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COMMUNICATION

The Effect of Polymorphism on Powder Compaction and Dissolution Properties of Chemically Equivalent Oxytetracycline Hydrochloride Powders

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ABSTRACT

In South Africa, oxytetracycline is identified as an essential drug; many generic products are on the market, and many more are being developed. In this study, six oxytetracycline hydrochloride powders were obtained randomly from manufacturers, and suppliers were compared. It was found that compliance to a pharmacopoeial monograph was insufficient to ensure the optimum dissolution performance of a simple tablet formulation. Comparative physicochemical raw material analysis showed no major differences with regard to differential scanning calorimetry (DSC), infrared (IR) spectroscopy, powder dissolution, and particle size. However, the samples could be divided into two distinct types with respect to X-ray powder diffraction (XRD) and thus polymorphism. The two polymorphic forms had different dissolution properties in water or 0.1 N hydrochloride acid. This difference became substantial when the dissolution from tablets was compared. The powders containing form A were less soluble than that containing form B.
Key Words: *Compaction; Dissociation; Oxytetracycline; Polymorphism; Powder.*

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INTRODUCTION

Oxytetracycline hydrochloride absorption varies according to the oral pharmaceutical form (1). Serum levels reached with the formulation in capsules were superior to those observed with coated tablets, and the simultaneous administration of two 250-mg capsules led to higher serum levels compared to that reached with one 500-mg capsule. Brice and Hammer (2) performed disintegration and dissolution tests on oxytetracycline tablets and found that batches that gave poor serum levels had slower in vitro dissolution rates. Other investigations (3,4) reported that the dissolution rate profiles also varied among generic brands from different manufacturers and between and within batches of one source.

The occurrence of crystal polymorphism could be one factor that negatively influences absorption and especially in vitro dissolution rates. Oxytetracycline hydrochloride appears in at least three crystal forms, two polymorphs (A and B) and a stable adduct compound with either ethanol or methanol (C) (5). Their physical and physicochemical properties differ in a decisive way. The solubility of form B at ambient temperature in water is 28 times higher than that of form A. In contrast to forms B and C, form A is not hygroscopic. Esezebo and Pilpel (6) studied the effect of various formulations and processing factors on the dissolution of uncoated oxytetracycline tablets. It was found that the dissolution rate constants depended on the gelatin content and packing fraction of the tablets. Oxytetracycline hydrochloride was also examined for possible incompatibility with a variety of excipients in tablet formulations and was found to be incompatible with magnesium stearate, sodium alginate, mannitol, and anhydrous dextrose (7,8). Polymorphism, formulation differences, processing factors, and incompatibilities all can adversely affect the dissolution properties of oxytetracycline tablets and subsequently the in vivo absorption.

In South Africa, raw materials from different sources and at substantially different prices are available for the generic manufacturer. The scope of this study was to ascertain whether six randomly chosen samples of oxytetracycline hydrochloride were within acceptable limits of performance and thereby equivalent for substitution in pharmaceutical manufacturing. To ascertain substitutability, both compliance to compendial tests and a general preformulation assessment of the powder samples were determined. These tests included differential scanning calorimetry (DSC), X-ray powder diffraction (XRD), infrared (IR) spectroscopy, particle size analysis, and powder dissolution studies. Preformulation assessment included measurement of the disintegration, hardness, and dissolution properties of tablets containing the powders.

MATERIALS AND METHODS

Chemicals

The oxytetracycline hydrochloride powder samples (Table 1) were supplied with certificates of analysis, and all of them complied with the monograph of the BP 1988 (9) and USP 23 of 1995 (10). Solvents used were analytical grade and were supplied by Saarchem (Krugersdorp, South Africa). All materials were used as supplied.

Characterisation of Powders

The IR spectra of the samples (Fig. 1) were recorded on a Shimadzu FTIR 4200 spectrometer (Shimadzu, Kyoto, Japan) over a range of 600–4000 cm^{-1}. The KBr disk technique was used. XRD profiles (Fig. 2) were ob-

Table 1

Description and Assay Values of the Oxytetracycline Hydrochloride Powders

Code	Color of the Samples	Assay Result Certificate of Analysis Dried (μg base/mg)	Assay Result SABS[a] (μg base/mg)
GA	Yellow	890.0	885.5
JB	Yellow	892.0	925.7
MC	Yellow/brown	900.5	934.6
RD	Yellow	895.9	935.6
TE	Yellow/brown	894.1	940.3
WF	Yellow	893.0	932.8

[a] South African Bureau of Standards, Pretoria.

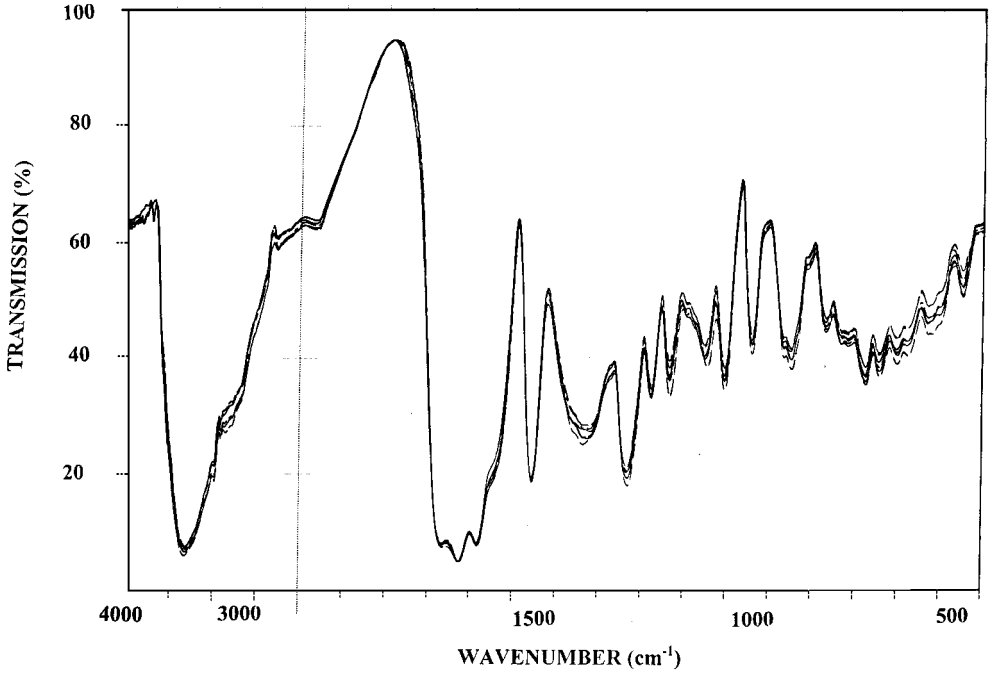

Figure 1. IR spectra of the six different oxytetracycline hydrochloride samples.

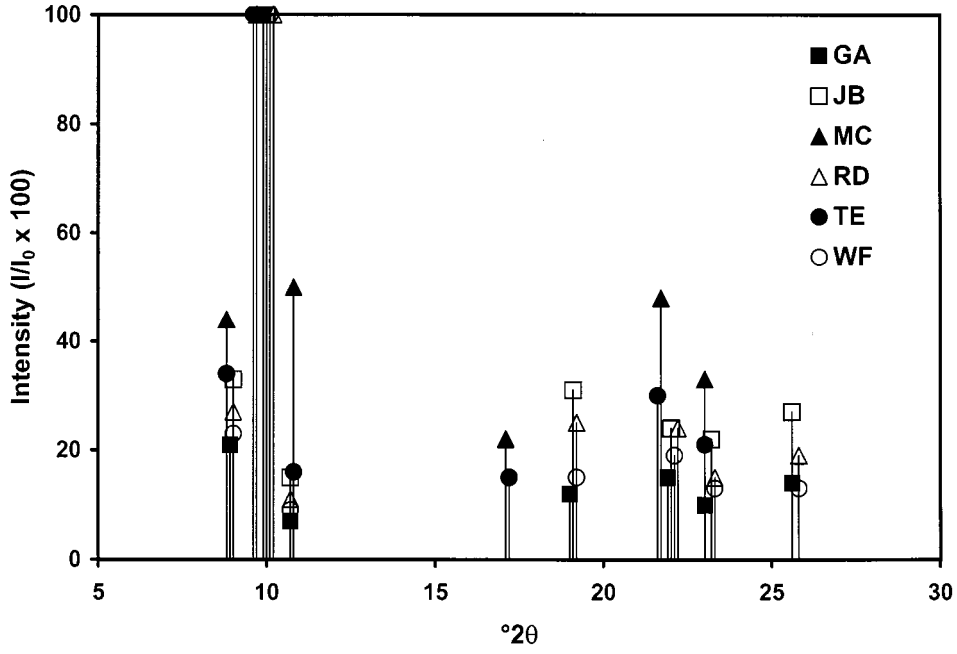

Figure 2. XRD patterns of the six different oxytetracycline hydrochloride samples.

tained at room temperature with a Philips PM9901/00 diffractometer. The measurement conditions were target, CoK_α; iron filter; 40 kV voltage; 20 mA current; 0.2-nm slit; and 2°/min scanning speed. Approximately 200 mg of sample was loaded into an aluminum sample holder, taking care not to introduce a preferential orientation of the crystals. DSC thermograms were recorded with a Shimadzu DSC-50 instrument using the following measurement conditions: sample weight, approximately 2 mg; sample holder, aluminum crimp cell; gas flow, nitrogen at 20 ml/min; heating rate, 10°C per minute.

Dissolution Studies

Powder dissolution rate profiles were measured using method II, paddle, of the USP 23 (10) or BP (9) as described for oxytetracycline hydrochloride capsules. A VanKel six-station dissolution apparatus was used (VanKel, Edison, NJ). The paddles rotated at 75 rpm or 100 rpm, and samples were taken from the dissolution medium, either water or 0.1 N hydrochloride acid, at 7.5, 15, 30, 45, and 60 min. To comply with the USP specification, not less than 80% (*Q*) of the oxytetracycline hydrochloride must be dissolved in water in 60 min, and 70% (*Q*) in 0.1 N hydrochloride acid in 45 min is required by the BP.

The powder sample (250 mg) was rinsed from the glass weighing boat into a 10-ml test tube with exactly 2 ml of the dissolution solution. Glass beads (125 mg) with a mean size of 0.1 mm were added to the suspension, and the mixture was agitated for 60 sec using a vortex mixer. The contents of the test tubes were transferred immediately to 900 ml of dissolution medium kept at 37°C. The concentration of dissolved drug was determined from the ultraviolet (UV) absorbance at 273 nm for the USP method and 353 nm for the BP method (Beckman DU 650I spectrophotometer, Beckman, Puerto Rico).

Particle Size Measurements

Particle size distributions in suspension were measured with a Galai-Cis-1 particle size analyzer (Galai, Jerusalem, Israel). This analyzer uses dual-discipline analysis, integrating laser diffraction and image analysis for particle sizing. Samples of the powder suspended in a suitable dispersing solution were each placed in a small cuvette, and the cuvette was fitted into the analyzer. A small magnetic stirrer inside the cuvette prevented sedimentation of the particles during the measurement. The acquired data were used to compute means, medians, and standard deviations based on the total particle population. Allen (12) gives a detailed discussion of these calculations.

Preparation of Tablets

The oxytetracycline hydrochloride powders were mixed in a ratio of 5:1 with directly compressible microcrystalline cellulose powder (Avicel PH200, FMC, Cork, Ireland). The tablets weighed 300 mg and contained 250 mg oxytetracycline hydrochloride. Each had a diameter of 13 mm and were compressed at a constant pressure of 1500 kPa using a 25-ton ring press (RIIC, London, England) used to compress KBr tablets for infrared spectroscopic analysis.

Characterization of Tablets

The dissolution of oxytetracycline hydrochloride from tablets was measured using the dissolution apparatus and conditions described for powder dissolution measurements. Results are the mean for 6 tablet samples. The time it took for individual tablets to disintegrate was measured with a Manesty tablet disintegration tester (Liverpool, England). Results are the mean for 10 tablet samples, and measurements were obtained in water at 37°C. Tablet hardness was measured using a Pharmatest PTB 311, tablet hardness meter (Pharmatest, Hamburg, Germany). Tablet hardness and dimensions were used to calculate the tensile strength for 10 tablets. The Student-Newman-Keuls test was used to determine any statistically significant differences in disintegration times and tensile strength measurements.

RESULTS AND DISCUSSION

The overlaid IR spectra of the six samples (Fig. 1) were virtually identical and therefore indicated that the six samples were identical with respect to chemical structure. All of the powders complied to the USP (10) and BP (9) potency specifications (Table 1) of 835 or 860 μg base/milligram, respectively. The samples also passed the test for light absorption impurities (i.e., the test for breakdown products). Based on these results, the six oxytetracycline hydrochloride powders complied with all official quality control tests and could be used in the formulation of dosage forms.

Powder dissolution rate profiles (Figs. 3 and 4) showed that all six raw materials dissolve practically immediately in water or 0.1 M HCl. This is to be expected since oxytetracycline hydrochloride is very soluble in water (12). The dissolution rates of the oxytetracycline hydrochloride powders from tablets compressed at the same pressure and composition (Figs. 5 and 6) were not the same, and were slower in both water and 0.1 M HCl.

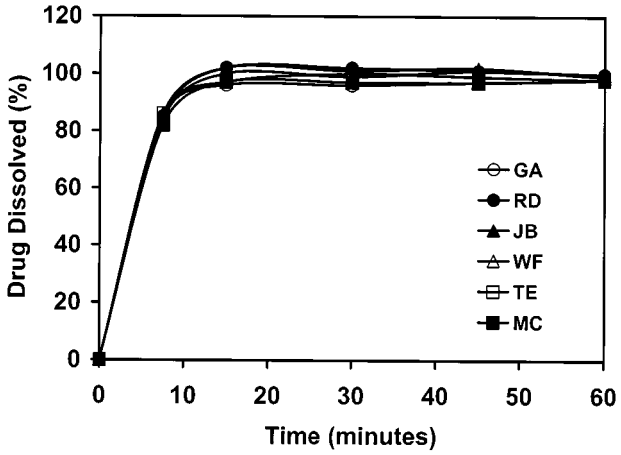

Figure 3. Dissolution of the powder in water (mean of six determinations) measured according to the USP (1995) test for oxytetracycline hydrochloride capsules.

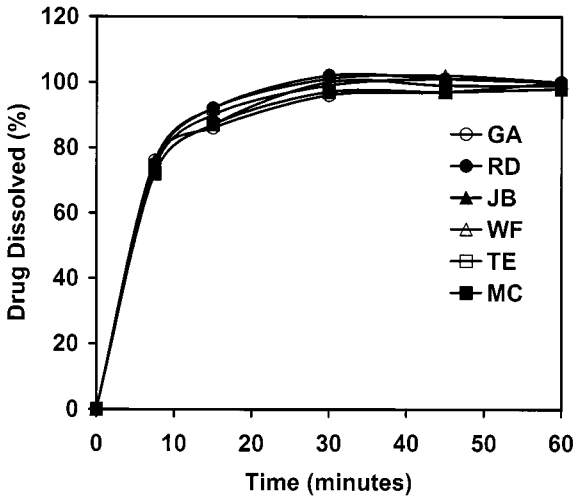

Figure 5. Dissolution of the tablets in water (mean of six determinations) measured according to the USP (1995) test for oxytetracycline hydrochloride capsules.

Compared to the powder dissolution results, tablets prepared with powders GA and RD were almost equivalent, WF and JB were slightly slower, and TE and MC were slowest. Both the powder and tablet dissolution rates complied with the USP (10) specification for capsules (Table 2) that not less than 80% of the labeled oxytetracycline hydrochloride amount should be dissolved in 60 min. Dissolution tests performed according to the BP (9) test in 0.1 N hydrochloride acid (Table 2) showed that dissolution from tablets prepared with powders TE and MC did not comply with the specification that 70% must be dissolved in 45 min.

To determine if particle size difference might explain the differences in dissolution rates, the median particle diameters (volume) and particle size distributions (Table 3) were measured. It was concluded that the samples are fairly comparable with respect to particle size, although sample JB had a slightly smaller mean (volume) particle size. Measured disintegration times (Table 2) showed

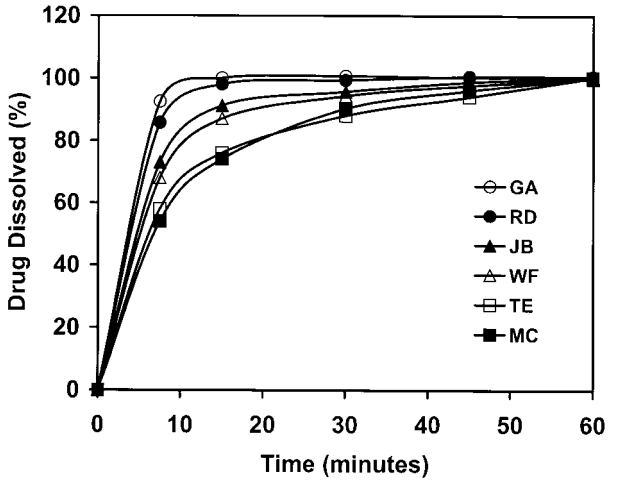

Figure 4. Dissolution of the powder in 0.1 M HCl (mean of six determinations) measured according to the BP (1988) test for oxytetracycline hydrochloride capsules.

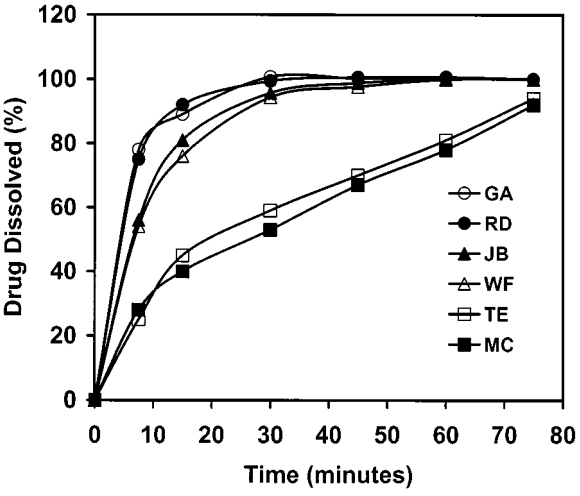

Figure 6. Dissolution of the tablets in 0.1 M HCl (mean of six determinations) measured according to the BP (1988) test for oxytetracycline hydrochloride capsules.

Table 2

Mean Tablet Dissolution Values (Q) According to the USP (1995) and BP (1988) Tests for Oxytetracycline Hydrochloride Capsules and Disintegration and Tablet Tensile Strength Results

Powder	Dissolved in 60 min (USP) (% *Q*)	Dissolved in 45 min (BP) (% *Q*)	Disintegration Time (sec)	Tablet Tensile Strength ($\times 10^5$ Nm^{-2})
GA	100 ± 1.5	98 ± 3.1	83 ± 10	8.3 ± 0.5
JB	99 ± 2.7	99 ± 2.6	148 ± 15	18.1 ± 1.1
MC	100 ± 2.3	67 ± 3.4	169 ± 12	11.7 ± 0.6
RD	100 ± 2.6	100 ± 2.3	84 ± 16	9.3 ± 0.8
TE	100 ± 4.9	69 ± 2.5	170 ± 10	12.9 ± 1.0
WF	99 ± 1.9	97 ± 3.6	145 ± 15	20.4 ± 1.1

that tablets with slow dissolution rates had significantly slower disintegration times ($p < .05$). The mean tablet tensile strength (Table 2) of the slow-dissolving tablets was significantly higher ($p < .05$) than that of fast-dissolving tablets. Although these results might explain the huge differences in dissolution, the tablet hardnesseses all were below 80 N, and the tablets disintegrated within 5 min.

The low intrinsic solubilities of the oxytetracycline powders TE and MC were the biggest contributors to poor dissolution. XRD (Fig. 2) intensity values at the main diffraction peak angles (Table 4) showed there were two polymorphic modifications present among the samples. Samples GA, JB, RD, and WF fell into one group and had a yellow color. Samples MC and TE belonged to the second group and had a much darker color, which could be described as yellow/brown. This color difference was confirmed by microscopic evaluation, and although it could be coincidental, it was nevertheless striking that a correlation between color and polymorphic form was observed. Burger, Ratz, and Brox (5) prepared and identified two oxytetracycline hydrochloride polymorph forms. Form A was 28 times less soluble than form B. XRD results (Table 4) confirmed that samples MC and TE were similar to form A. The poor dissolutions obtained from tablets containing samples MC and TE were largely due to the poor solubility of this crystal form present in these powders.

The oxytetracycline hydrochloride DSC thermograms had no sharp melting endotherms (Fig. 7). A broad endotherm seen between 70°C and 130°C was probably due to the absorption of moisture (5). Burger et al. (5) demonstrated that form B was hygroscopic, and form A was not. The differences in endotherm size and range provide further proof for the conclusion made from the X-ray study, namely, that samples MC and TE were form A and not the commonly used, and more hygroscopic, form B. The broad endotherm is followed by two exotherms, the first of which appears at 180°C–200°C. It can be concluded that the DSC thermograms of the samples were comparable, and although not suited for detailed characterization of forms A and B, the size of the broad endotherm indicated that the extent of water adsorption on form A powders was less.

Table 3

Median Particle Diameter by Volume and Particle Size Distribution of the Oxytetracycline Hydrochloride Samples

Sample	Median Diameter by Volume (μm)	Particle Size Distribution by Volume (μm ± SD)
GA	45	10.42 ± 8.52
JB	24	10.18 ± 7.27
MC	36	12.59 ± 9.41
RD	37	11.61 ± 9.56
TE	41	14.95 ± 12.41
WF	46	10.45 ± 8.19

CONCLUSION

In South Africa, oxytetracycline is identified as an essential drug; many generic products are on the market, and many more are being developed. In this study, in which six oxytetracycline hydrochloride powders obtained randomly from manufacturers and suppliers were compared, it was found that compliance to a pharmacopoeial monograph was insufficient to ensure the optimum dissolution performance of a simple tablet formulation. A preformulation solid-state characterization of the drug

Table 4

Intensity Values (I/I_0) at the Main X-ray Diffraction Peak Angles (°2θ)

Main X-ray Peaks	°2θ ($I/I_0 \times 100$)					
	GA	JB	MC	RD	TE	WF
1	8.9 (21)	9.0 (33)	8.8 (44)	9.0 (27)	8.8 (34)	9.0 (23)
2	9.9 (100)	10.0 (100)	9.7 (100)	10.2 (100)	9.6 (100)	10.1 (100)
3	10.7 (7)	10.7 (15)	10.8 (50)	10.7 (11)	10.8 (16)	10.7 (9)
4			17.1 (22)		17.2 (15)	
5	19.0 (12)	19.1 (31)		19.2 (25)		19.2 (15)
6	21.9 (15)	22.0 (24)	21.7 (48)	22.2 (24)	21.6 (30)	22.1 (19)
7	23.0 (10)	23.2 (22)	23.0 (33)	23.3 (15)	23.0 (21)	23.3 (13)
8	25.6 (14)	25.6 (27)		25.8 (19)		25.8 (13)

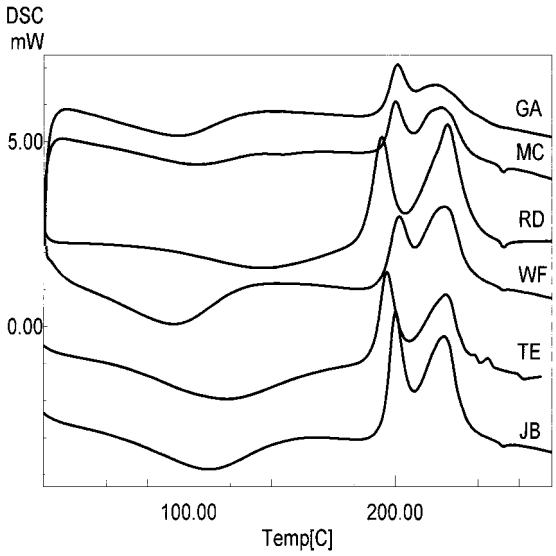

Figure 7. DSC thermograms of the oxytetracycline hydrochloride samples.

powders combined with the evaluation of simple tablet formulations pointed out significant differences in the solubility of the powder samples.

The solubility difference was because the samples contained different polymorphic forms. The question whether this difference is important from a manufacturer's point of view and/or in terms of bioavailability was demonstrated by the fact that the dissolution rate from tablets prepared with the poorly soluble powders were significantly slower. On the basis of the variability reported for the fast-disintegration tablets, it might be expected that a similar variability would be seen with capsules.

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