the most characteristic properties of a compound. This technique can be used for both qualitative and quantitative determinations of polymorphs (6).

In qualitative determination, the number of absorption bands in an infrared spectrum may be considerable. If two compounds are the same, the position and relative intensity of the bands will be agreed in all respects. Sometimes the spectra of the two compounds obtained in solid state are not identical, those two compounds will be recrystallized from the same conditions of solvent, and then repeated the infrared determinations again. If the infrared spectra are also difference, this indicates that the two compounds are unidentical. The recrystallization of the crystal is necessary because various crystalline forms of the same substance may give rise of the different spectra (22).

Quantitative Determination by Infrared Spectrophotometry

In spectrophotometric practice, quantitative analysis is based on the application of Beer-Lambert's Law

Beer-Lambert's law expressed as:

$$A = \log \frac{1}{T} = \log \frac{I_o}{I} = ECL$$

A = absorbance or optical density

T = transmittance

I = transmitted radiation

I_o = incident radiation

C = concentration in gramme mole/l

L = path length in cm

E = extinction coefficient, (absorptivity)

In Beer-Lambert's law, C can be considered generally as the concentration of a substance in the sample and E as a constant for one particular substance at a given frequency. When two or more components present in a system and absorb at the same frequency, the total absorbance is equal to the summation of absorbances of the components at this frequency.

Beer's law is applied to the absorbance of a material in solution, assuming that the solvent does not absorb and the cell used in the experiments does not scatter or reflect light. In practice, however, scatter and reflection losses from the cell are also measured and the 'true' absorbance as defined in Beer's law becomes,

'True' absorbance = 'Apparent' absorbance minus Cell absorbance

In quantitative analysis the "base line" method is the most commonly used technique of obtaining an absorbance proportional to the

concentration of components to be analysed. This method generally overcomes scattering and reflection losses and also background absorption of the other components. It can be applied not only to solutions but also to liquid mixtures and solids such as polymer films and alkali halide discs (19). The base line technique is useful for the determination of the content of one polymorphic form of a substance when present in another, e.g. the determination of the contents of polymorph A and non polymorph A of chloramphenicol palmitate (11, 12) described in USP XX (20) and B.P. 1980 (21).

The outline of this study was as follows:

1. Studied the crystallization of cimetidine polymorphs A and B in various kinds of solvents to obtain an optimum yield of pure polymorphs, and confirmed the identities of the polymorphs by infrared spectroscopy and differential thermal analysis.

2. Studied the infrared spectra of cimetidine polymorphs A and B to find the different characteristic absorption bands of the two forms and to select the bands suitable for the quantitative analysis of mixture of polymorphs A and B.

3. Studied the possible cause of the polymorphs alteration in potassium bromide disc technique by using vibration grinder.

4. Determined the reproducibility of the proposed method.

5. Analysed the of commercial cimetidine raw materials and theirs respective tablet formulations and compared the results obtained, to see the effect of manufacturing process on polymorphs alteration.

The contribution of this thesis to the pharmaceutical quality control technology.

1. It is the first study of the quantitative IR analysis of cimetidine polymorphs A and B in commercial raw materials and tablet formulations.

2. The developed method is suitable for the analysis of cimetidine polymorphs A and B in raw materials and pharmaceutical preparations.

3. The dissemination of the knowledge gained from this study to local pharmaceutical manufacturers and to other analysts will enable them to carry out the analysis of the polymorphic forms of cimetidine in raw material and in tablet formulation. It will also advise them to keep close observation to the polymorphism of other drugs.

4. The principle of the quantitative infrared analysis of a mixture of polymorphs was studied. The knowledge gained will be useful for further studies of other drugs bearing active and inactive polymorphic forms.