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Stability of Solid Dosage Forms. II.¹⁾ Hydrolysis of Meclofenoxate Hydrochloride in Commercial Tablets

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The kinetics of hydrolysis of meclofenoxate hydrochloride (MF-HCl) in commercial tablets were studied in comparison with those of the pure solid. MF-HCl in tablets was found to be decomposed by water vapor in the same way as the pure solid. At a humidity above the critical relative humidity (CRH) of the system, the degradation ratio, x could be correlated to time by the equation

$$x = kt^n$$

where k and n are parameters. At humidities below the CRH, on the other hand, the degradation did not conform to this equation because of the fast decomposition at the initial stage.

The stability of several commercial MF-HCl tablets was studied, and some excipients such as magnesium carbonate were found to reduce the stability of the drug.

Keywords—meclofenoxate hydrochloride; commercial tablets; excipient; hydrolysis in solid state; kinetic; stability

In a previous paper,¹⁾ we reported on the hydrolysis of a water-soluble pharmaceutical solid, meclofenoxate hydrochloride (MF-HCl) pure solid, and proposed a mechanism for the decomposition.

In the present study, the decomposition of MF-HCl in commercial tablets was studied kinetically in comparison with that of the pure solid. Furthermore, the stability of several commercial MF-HCl tablets was studied to clarify the effects of various factors, such as excipients, on the stability of the drug in the tablets.

Experimental

Materials—The MF-HCl tablets used were five different commercial film-coated tablets containing 100 mg of MF-HCl. Pure solid MF-HCl (Toyama Kagaku Co.) was recrystallized from acetone. Corn starch, lactose, magnesium carbonate and magnesium stearate were of J.P. IX grade. Other chemicals used were of reagent grade.

Kinetic Studies—The kinetic studies were carried out in the same manner as described in the earlier paper.¹⁾ Three tablets on polyvinyl chloride dishes were placed in a reaction vessel containing a saturated solution of an inorganic salt (KCl, NaNO₃, NaBr or KF). The reaction vessels were each placed in a thermostated bath (50, 60 or 70 °C).

The kinetics were also studied with powder samples (milled tablets) which were prepared by passing the pulverized tablets through an 88 μ m sieve to remove the coating film. Accurately weighed powder samples each corresponding to 12.5 mg of MF-HCl, based on the label, were transferred to dishes, which were each placed in a reaction vessel.

Furthermore, the effect of the ingredients on the decomposition of MF-HCl was studied with powder mixtures. One hundred mg of MF-HCl was mixed with 50 mg of corn starch, 50 mg of lactose, 30 mg of magnesium carbonate and/or 2 mg of magnesium stearate, all of which had been passed through an 88 μ m sieve, and kept over silica gel under reduced pressure. Each powder mixture sample (corresponding to 12.5 mg of MF-HCl) was placed in a reaction vessel.

Each kinetic run was repeated twice.

Determination of MF-HCl and Its Decomposition Product by High-Performance Liquid Chromatography (HPLC)—The sample in a dish was removed from the reaction vessel at the appropriate time and weighed to estimate the extent of water adsorption in the same manner as described in the earlier paper.¹⁾ Remaining MF-HCl was determined by HPLC after extraction by the following method. Each tablet was crushed into powder, which was transferred to a flask and shaken with 50 ml of CH₃CN. After centrifugation, 2 ml of supernatant solution was added to 2 ml of 3-methylsalicylic acid solution (0.3% in CH₃CN). The solution was brought up to 20 ml with CH₃CN and 5 μ l of the solution was subjected to HPLC. Each powder sample was analyzed by the same method except that it was extracted with 10 ml of CH₃CN.

The HPLC conditions were the same as in the previous paper.¹⁾

Results and Discussion

Kinetics of Hydrolysis of MF-HCl in Tablets

Kinetic studies were carried out with a tablet (Brand A), which was comparatively stable among the five different commercial tablets tested, as will be described later, in order to compare the decomposition mechanism of MF-HCl in tablets with that of the pure solid. Figure 1 shows typical time courses of the decomposition of MF-HCl tablets stored at 60 °C, and 50 or 68% relative humidity (RH), in comparison with those of MF-HCl pure solid (149–177 μ m) reported in the previous paper.¹⁾ The decomposition of the powder sample (milled tablets) prepared by pulverizing Brand A tablets was also studied to clarify the effect of tableting and film coating on the decomposition, and typical plots are also shown in Fig. 1. Both in tablets and milled tablets, MF-HCl was found to be hydrolyzed to *p*-chlorophenoxyacetic acid and dimethylaminoethanol hydrochloride (DMAE-HCl) in a pattern similar to that of the pure solid. The fact that MF-HCl in tablets decomposed faster than the pure solid suggests that characteristics of the tablets, such as the presence of excipients, may accelerate the decomposition. Furthermore, the faster decomposition in milled tablets shows that tableting and film coating tend to retard the decomposition.

Figures 2 and 3 show the water adsorption observed in the decomposition of tablets and milled tablets, respectively. In both cases, water was adsorbed rapidly from the beginning of the reaction in the higher range of RH, while it was adsorbed slowly with an increase in decomposition products at lower RH, as in the decomposition of the pure solid.

As reported in the earlier paper,¹⁾ the initial decomposition of MF-HCl pure solid can be represented by equation (1)

$$x = kt^n$$

(1)

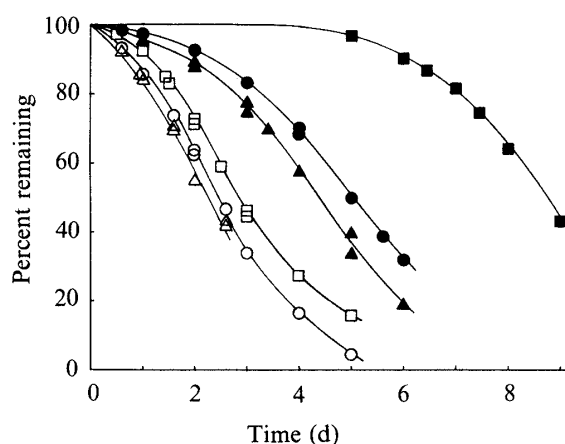


Fig. 1. Decomposition of MF-HCl in the Solid State

■, pure solid; ○, tablet; △, milled tablet.
 □, 60 °C, 68% RH; ●, 60 °C, 50% RH.

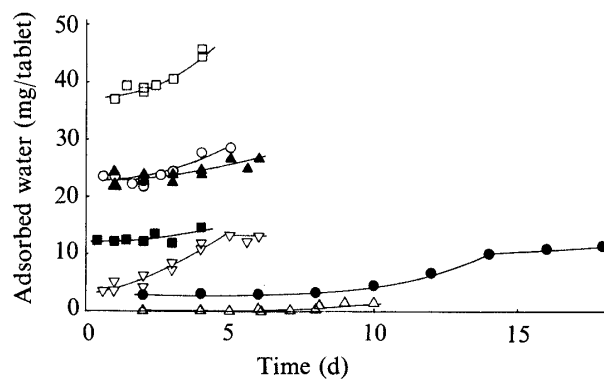


Fig. 2. Water Adsorption by Tablets

□, 50 °C, 81%; ○, 60 °C, 68%; ▲, 50 °C, 68%; ■, 70 °C, 51%; ▽, 60 °C, 50%; ●, 50 °C, 50%; △, 70 °C, 21% RH.

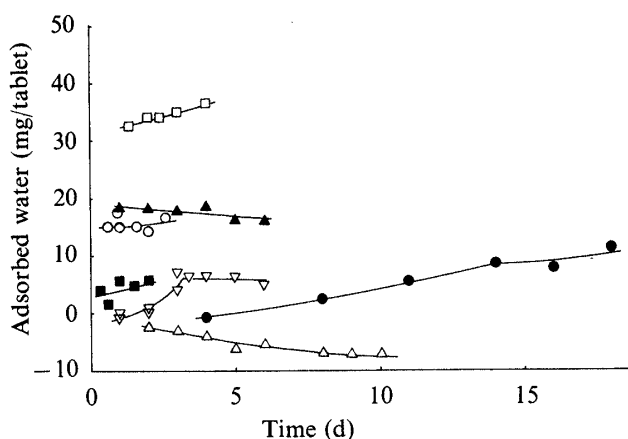


Fig. 3. Water Adsorption by Milled Tablets

□, 50°C, 81%; ○, 60°C, 68%; ▲, 50°C, 68%; ■, 70°C, 51%; ▽, 60°C, 50%; ●, 50°C, 50%; △, 70°C, 21% RH.

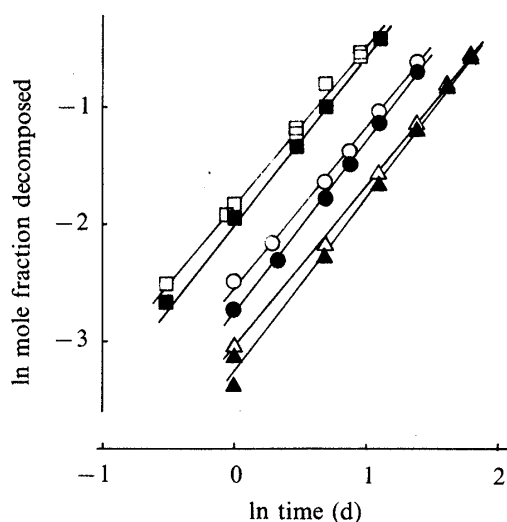


Fig. 4. Decomposition at Humidities above the CRH of MF-HCl

■, 60°C, 68%; ○, 50°C, 81%; ▲, 50°C, 68% RH.
□, ○, milled tablet; ■, ●, tablet.

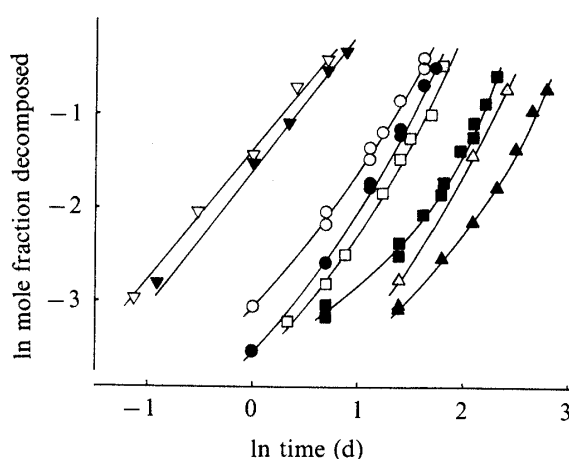


Fig. 5. Decomposition at Humidities below the CRH of MF-HCl

▽, 70°C, 51%; ○, 60°C, 50%; □, 70°C, 21%; ▲, 50°C, 50% RH.
▽, ○, □, milled tablet; ▼, ●, ▲, tablet.

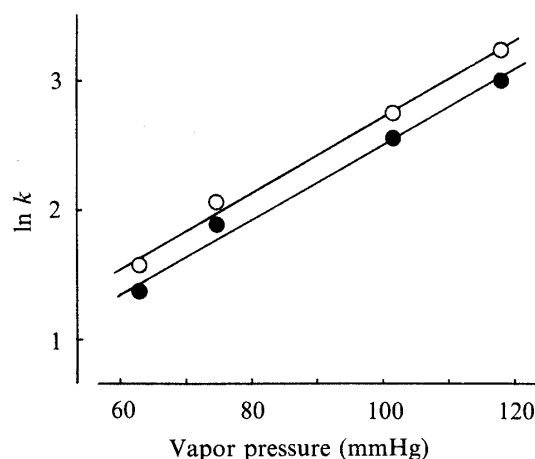


Fig. 6. Relationship between Vapor Pressure and Decomposition Rate Constant

○, milled tablet; ●, tablet.

where k and n are constants and x is the percent decomposed. Two distinct values of n are obtained at RH above and below the critical relative humidity (CRH) of MF-HCl, but n is independent of temperature and humidity in each RH range. In regard to the decomposition in tablets and milled tablets, the logarithm of the percent decomposed is plotted against that of time in Figs. 4 and 5. As can be seen in Fig. 4, a linear relationship, namely a conformity to equation (1), was observed for both tablets and milled tablets at RH above CRH, as in the case of the pure solid. n was estimated to be 1.5 and 1.4 for tablets and milled tablets, respectively, by the non-linear least-squares method ($n=1.6$ for pure solid). Furthermore, the dependence of calculated k on the vapor pressure was similar to that in the case of the pure solid, as shown in Fig. 6. These results suggest that MF-HCl in tablets may decompose in the same way as the pure solid, regardless of the presence of excipients, when water is adsorbed sufficiently by the tablets. At RH below CRH, however, the decomposition in the tablets did not conform to equation (1) except for the decomposition at 70°C, 50%RH, as can be seen in Fig. 5, while the decomposition of the pure solid could be represented by equation (1) with

$n=5.2$. Since the inconformity with equation (1) was also observed in the decomposition of milled tablets, as in that of tablets, it cannot be ascribed to the film coating or tableting. The deviation (rapid decomposition at the initial stage) from equation (1) may be ascribed to hydrolysis by the water originally present in tablets as well as by water vapor. This contribution to the overall decomposition may increase with decreasing water vapor pressure and decreasing rate of hydrolysis by water vapor. As shown in Fig. 5, the decomposition at 70 °C, 51%RH conformed to equation (1) even at RH below the CRH of MF-HCl, and n was estimated to be 1.5 and 1.4 for tablets and milled tablets, respectively, as at RH above the CRH. This may result from the effect of the excipients, which make the CRH of the system lower than the RH. The CRH of the tablet was not determined, but it seems to range from 30 to 50% at 70 °C.

In conclusion, MF-HCl in tablets can be considered to decompose in the same way as the pure solid dealt with in the previous paper¹⁾—the hydrolysis is initiated by water vapor, and further accelerated by adsorbed water, which increases with increasing amount of decomposition product (DMAE-HCl). However, the fact that the decomposition at RH below the

TABLE I. Stability of Commercial MF-HCl Tablets

| Sample | Percent retained | | | | |
|--------|------------------|----------------|----------------|----------------|----------------|
| | 60 °C, 68% RH | | | 60 °C, 50% RH | |
| | 0 | 0.6 | 2.6 | 2 | 5 d |
| A | 99.3 (99.3) | 93.0 (91.8) | 46.6 (42.2) | 90.7 (88.0) | 49.8 (36.3) |
| B | 99.3 (99.0) | 93.0 (84.5) | 57.6 (5.2) | 86.5 (62.0) | 51.6 (10.0) |
| C | 99.3 (99.3) | 89.1 (83.1) | 34.1 (16.7) | 83.4 (67.6) | 26.2 (3.8) |
| D | 99.0 (98.9) | 75.1 (71.8) | 14.9 (7.4) | 62.1 (49.8) | 7.0 (1.8) |
| E | 92.4 (85.0) | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.0) |

(), milled tablet.

TABLE II. Effect of Additives on Decomposition of MF-HCl

| No. | MF | Formulation (mg) | | | | Percent remaining | | | | |
|-----|-----|------------------|---------|---------------------|--------------------|-------------------|------|------|---------------|------|
| | | Corn starch | Lactose | Magnesium carbonate | Magnesium stearate | 60 °C, 68% RH | | | 60 °C, 50% RH | |
| | | | | | | 0 | 0.6 | 2.6 | 2 | 5 d |
| 1 | 100 | — | — | — | — | 100 | 96.0 | 57.0 | 100 | 95.6 |
| 2 | 100 | 50 | — | — | — | 100 | 69.3 | 4.3 | 89.5 | 37.9 |
| 3 | 100 | — | 50 | — | — | 100 | 85.7 | 57.6 | 97.6 | 82.8 |
| 4 | 100 | 50 | — | 30 | — | 96.8 | 0.0 | 0.0 | 0.0 | 0.0 |
| 5 | 100 | — | 50 | 30 | — | 92.6 | 0.0 | 0.0 | 0.0 | 0.0 |
| 6 | 100 | 50 | — | — | 2 | 100 | 77.8 | 32.4 | 72.1 | 19.2 |
| 7 | 100 | — | 50 | — | 2 | 100 | 66.3 | 2.9 | 73.6 | 14.4 |
| 8 | 100 | 50 | — | 30 | 2 | 95.4 | 0.0 | 0.0 | 0.0 | 0.0 |
| 9 | 100 | — | 50 | 30 | 2 | 90.6 | 0.0 | 0.0 | 0.0 | 0.0 |

CRH could not be represented by equation (1), which holds for the decomposition of the pure solid, indicates the complexity of the decomposition mechanism in tablets, and this can be ascribed to various factors involved in the tablets. Further studies to develop rate equations which take other factors (such as water content in tablets and the permeability of the coating film) into account are required to predict the stability of tablets precisely.

Stability of MF-HCl Commercial Tablets

Table I shows the stability of five different commercial tablets. Large differences in stability were observed among tablets. Some tablets (Brands D and E) showed poor stability, which suggests the presence of incompatible excipients in the formulations. The effects of some excipients formulated in commercial tablets on the hydrolysis of MF-HCl were studied with powder mixtures prepared by adding the excipients to MF-HCl pure solid, and the results are shown in Table II. The rapid decomposition in formulations 4, 5, 8, and 9 indicates that magnesium carbonate accelerates the hydrolysis. This may be ascribed to the basicity of magnesium carbonate on the basis of the report that the hydrolysis of MF-HCl in aqueous solution is subject to specific base catalysis.²⁾ Furthermore, Table II shows that corn starch is more incompatible than lactose. The addition of magnesium stearate tends to reduce the stability drastically in the case of the formulation with lactose, while it seems to stabilize the formulation with corn starch at higher RH. These effects may be due to the changes in CRH or water content of the system.

These results should be of considerable interest to formulators.

References

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