Tablet Formulation Containing Meloxicam and β-Cyclodextrin: Mechanical Characterization and Bioavailability Evaluation

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ABSTRACT

The purpose of this research was to evaluate β-cyclodextrin (β-CD) as a vehicle, either singly or in blends with lactose (spray-dried or monohydrate), for preparing a meloxicam tablet. Aqueous solubility of meloxicam in presence of β-CD was investigated. The tablets were prepared by direct compression and wet granulation techniques. The powder blends and the granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to thickness, diameter, weight variation test, drug content, hardness, friability, disintegration time, and in vitro dissolution studies. The effect of β-CD on the bioavailability of meloxicam was also investigated in human volunteers using a balanced 2-way crossover study. Phase-solubility studies indicated an A_L-type diagram with inclusion complex of 1:1 molar ratio. The powder blends and granules of all formulations showed satisfactory flow properties, compressibility, and drug content. All tablet formulations prepared by direct compression or wet granulation showed acceptable mechanical properties. The dissolution rate of meloxicam was significantly enhanced by inclusion of β-CD in the formulations up to 30%. The mean pharmacokinetic parameters (C_{max}, K_e, and area under the curve $[AUC]_{0-\infty}$) were significantly increased in presence of β-CD. These results suggest that β-CD would facilitate the preparation of meloxicam tablets with acceptable mechanical properties using the direct compression technique as there is no important difference between tablets prepared by direct compression and those prepared by wet granulation. Also, β-CD is particularly useful for improving the oral bioavailablity of meloxicam.

KEYWORDS: meloxicam, β-CD, tablet, solubility, bioavailability

INTRODUCTION

Cyclodextrins and their derivatives play an important role in the formulation development of drugs because of their multifunctional characteristics and bioadaptability as they are capable of alleviating the undesirable properties of drug molecules through the formation of inclusion complexes. From a pharmaceutical standpoint, a drug-β-CD solid inclusion complex is convenient for oral administration.[1-3] In addition, β-CD represents the first choice in tablet formulations as filler-binder from several points of view (eg, inclusion compound formation, economical and commercial availability).[4,5]

Meloxicam (MX), (4-hydroxy-2methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide), is a nonsteroidal antiinflammatory of the group oxicam derivative. The solubility and dissolution rate of MX in acid media are very poor. This characteristic affects its bioavailability. Recently many studies have investigated the effect of β-CD on improving MX solubility, dissolution rate, and bioavailability.[6-10]

The aim of this study was to evaluate the effect of β-CD as a vehicle, either singly or in blends with other fillers, on tableting and mechanical properties of the formed MX tablets prepared by direct compression and wet granulation. In addition, the implication of MX-β-CD complex formation on the solubility, dissolution, and bioavailability of the drug was investigated.

MATERIALS AND METHODS

Materials

MX and Piroxicam were a gift from MUP Co (Abu-Sultan, Ismailia, Egypt). The solvents used for high-performance liquid chromatography (HPLC), acetonitrile (Merck, Darmstadt, Germany), and acetic acid (Avonchem, Macclesfield, Cheshire, UK) were of chromatographic grade; β-CD, *United States Pharmacopeia* (*USP*) (Wacker-Chemie GmbH, Hauptverwaltung, München, Germany); spray-dried lactose, and lactose monohydrate, *USP* (Quest International, Hoffman Estates, IL); Crospovidone, *USP* (BASF, Ludwigshafen, Germany); Aerosil 200, *USP* (Degussa, Bitterfeld, Germany); Povidone k30, *USP* (ISP, Köln-Rodenkirchen, Germany); and magnesium stearate, *USP* (Mallinckrodt, NJ). All other reagents are of pharmaceutical grade.

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Methods

Solubility Studies

A pH-solubility profile of MX was obtained in a wide pH range at 25ºC ± 0.5°C, in hydrochloric acid buffer (*USP* 23) of pH 1.2 and 2.0, and in citrate phosphate buffer (McIlvaine, *USP* 23), (Merck, Darmstadt, Germany) of pH 4.0, 5.5, 6.0, and 7.0 and in distilled water as a blank (n = 3). MX concentration was determined by the UV spectroscopy after appropriate dilution.

For the determination of solubility, known excess of the drug was added to aqueous solutions containing various concentrations of β-CD ranging between 1 and 16 mmol and water as a blank in Pyrex test tubes with Teflon-lined screw caps (n = 3). After equilibration for 5 days in a shaking water bath at 25°C ±0.5°C, the saturated solutions were centrifuged, and the supernatants were filtered with 0.45-µm Millipore filters (Millipore Corporation, Billerica, MA). The concentration of drug in the saturated solution was determined by UV spectrophotometer (UV-2401 PC, Shimadzu, Kyoto, Japan) after dilution with methanol, using β-CD solutions as the reference. The absorbance was determined at the wavelength of maximum absorbance for MX (375 nm). No appreciable degradation of MX was observed under the conditions of the solubility experiments, where intact MX was determined quantitatively before and after shaking using spectrophotometer at 375 nm, after dilution with methanol.

Preparation of Tablets

Tablet matrixes prepared by direct compression consisted of 6 parts drug and 94 parts β-CD/spray-dried lactose at the following ratios (% wt/wt): 0:100, 10:90, 30:70, 50:50, 70:30, 90:10, and 100:0. The ingredients were manually screened through 0.5-mm screen. The drug, β-CD, and spray-dried lactose were blended (in a plastic bag) for 15 minutes. Five and a half percent (5.5%) crospovidone (disintegrant) and 0.7% Aerosil 200 were added, and the mixture was blended further for 10 minutes. Finally, 1% magnesium stearate as a lubricant was added and the mixture was blended for 5 minutes.

In tablets prepared by wet granulation, lactose monohydrate was used instead of the spray-dried lactose. The batch size was 200 g. The drug, lactose, β-CD, and 50% of the crospovidone[11] were mixed thoroughly, and a sufficient volume of ~40 mL of 1% Povidone K-30 aqueous solution (as a granulating agent) was added slowly to the powder blend and kneading was performed for ~10 minutes until formation of wet mass with enough cohesiveness. The wet mass was forced through a no. 16 sieve (1180 µm) and dried at 50°C in a hot air oven for 10 hours. Moisture content of the granules was determined using a Moisture Analyzer (Sartorius MMA30, Gottingen, Germany). The dried granules were resieved through a no. 20 sieve (850 µm). The granules were then evaluated for several tests prior to mixing thoroughly with the rest of the crospovidone and magnesium stearate.

The formulations were compressed in a single-punch Erweka tablet press (Erweka EK-0, Motor Drive AR 402, Heusenstamm, Germany), using 9-mm diameter, circular punches with flat faces. The machine settings were adjusted to produce tablets having approximately the same hardness and weight. A minimum of 400 tablets was prepared per batch, with a target weight of 260 mg.

Evaluation of Granules

The bulk and tapped density of the granules were assessed in accordance with the *USP* 25 using a tapped volumeter apparatus (Erweka, SVM101, Heusenstamm, Germany). Compressibility index of the granules was determined by Carr's compressibility index.[12-15] Total porosity was also determined as described before[12-15] by measuring the volume occupied by selected weight of a powder and the true volume of granules.

Characterization of Tablets

Tablets' physical properties were determined according to the *USP* 24 method. Friability was determined by using an Erweka friabilator (Erweka, TA, Heusenstamm, Germany) with 20 tablets for 4 minutes (100 revolutions). The disintegration time was determined for 6 tablets with *USP* disintegration apparatus (Erweka, ZT43, Heusenstamm, Germany) at 37°C ± 0.5°C, in water. Drug dissolution testing was performed according to the *USP* 24 specifications with Apparatus II (n = 6). For each sample, 900 mL of distilled water were stirred at 100 rpm and maintained at 37°C ± 0.5°C. Also, for comparison study between a selected formula and commercially available tablets, a dissolution medium of 900 mL 0.1 N HCl was used. Aliquot samples were withdrawn for a period of 60 minutes, filtered through a 0.45-µm Millipore filter, and replaced by an equivalent volume of fresh dissolution medium. The amount of drug dissolved was determined by HPLC method as described under HPLC analysis. The dissolution profiles of the MX-β-CD tablet and MX commercial tablet were compared using the difference factor, f_1, and similarity factor, f_2, as recommended in Food and Drug Administration (FDA) dissolution guidelines.[16]

Bioavailability Study

Selected formula with maximum dissolution rate (containing 30% β-CD near molar ratio with the drug) and reference product were subjected to single-dose comparative pharmacokinetic studies. Clinical approval was obtained for the experiments by the medical committee and informed consent was obtained after the nature and possible consequences of

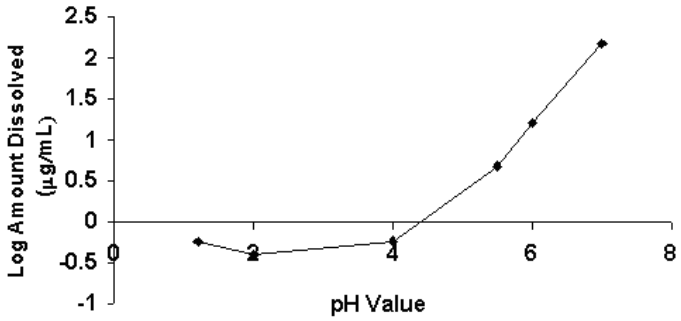

Figure 1. pH-Solubility profile of meloxicam at different pH values.

the studies were explained. The study was a crossover bioavailability design that was performed using 8 healthy adult male volunteers between the ages of 22 and 30 years and weighing between 60 and 85 kg. The volunteers were prevented from taking any alcohol or drugs for the 2 days prior to the experiment and during the study. The volunteers fasted for 8 hours before drug administration. According to the treatment schedule, each subject ingested 2 compressed tablets of MX (commercial tablet) or its β-CD complex (equivalent to 15 mg MX). An interval of 14 days was allowed prior to the next treatment. Whole blood samples were taken from a forearm vein predose and at predetermined intervals after MX administration. The blood was centrifuged at 5000 rpm for 10 minutes, and the plasma obtained was stored at –20°C until analysis.

High-Performance Liquid Chromatography Analysis

Serum MX was analyzed by a validated HPLC method using Piroxicam as the internal standard. One and a half milliliters acetonitrile was added to 0.5 mL of plasma spiked (Piroxicam 25 µg/mL) with the internal standard, shaken for 15 seconds, and then centrifuged at 5000 rpm for 5 minutes. A 30-µL aliquot of the supernatant was injected into an HPLC system with a variable wavelength UV detector (model LC-10VP, Shimadzu) equipped with a manual injector. The analytical column was a C_{18} (5 µm, 300 × 3.9 mm inner diameter) (µ Bondapak, Waters, Milford, MA). The mobile phase consisted of sodium acetate buffer (pH 3.3, 170 mmol):acetonitrile (62:38 vol/vol) mixture, with flow rate of 2 mL/min, and the elute was monitored at 364 nm. The response was linear over the range of 0.1 to 5 µg/mL in human plasma, with a correlation coefficient of 0.999.

Results and Discussion

The solubility study of MX in different pH at 25°C reveals that aqueous solubility of MX was only 13.7 ± 0.288 mg/100 mL (Figure 1). The solubility was gradually decreased and reached a minimum value of 0.057 ± 0.008 mg/100 mL at pH 1.2 and 0.039 ± 0.006 mg/100 mL at pH 2, and then there was a gradual increase in solubility up to pH 4, where the minimum value was 0.058 ± 0.012 mg/mL. There was then a sharp rise in solubility at pH 5.5 and 6, where the minimum values were 0.47 ± 0.068 mg/100 mL and 1.60 ± 0.021 mg/100 mL, respectively. Above pH 7, MX was freely soluble in water as expected. Because MX is an acidic drug, the percentage of drug ionized and thus the solubility increase with an increase in the pH value (ie, the solubility of MX is pH dependent). This shows low aqueous solubility in acidic medium, which is an important factor for the absorption of the drug because before absorption the drug must go into solution. Hence, if the aqueous solubility of the drug is increased, it will result in greater absorption. Thus, the contribution of complexation with β-CD will be highly appreciated, as an additive that increases drug solubility.

The existence of 1:1 stoichiometric ratio of drug-β-CD complex was attributed to the linear increase in drug solubility as a function of β-CD concentration and formation of A_L type diagram according to Higuchi.[17] This finding is in good agreement with the previously reported studies.[6-10] As the purpose of this study was not to prove stoichiometry of the complex or stability of the formed complex, based on this assumption no further investigations were done on MX-β-CD complex.

Table 1 shows that the bulk densities of the prepared granules were found to decrease slightly by increasing β-CD concentrations. This result may be due to the formation of larger agglomerates and the decrease in fines in the granules, as increasing β-CD concentrations provides more binding to the granules. The results of compressibility index (Table 1) indicate a decrease in flowability with increasing β-CD concentrations; however, all formulations show good flow properties. In general, compressibility index values up to 15% result in good to excellent flow properties.[13] The percentage porosity values of the granules ranged from 30.29% to 38.32%, indicating that the granules are loosely packed and confirming that the particles are not of greatly different sizes. In general, a percentage porosity value below 26% shows that the particles in the powders are of greatly different sizes, and a value greater than 48% shows that particles in the powder are in the form of aggregates or flocculates.[14] All these results indicate that the granules possessed satisfactory flow properties, compressibility, and porosity.

Tables 2 and 3 show that a good degree of uniformity of weight and thickness was achieved for all formulations prepared by either direct compression or wet granulation. The SD indicates a good uniformity of weight and thickness for tablets containing up to 50% β-CD, but variation in weight increase for the formulations containing more than 50%. This finding may be attributed to the fact that spray-dried lactose has superior flow properties compared with β-CD and is in

Table 1. Granules Properties*

Percentage		Loose Bulk Density(g/cm^3)	Tapped Bulk Density(g/cm^3)	Compressibility Index(%)	Total Porosity(%)
β-CD	Lactose	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
0	100	0.543 ± 0.05	0.592 ± 0.06	8.28 ± 0.93	30.29 ± 2.34
10	90	0.557 ± 0.03	0.605 ± 0.04	7.93 ± 0.25	33.29 ± 2.67
30	70	0.540 ± 0.03	0.605 ± 0.03	10.75 ± 0.76	35.96 ± 3.32
50	50	0.526 ± 0.04	0.599 ± 0.04	12.19 ± 0.91	34.95 ± 2.39
70	30	0.512 ± 0.03	0.588 ± 0.04	12.63 ± 0.89	36.52 ± 3.37
90	10	0.508 ± 0.05	0.589 ± 0.04	13.75 ± 1.02	36.89 ± 3.02
100	0	0.498 ± 0.04	0.573 ± 0.02	13.09 ± 1.11	38.32 ± 2.69

*All values are expressed as mean ± SD, n = 5.

Table 2. Physical Properties and Dissolution Profile for MX-β-Cyclodextrin Prepared by Direct Compression*

Percentage		Weight† (mg)	Thickness‡ (mm)	Hardness‡ (kp)	Friability† (%)	Disintegration‡ Time (minutes)	% Dissolved After 45 Minutes
β-CD	Lactose	Mean ± SD	Mean ± SD	Mean ± SD			T45 ± SD
0	100	260.5 ± 0.97	3.20 ± 0.11	4.93 ± 1.46	0.73	1.4	35 ± 3.33
10	90	261.3 ± 0.99	3.13 ± 0.15	11.44 ± 0.27	0.88	1.2	38 ± 3.67
30	70	249.6 ± 1.72	3.04 ± 0.12	10.65 ± 0.93	0.42	3.7	50 ± 4.85
50	50	263.4 ± 2.95	3.14 ± 0.21	12.85 ± 1.06	0.39	5.4	44 ± 2.39
70	30	266.8 ± 3.83	3.21 ± 0.17	11.88 ± 0.56	0.22	6.0	41 ± 3.57
90	10	251.7 ± 2.86	3.05 ± 0.19	12.32 ± 0.43	0.14	6.2	43 ± 3.10
100	0	251.5 ± 5.74	3.05 ± 0.20	11.31 ± 0.98	0.09	6.8	40 ± 2.59

*MX indicates meloxicam.

†All values are expressed as mean ± SD, n = 20.

‡All values are expressed as mean ± SD, n = 6.

Table 3. Physical Properties and Dissolution Profile for MX-β-Cyclodextrin Prepared by Wet Granulation*

Percentage		Weight† (mg)	Thickness‡ (mm)	Hardness‡ (kp)	Friability† (%)	Disintegration‡ Time (minutes)	% Dissolved After 45 Minutes
β-CD	Lactose	Mean ± SD	Mean ± SD	Mean ± SD			T45 ± SD
0	100	259.2 ± 1.67	3.01 ± 0.08	12.45 ± 0.37	0.39	1.2	36 ± 2.10
10	90	264.3 ± 1.99	3.19 ± 0.14	12.87 ± 0.58	0.22	2.1	38 ± 4.51
30	70	261.4 ± 1.09	3.23 ± 0.09	16.10 ± 0.84	0.17	5.4	40 ± 3.85
50	50	259.4 ± 2.75	3.19 ± 0.11	17.67 ± 0.79	0.09	8.3	40 ± 4.21
70	30	264.7 ± 2.43	3.12 ± 0.17	16.65 ± 0.67	0.11	11.4	38 ± 4.61
90	10	253.7 ± 2.76	3.15 ± 0.13	19.24 ± 0.93	0.06	13.2	40 ± 4.10
100	0	258.3 ± 3.62	3.02 ± 0.15	17.02 ± 0.67	0.04	13.5	36 ± 3.21

*MX indicates meloxicam.

†All values are expressed as mean ± SD, n = 20.

‡All values are expressed as mean ± SD, n = 6.

agreement with the findings of El-Shaboury.[18] It is also clear from the tables that all the tablets exhibited good mechanical properties with regard to both hardness and friability. Nonsignificant differences in hardness values within each of the drug formulations were observed, while the friability decreased as the concentration of β-CD increased. Tablets containing 100% β-CD displayed the lowest value of friability for wet granulation and direct compression. This finding may be due to the greater binding strength of β-CD, which has water of crystallization (14%) that helps in binding of the particles thus producing stronger tablets.[19] This also has implications for the disintegration time of the tablets as an increase in disintegration time with β-CD concentration is shown in Tables 2 and 3. However, disintegration time for tablets prepared with wet granulation showed higher disintegration time. This finding can be explained by the fact that the wet granulation method results in increased hardness in tablets and the formation of tablets with different porosity (ie, tablets with different pore size distribution).

The percentage dissolved after 45 minutes was used to represent the dissolution profiles of the prepared tablets. The data in Tables 2 and 3 reveal that wet granulation yields tablets

Table 4. Effect of Complexation With β-Cyclodextrin on the Pharmacokinetic Parameters of Meloxicam in Human Subjects Receiving a Single Oral Dose of the Drug*

Formulation	C_{max} (µg/mL)	T_{max} (hours)	K_e (hours)	AUC_{0-36} (µg/mL.h)	$AUC_{0-\infty}$ (µg/mL.h)
Commercial tablet (free MX)	1.20 ± 0.24 (0.88 - 1.59)	5.6 ± 3.2 (2.5 - 12)	0.046 ± 0.010 (0.036 - 0.064)	29.17 ± 7.06 (17.58 - 39.06)	37.70 ± 9.50 (21.68 - 46.62)
MX-β-CD complex	‡1.76 ± 0.44 (1.31- 2.49)	‡2.8 ± 0.8 (1.5 - 4)	†0.034 ± 0.013 (0.019 - 0.054)	*35.75 ± 6.92 (28.71 - 46.24)	‡55.8 ± 17.10 (32.53 - 92.22)

*AUC indicates average area under the serum concentration time curve. All data are the means ± SD of 8 human subjects; ranges are shown in parentheses.
†Not significant.
‡Significant (using *t* test).

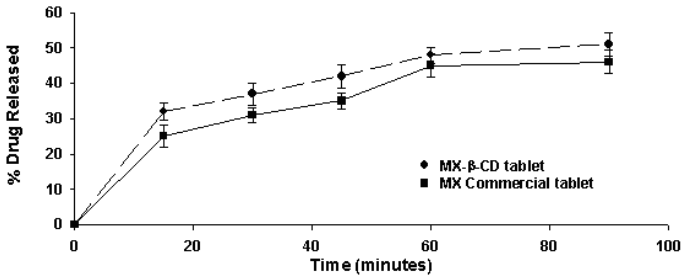

Figure 2. Effect of β-Cyclodextrin on the dissolution rate of Meloxicam determined by the *USP* method in 0.1N hydrochloric acid at 37°C.

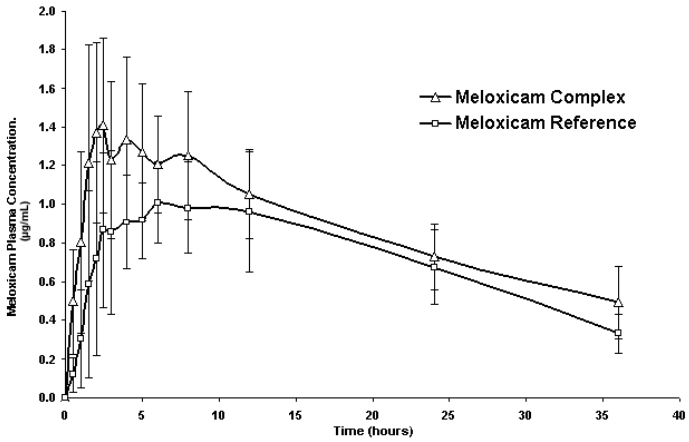

Figure 3. Mean plasma levels of Meloxicam following oral administration of the drug.

with nearly slower dissolution rate than those prepared by direct compression irrespective of the vehicle used. This may be due to the availability of the drug to the dissolution medium when using direct compression, and no need for splitting granules as in the case of tablets prepared by wet granulation. However, maximum effectiveness of increase in dissolution rate was shown at 30% β-CD of the CD-lactose matrix (near molar ratio with the drug) after which the dissolution rate was not significantly changed. The profiles of the cumulative MX fraction dissolved from selected MX-β-CD tablet with 30% β-CD (near molar ratio) and the commercially available tablet in 0.1N HCl as a dissolution medium are illustrated in Figure 2. The amounts of drug dissolved at all sampling times for the tablet with β-CD and the commercial tablet show significant difference at all points ($P \leq .05$) except at 60 minutes. The corresponding f_1 and f_2 values for the MX-β-CD tablets and the commercial tablets were greater than 15 and less than 50, respectively, suggesting that the dissolution from both tablets (complex and commercial) was not similar. Complexation of MX with β-CD enhances the dissolution profile significantly, which might have an important implication on increasing the drug bioavailability as previously reported.[6-10]

Figure 3 shows the mean serum levels of MX following the oral administration of 15 mg MX or its ß-CD complex to 8 human volunteers. It is obvious that there exists a clear difference between the biological performance of both the commercial tablet (free drug) and the tablet with the complex, which reflects itself by the significant difference in the peak concentrations between MX and its ß-CD complex. Table 4 shows the mean pharmacokinetic parameters after administration of the drug and the complex. It is clear from the table that maximum serum level (C_{max}) of 1.203 ± 0.238 µg/mL was attained after 5.6 ± 3.2 hours. On the other hand, the ß-CD complex resulted in significantly rapid appearance of MX in serum, showing C_{max} value of 1.758 ± 0.443 µg/mL after 2.8 ± 0.8 hours. Comparing the value of K_e for the drug with that for the complex reveals the marked effect of complexation on increasing the duration of action of MX. The average area under the serum concentration time curve (AUC_{0-36}) of ß-CD complex up to 36 hours postadministration was 35.75 ± 6.92 µg.h/mL, while the AUC_{0-36} following administration of the commercial tablets was 29.17 ± 7.06 µg.h/mL, demonstrating that the bioavailability of MX-ß-CD complex is insignificantly higher than that of the drug. While, a significant increase is shown in the average area under the serum concentration time curve ($AUC_{0-\infty}$) of ß-CD complex compared with that of the commercial tablets.

In conclusion, inclusion complexation of MX in ß-CD results not only in an improvement of the bioavailability of the drug but also in the rapid plasma appearance of the drug observed for the complex, which would be highly advantageous for the use of this form in oral MX therapy. Furthermore, the use of ß-CD would facilitate the pharmaceutical preparation of the tablets, particularly from the viewpoint of enhancement of the dissolution rate and compression behavior, which give good mechanical properties when used as a direct compression vehicle.

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