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THE SIGNIFICANCE OF FORMULATION IN DRUG BIOAVAILABILITY

I. A study with Cimetidine Tablets

by

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From a variety of commercially available cimeditine products, an arbitrary sampling of seven tablet-forms, as well as, the active compound, were examined by a series of tests for the veryfication of the purity of content, the dissolution rate, disintigration time, hardness etc.
It was found that some of the products did not comply with the formulation standards, resulting in insufficient bioavailability.

The inability of the antihistaminic drug (H_2-receptor antagonists) to inhibit histamine-stimulated gastric acid secretion has been known for many years (1,2).

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Robertson and Grossman (3) have screened several compounds in search of gastric acid secretion inhibitors and a study has been reported on compounds, chemically related to histamine, which were examined for their action on acid secretion (4).

The effects of cimetidine on gastric acid secretion have been investigated in several preparations and has been found that in all cases the product was approximately equiactive in inhibiting histamine-stimulated and pentagastrin-stimulated and secretion and, also, that it was a little more active than other compounds, namely metiamide (5). Cimetidine acts as a specific competitive antagonist on histamine at H_2-receptor (6).

Cimetidine is a very polar molecule which has a low octanol-water partition coefficient, and this is reflected in observed excretion patients. It is excreted rapidly and largely unchanged, although a proportion is oxidatively metabolized to sulphoxide which is even more polar and more hydrophylic (5).

However an important factor in drug activity and eficacy is also the proper formulation of the product. In the present investigation a correlation is attempted between several pharmaceutical formulations, of various origins, in the tablet form and their bioavailability standarts.

E X P E R I M E N T A L P A R T

1) MATERIALS

Seven commercially available products, all in the tablet form, indentified as Products I-VI and Tagamet^R, and the active ingredient cimetidine were employed.

2) EQUIPMENT

The following instruments were used : U.V. - Perkin Elmer 555, I.R. - Perkin Elmer Model 117, HPLC-Dupont, 830 Liquid Chromatograph, Haberlein hardness tester, the USP XX recommended rotating basket and a TLC system (Kieselgel F 254 Merk thin layer plates).

3) METHODS

a) Dissolution Rate.

One tablet was placed in each of the six tubes of the basket assembly, as described in the Dissolution Test Method of the USP XX[7]. The basket was immersed in a 1.000 ml beaker containing 900 ml distilled water at 37 $\pm$ 0.5°C. After 15, 30 and 60 minutes of continuous mouvement, aliquots of 2ml were withdrawn, and diluted with 0.1 N sulfuric acid to 250 ml (for 200 mg tablets) and 500 ml (400 mg tablets).

The absorbance was measured at 218 nm and 260 nm in a 1 cm silica cell, using 0.1 N sulfuric acid as reference. The dissolution, as % of claim, was calculated by the equation .

$$\frac{\Delta A \times 900 \times V \times 100 \times 1000}{E^{1\%}_{1cm} \times 100 \times 6 \times P \times 2}$$

where $\Delta A = A_{218} - A_{260}$

V = 250 for 200 mg and 500 for 400 mg tablets.

P = mg cimeditine per tablet claimed

and 769 = $E^{1\%}$ of cimetidine in 0.1 N sulfuric acid.

b) Disintegration

The disintegration time was measured by the method described in the B.P. 1980, Appendix XII[8].

c) Cimetidine Content

i) By Ultra-Violet Method

Twenty tablets were finely powdered, and the equivalent of 100 mg cimetidine was accurately weighed into a 250 ml volumetric flask and 100 ml of 0.1 N sulfuric acid were added and the solution was shaken mechanically for 20 minutes. 0.1 N sulfuric acid was added to volume, filtered, and 5 ml of the filtrate were diluted to 250 ml with 0.1 N sulfuric acid. The absorbance was measured at 218 nm and 280 nm, using 0.1 N sulfuric acid as blanc.

The cimetidine, % per tablet, was calculated using the following formula :

$$\frac{\Delta A \times 250 \times 250 \times 1000 \times \text{Av.wt./tab. (g)}}{E^{1\%}_{1cm} \times 5 \times 100 \times \text{wt.samble (g)}}$$

ii) By High Pressure Liquid Chromatograph

Sample solution :

Twenty tablets were finely pow dered, and the equivalent of 200 mg of cimetidine was placed into a 50 ml volumetric flask. To this solution was added 10 ml methanol and 10 ml of the internal standard, and shaken mechanically for 10 minutes.

The mixture was diluted to volune with methanol and filtered.

Standard solution :

0.2 g of cimetidine reference standard was accurately wighed and placed into 50 ml volumetric flask. 10 ml of methanol was added, followed by 10 ml internal standard and diluted to volume with methanol.

Chromatography

The following conditions were employed. A Zorbax-sil 25 cm with 2.1 mm i.d. column at a 1.5 ml/min (1000 psi) flow rate and x8 attenuation under ambient temperature. The chart speed was set at 2.5 min/cm using a U.V. precision photometer at 254 nm. The mobile phase was consisted of acetonitrile :methanol : water : ammonia 875/100/20/5 respectively. Cimetidine peaks were eluted at 5 1/2 min. (i.s. 4 1/2 min.).

The amount of cimetidine (in mg) per tablet was calculated using the formula :

$$\frac{R \text{ samle} \times \text{wt. standard (mg)} \times \text{av. tab. wt. (g)}}{R \text{ standard} \times \text{wt. samle (g)}}$$

where $R = \frac{\text{cimetidine peak height or area}}{\text{i.s. peak height or area}}$

d) Polymorphism

By Infrared Spectrum

Powdered tablet sample was added to KBr grinded powder mixed, pressed and the infrared spectra of the disk was recorded.

e) Thin Layer Chromatography

15 cm from the bottom of a Kieselgel F254 precoated thin layer plate cimetidine sample and reference solution were applied, using a ethyl acetate : methanol : ammonia : 100:20:10 developing system.

The spots were diluted with iodine crystals in a tank.

RESULTS AND DISCUSSION

The results are depicted in Table I, after all necessary calculations and extrapolations were performed.

It is interesting to note that Tagamet^{R} responded favorably to all tests carried out undet the experimental conditions outlined in the relevant part. Product I, on the other hand, appeared to have a rather small amount (26.5%) liberated in the 15 first minutes, while its disintegration time was extremely long and its content per dosage unit was above the accepted average. The active compound was of the appropriate polymorph A.

Product II failed the dissolution (9.1%) and disintegration tests, while its content/dosage and polymorphism were within the accepted standards. The third formulation could be considered within the limits of disintergration time, it was of the proper polymorphic form and content/dosage unit, but failed the dissolution test.

Product IV, a 400 mg dosage form, was found to be outside the limits for dissolution (11%) and disintegration but complied with content/dosage unit and polymorphic characteristics.

Finally, Products V and VI, while of similar manufacturer, represented different batches. From those, number V did not follow either dissolution rate (9.6%) or disintegration time, and although it was within the content/dosage unit area, it represented (from IR studies) a polymorphic B compound, i.e. a cimetidine of unknown, as yet, pharmacologi-

TABLE I

PRODUCT*	DOSAGE	DISSOLUTION % in 15 min	Pass/Fail	DISINTEGRATION min	Pass/Fail	CIMETIDINE CONTENT mg/tablet	POLYMORPH PRESENT
TAGAMET^{R}	200 mg	85.0	P	15	P	190-210	A
PRODUCT I	200 mg	26.5	F	240	F	213	A
PRODUCT II	200 mg	9.1	F	60	F	190.5	A
PRODUCT III	200 mg	31.8	F	38	F	203.9	A
PRODUCT IV	400 mg	11.2	F	240	F	398	A
PRODUCT V	200 mg	9.6	F	60	F	195.3	B
PRODUCT VI	200 mg	83.8	F	1.25	P	199.3	A

* All products were in the tablet form
Products II and III were "coated tablets"

cal usefulness, since all experiments for this compound have been conducted, and thoroughly studied, with the A polymorphic form.

Furthermore, it was observed during purity tests, such as those performed by TLC or HPLC methods, that some of the products appeared to have extra peaks (on HPLC) or spots (on TLC). However, such entities are of doubtfull significance since these extra weak spots or peaks may be due to either different vehicles or different sources for certain excipients. It is not uncommon, though, that the addition of some inactive compounds, the tablet hardness, thickness etc. may affect the disintegration times and dissolution rates of pharmaceutical dosage forms.

Since the effectiveness of a drug is related to the proper, and according to the rules of the good manufacturing practice formulation, it is necessary that such conditions must be followed during drug manufacturing.

In the present investigation, of the seven randomly selected, commercially available pharmaceutical dosage forms, appears that only one, namely Tagamet^{R}, complies with the *in vitro* bioavailability studies, while Products I-VI gave insufficient results.

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