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Dissolution behavior and bioavailability of cimetidine-HCl (cimetidine monohydrochloride monohydrate)

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Cimetidine, N-cyano-N′-methyl-N″-(2-[(5-methyl-1H-imidazol-4-yl) methyl]thio ethyl)quanidine, is a competitive histamine H_2-receptor antagonist which inhibits gastric acid secretion and is used for the treatment of gastric ulcer. In previous papers (Shibata et al., 1983a; Kokubo et al., 1984), we reported physicochemical properties of four polymorphiric crystalline forms of cimetidine (forms A, B, C and D). The results showed that the bioavailability of cimetidine was dependent on the physicochemical properties of the crystalline form. Recently, cimetidine monohydrochloride monohydrate (cimetidine-HCl) was prepared in a crystalline form (Shibata et al., 1983b). In this paper, the relation between in vitro dissolution behavior and in vivo bioavailability in rats of cimetidine-HCl was studied.

Cimetidine-HCl was crystallized as monohydrate by slow evaporation of a 1 N HCl solution saturated with cimetidine. The crystals were identified by IR spectroscopy using the KBr disc method. The IR spectra of cimetidine (form A) and cimetidine-HCl were shown in Fig. 1.

The dissolution rate was determined by the rotating method described previously (Shibata et al., 1983a). The disk samples of cimetidine-HCl and cimetidine, 1.3 diameter (surface area is 1 cm^2) were prepared by compressing 400 mg of cimetidine-HCl and cimetidine (form A) under 1.5 tons/cm^2. The preparations of disk samples did not affect the crystalline forms as determined by IR spectra. Dissolution

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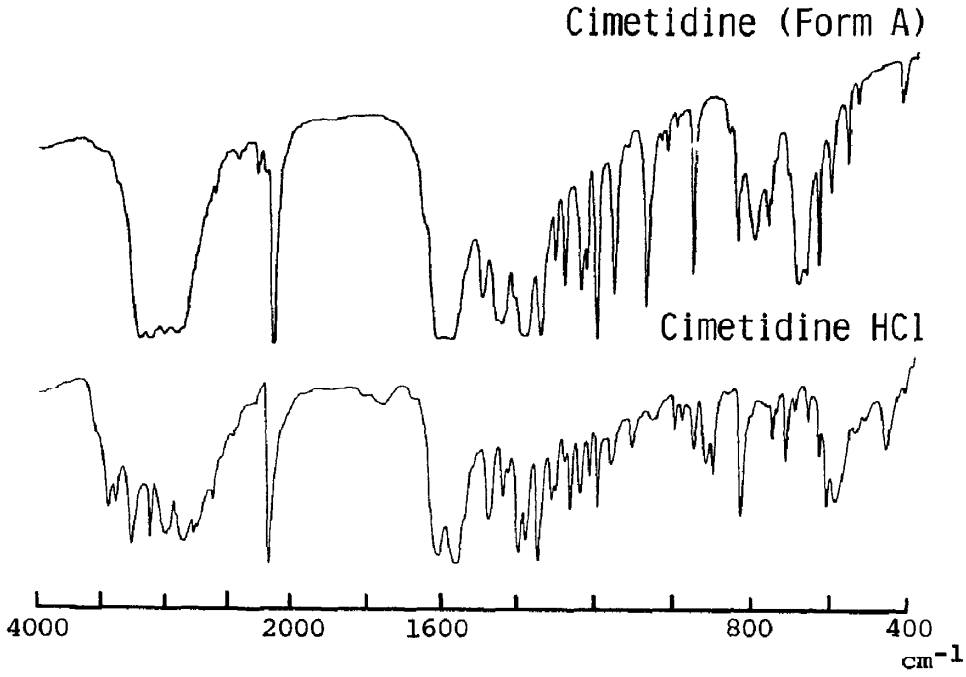

Fig. 1. Infrared absorption spectra of cimetidine-HCl and cimetidine (form A).

Fig. 2.

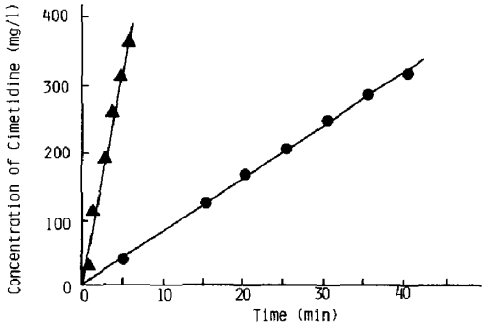

Fig. 3.

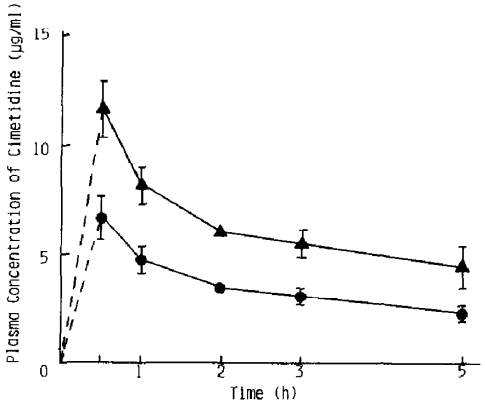

Fig. 2. Dissolution profiles of cimetidine-HCl and cimetidine (form A) in water in the rotating disk systems at 37°C. ▲, cimetidine-HCl; ●, cimetidine (form A).

Fig. 3. Plasma concentration of cimetidine after intragastric administration of cimetidine-HCl and cimetidine (form A) in rats. ▲, cimetidine-HCl; ●, cimetidine (form A).

TABLE 1

BIOAVAILABILITY PARAMETERS OF CIMETIDINE-HCl AND CIMETIDINE (FORM A) AFTER ORAL ADMINISTRATION IN RATS

	Dose (mg/ml)	C_{max} (μg/ml)	t_{max} (h)	AUC_0^5 ($\mu g \cdot h\ ml^{-1}$)	F (%)
Cimetidine (form A)	100	6.7	0.5	17.6	27.4
Cimetidine-HCl	100	11.7 *	0.5	30.9 *	48.1 *

F = bioavailability.

* Significantly different from cimetidine (form A), $P < 0.005$.

tests were performed in 1000 ml of degassed water at 37°C at a rotation rate of 100 rpm.

Wistar strain male rats (220–250 g), fasted for 15 h prior to the experiments but with access to water, were used. Powdered cimetidine-HCl and cimetidine (form A) (44–74 μm in diameter) were administered orally to the rat stomach with 0.8 ml of water (dose: 100 mg/kg) through a catheter. After pentobarbital (50 mg/kg) anesthesia, blood samples were collected from the inguiginal vein at the appropriate time. On the other hand, the cimetidine solution (in NaCl saline) was administered via a femoral vein at the dose of 100 mg/kg. The plasma concentration of cimetidine was measured by high-performance liquid chromatography (HPLC) using UV-detector (220 nm) according to the method described by Randolph et al. (1977). The area under the curve (AUC) was calculated according to the method of Kaplan et al. (1973) by means of the trapezoidal rule.

Fig. 2 shows the dissolution profiles for cimetidine-HCl and cimetidine (form A) measured by the rotating disk method. The dissolution rate constants calculated from the slopes of these curves were 67.00 $mg \cdot l^{-1} \cdot min^{-1} \cdot cm^{-2}$ and 8.06 $mg \cdot l^{-1} \cdot min^{-1} \cdot cm^{-2}$ for cimetidine-HCl and cimetidine (form A), respectively. The dissolution rate constant for cimetidine-HCl was 8.3 times greater than that for cimetidine (form A). Fig. 3 shows the time course of the plasma concentration of cimetidine following oral administration of cimetidine-HCl and cimetidine (form A). The peak plasma levels were reached within 30 min after administration with both cimetidine-HCl and cimetidine (form A). The C_{max} and AUC_0^5 after oral administration of cimetidine-HCl was significantly higher than that of cimetidine (form A) (Table 1). The absolute bioavailabilities of cimetidine-HCl and cimetidine (form A) were 48.1% and 27.4%, respectively, indicating that the bioavailability of cimetidine-HCl was 1.8 times larger than that of cimetidine (form A).

In conclusion, the dissolution rate of cimetidine-HCl was 8.3 times larger than that of cimetidine (form A) and the bioavailability of cimetidine-HCl was 1.8 times larger than that of cimetidine (form A).

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