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Preparation and *in Vitro* Drug Release Evaluation of Once-Daily Metformin Hydrochloride Sustained-Release Tablets

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ABSTRACT

The objective of this study was to develop once-daily metformin hydrochloride sustained-release tablets (MHSRT) and evaluate their *in vitro* release behavior. MHSRT were prepared by the film coating method. The *in vitro* drug release rate of MHSRT and the commercial tablets Fortamet® made in the United States of America in water was fitted with zero order kinetic equation, and Ritger-Peppas kinetic equation in 0.1 M HCl and pH 6.8-phosphate buffer, respectively. The similarity factor f_2 values of MHSRT in three different dissolution medium were 82, 80 and 74, respectively in comparison with imported Fortamet®, which were all greater than 50. The results of storage-stability showed that MHSRT were stable for at least 6 months under stress condition (40˚C ± 2˚C, RH 75% ± 5%). Therefore, in this study, MHSRT were successfully prepared using optimized formulation technologies that meet mass produce. The *in vitro* release behavior of MHSRT was almost similar to that of imported Fortamet®.

Keywords: Sustained-Release Tablets; Metformin Hydrochloride; *In Vitro* Release Rate; Similarity Factor; Kinetic Model

1. Introduction

Metformin hydrochloride (MH) is a biguanide oral anti-diabetic drug which is widely used to treat non-insulin dependent diabetes mellitus (type 2 diabets). Its mode of action is thought to be multifactoral and includes delayed uptake of glucose from the intestinal tract, increased peripheral glucose utilisation mediated by increased insulin sensitivity and decreased hepatic and renal gluconeogenesis. In clinical treatment, there are many advantages of MH such as the tendency to weight reduction and the ability to reduce blood glucose to normal level without significant hypoglycaemia [1]. However, because of its relative low bioavailability (40% - 60%) and short biological half-life (0.9 - 2.6 h) [2-5], the immediate release dosage forms of MH such as conventional tablets and capsules, have to be administered three times a day [3], which results in a significant fluctuation in the plasma drug concentration and poor patient compliance. In order to overcome these problems, sustained-release drug delivery systems of MH including sustained-release matrix tablets [2,6-8], sustained-release pellets [3,9], sustained-release microparticles [10], prolonged release microspheres [11], gastroretentive drug delivery preparation [12], pH-controlled peroral delivery formulation [13] have been developed in recent years. Though sustained release formulations of MH have been reported to prolong drug release, formulation and technologies used in these studies were complicated and costly, which influence industrial scale and market expansion. At present, MHSRT produced by Bristol-Myers Squibb Company (USA) capture a major market share in China. However, many patients in our developing country could not accept it due to its high cost. Therefore, development of sustained release dosage form of MH that is similar to imported drug is to save pharmacy cost and improve clinical outcomes.

Therefore, in this study, MHSRT were prepared using optimized formulation technologies that meet mass produce. The *in vitro* drug release behavior of MHSRT was studied in water, 0.1 M HCl and pH 6.8-phosphate buffer as release medium and compared with the commercial tablets Fortamet® made in the United States of America.

2. Materials and Methods

2.1. Materials

Metformin hydrochloride (purity: 99.86%) was purchased

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from Huainan Jiameng Pharmaceutical Co., Ltd (China). Carboxymethyl cellulose sodium (CMC) and pregelatinized Starch was obtained from Anhui Shanhe Pharmaceutical Excipient Co., Ltd (China). Ethyl cellulose was purchased from Shandong Heda Co., Ltd (China). PEG-6000 was supplied by Liaoyang Aoke Nano Meterial Co., Ltd. (China). Hexadecanol was purchased from Hunan Erkang Pharmaceutical Co., Ltd (China). Magnesium stearate was purchased from Chongqing Chemical Reagent Co. Ltd. (China). Fortamet® (batch number: 4602094; expiry date: 20121102) were obtained from Watson Laboratories—Florida Ft. Lauderdale, FL 33314 (USA). were obtained from the United States of America. All chemicals and reagents used were of analytical grade. Water used in this study was double distilled water.

2.2. Preparation of MHSRT

Firstly, MH core tablets were prepared by wet granulation method. MH and CMC were mixed and the mixture was passed through a 100-mesh sieve. Granulation was done using water. The wet mass was passed through fourteen meshes using the pendular granulator and the wet granules were air dried for about 2 h. The granules were then sized by fourteen mesh sieve and mixed with pregelatinized starch and magnesium stearate. The core tablets were compressed on a tablet compression machine equipped with 12 mm convex punches. Secondly, the film coat suspension was prepared by dissolving and dispersing EC, PEG-6000 and hexadecanol in 95 % ethanol. In brief, the above core tablets were placed into a fluid-bed spray coater and prewarmed to 35˚C - 40˚C for 3 - 5 min. The coating solution was delivered using peristaltic pump with a flow rate of 1.8 mL/min. Coating was carried out at 50˚C inlet air temperature and 45˚C outlet air temperature. The resulted MHSRT were dried at 40˚C for 12 h and then were further performed quality evaluation.

2.3. Determination of Drug Content

According to the Chinese Pharmacopoeia (2010 version) about the determination of MH content, the samples (20 tablets) were taken and ground to fine powder. Then about 20 mg powder was accurately weighed and placed in a 100 mL volumetric flask containing 75 mL water. After it was dissolved using ultrasonication at room temperature for 20 min, this solution was diluted with water to 100 mL and mixed well, then filtered through a 0.45 μm hydrophilic membrane. 2.5 mL of the solution was accurately taken and transferred to a 100 mL volumetric flask, and then was diluted with water to 100 mL and mixed well. The drug content was measured using an UV-visible spectrophotometer at a wavelength of 233 nm.

2.4. Weight Variation Test

To study weight variation, 20 tablets of each batch samples were weighed using an electronic balance (BT214D, Germany Sartorius), and the test was carried out according to the Chinese Pharmacopoeia (2010 version) method.

2.5. Hardness and Friability Test

For each batch of MHSRT, the hardness and friability of 12 tablets was determined using tablet with four measuring instrument (78X-6A).

2.6. *In Vitro* Release Test

In vitro release studies of MHSRT was carried out by the rotating basket methods of Chinese Pharmacopoeia (2010 version) appendix XD No.1. Six tablets of each batch of MHSRT were taken and placed in rotating basket, respectively. Then the rotating basket was introduced into 900 mL of each dissolution medium (water, 0.1 M HCl and pH 6.8 phosphate buffer) at 37˚C ± 0.5˚C with a rotation speed of 100 rpm. 5 mL of sample solution was collected at different time intervals (2, 4, 6, 8, 10, 12 h) and filtered through a 0.45 μm hydrophilic membrane. 1.0 mL of subsequent filtrate was taken accurately to add into a 100 mL volumetric flask and diluted with the corresponding dissolution medium to 100 mL and mixed well. The amount of drug dissolved in the dissolution medium was measured using an UV-visible spectrophotometer at 233 nm. The same volume of fresh dissolution medium at the same temperature was added to replace the amount withdrawn after each sampling.

The drug amount of cumulative release from the MHSRT was calculated with a standard curve prepared using bracketed concentration of MH each dissolution medium solution in a range from 15 to 125% of a theoretical concentration of 5.5 μg/mL. The standard curve: $Y = 0.0746X - 0.0031$ for distilled water; $Y = 0.0758X - 0.0034$ for 0.1 M HCl and $Y = 0.0798X - 0.0037$ for pH 6.8 phosphate buffer were obtained with coefficient of correlation ($r = 0.9999$).

2.7. Data Analysis

In order to evaluate the drug release kinetic model of the MHSRT, four kinetic models including the zero-order release equation, first-order release equation, Higuchi's equation and Ritger-Peppas ((1)-(4), respectively) were chosen to process the *in vitro* drug release data.

$$Mt = k1t + b \quad (1)$$

$$\mathrm{Ln}(100 - Mt) = k2t + b \quad (2)$$

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$$Mt = k3t^{1/2} + b \quad (3)$$

$$\mathrm{Ln}Mt = k4\mathrm{Ln}t + b \quad (4)$$

where Mt is the cumulative release percentage at time t, the $k1$, $k2$, $k3$ and $k4$ are the rate constant of the above kinetic equation, respectively.

In order to compare the difference of *in vitro* drug release behavior between the MHSRT, the similarity factor f_2 is used in this study and defined by the following equation (5).

$$f_2 = 50 \times \log\left\{\left[1 + (1/n)^2\right]^{-0.5} \times 100\right\} \quad (5)$$

where n is the number of time point, Rt and Tt are the mean cumulative percentage drug dissolved at each time point, t. MHSRT developed in this study and imported Fortamet® made in the United States of America were chosen as test samples and reference preparation, respectively.

2.8. Stability Test of MHSRT

The accelerate stability testing was carried out according to the Technical Standard of Drug Stability Test of Chinese Pharmacopoeia (2010 version). The MHSRT samples were stored at 40˚C ± 2˚C, RH 75% ± 5% for 6 months and the *in vitro* release was measured after 1, 2, 3 and 6 months of storage.

3. Results and Discussion

3.1. Development of MHSRT

In the preliminary study, MH, CMC, pregelatinized starch and magnesium stearate were chosen to prepare the core tablets as formulation composition. In addition, the film coating formulation was composed of EC, PEG-6000 and hexadecanol. On the basis of single factor experiments, we have confirmed the dosage range of the formulation composition. Then an orthogonal array was used to investigate the key influence on preparation. In the current research, the optimal formation of the core tablets was MH (500 g), CMC (40 g), pregelatinized starch (30 g) and magnesium stearate (9 g), the optimal formulation of the film coating was composed of EC (15 g), PEG-6000 (6 g) and hexadecanol (6 g) dissolved or dispersed in 95% ethanol resulting in 300 mL coating suspensions.

In order to validate whether the optimized formulation technologies of MHSRT can be suitable for mass produce, the three batches of MHSRT (100000 tablets/batch) were produced by Chongqing Conquor Pharmaceutical Co., Ltd. and the results were shown in **Table 1** and **Figures 1-3**. Drug content was found to be uniform among the three batches of MHSRT and ranged from 97.85% ± 0.09% to 99.36% ± 0.07%. The mean percentage weight variation of 20 tablets of each batch was less

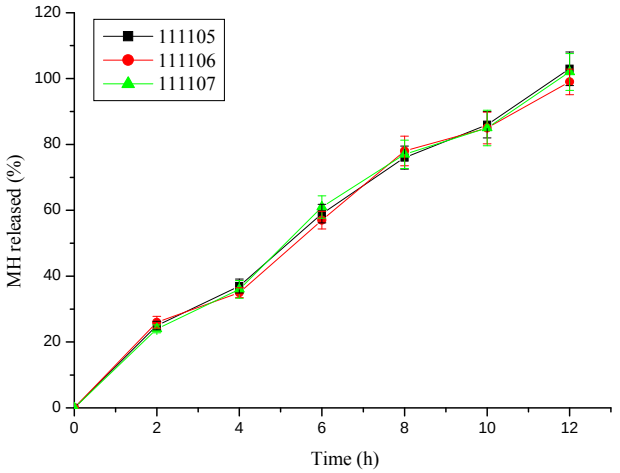

Figure 1. Drug release profiles of the three batches (111105, 111106, and 111107) of MHSRT in water as dissolution medium.

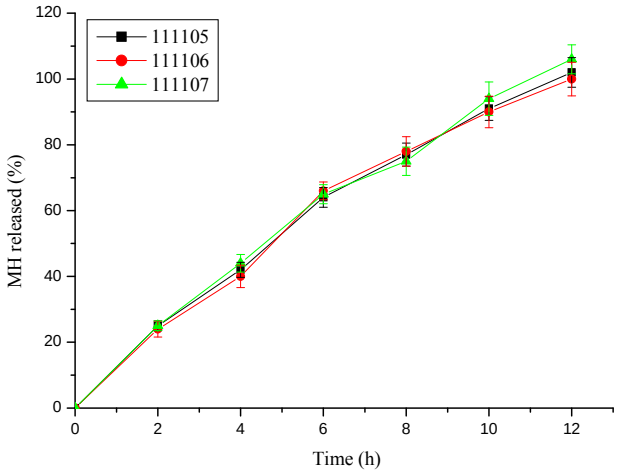

Figure 2. Drug release profiles of the three batches (111105, 111106, and 111107) of MHSRT in 0.1 M HCl as dissolution medium.

Table 1. Properties of the three batches of MHSRT prepared in this study.

Batch	Drug content (%)	Deviation in weight variation (%)	Hardness (kg/cm^2)	Friability (%)
111105	98.55 ± 0.05	3.26 ± 0.02	6.8 ± 0.22	0.72 ± 0.04
111106	99.36 ± 0.07	2.90 ± 0.04	6.1 ± 0.17	0.79 ± 0.05
111107	97.85 ± 0.09	3.86 ± 0.03	7.4 ± 0.26	0.55 ± 0.04

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than 5.0%. The hardness and percentage friability of the tablets of all batches ranged from 6.1 ± 0.17 kg/cm^2 to 7.4 ± 0.26 kg/cm^2 and 0.55% ± 0.04% to 0.79% ± 0.05%, respectively. The *in vitro* drug release behaviors of the three batches of MHSRT in three different dissolution medium were almost similar. Therefore, the optimized formulation technologies possess good reproduction, which are suitable for mass produce.

3.2. Evaluation of *in Vitro* Drug Release

The dissolution profiles of MHSRT developed in this study and imported Fortamet® made in the United States of America in water, 0.1 M HCl and pH 6.8 phosphate buffer as release medium are shown in **Figure 4**. It was found from **Figure 4** that the release rate of MHSRT was similar to that of Fortamet®. In the first 2 h, the cumulative release percentages of MHSRT and Fortamet® were 25% and 27% in water; 25% and 22% in 0.1 M HCl; 22% and 20% in pH 6.8 phosphate buffer, respectively. After 6 h, the cumulative release percentages of MHSRT and Fortamet® were 59% and 56% in water; 64% and 62% in 0.1 M HCl; 58% and 51% in pH 6.8 phosphate buffer, respectively.

As we all know, the different release kinetic models are assumed to reflect different release mechanisms [14]. Therefore, in this study, zero-order release equation, first-order release equation, Higuchi's equation and Ritger-Peppas were used to analyze the *in vitro* released data. Correlation coefficients of Zero-order, First-order, Higuchi's equation and Ritger-Peppas kinetic models used in this study were shown in **Tables 2-4**. It can be seen that the *in vitro* drug release rate of MHSRT and Fortamet® in water showed a zero order approximately kinetic model and could be described by the following equation: $Mt = 7.915t + 8.934$ (R = 0.996) and $Mt = 7.843t + 9.934$ (R = 0.996). However, the release rate of MHSRT and Fortamet® in 0.1 M HCl and pH 6.8 phosphate buffer was fitted with Ritger-Peppas kinetic models

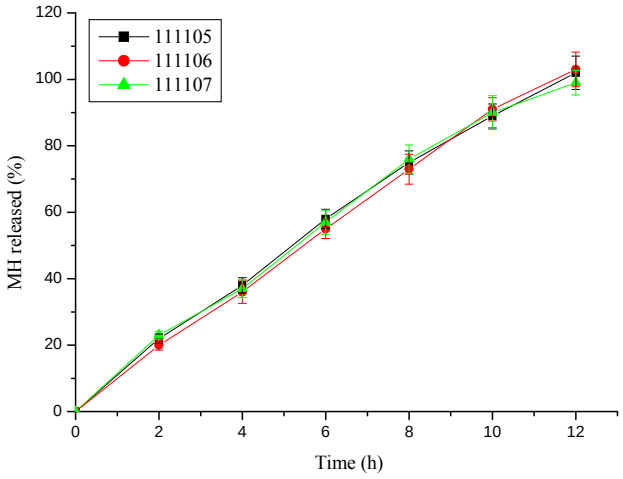

Figure 3. Drug release profiles of the three batches (111105, 111106, and 111107) of MHSRT in pH 6.8 phosphate buffer as dissolution medium.

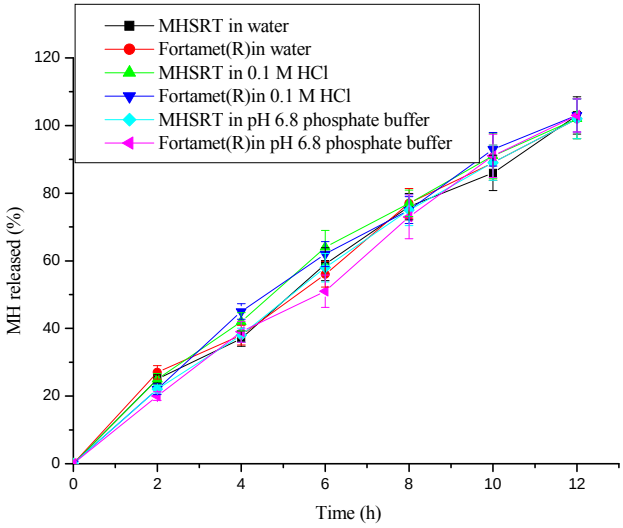

Figure 4. Drug release profiles of MHSRT developed in this study and imported Fortamet® in water, 0.1 M HCl and pH 6.8 phosphate buffer as dissolution medium.

Table 2. Correlation coefficients of kinetic models used for evaluate the *in vitro* release behavior of MHSRT and Fortamet® in water as dissolution medium.

Sample	Zero-order	First-order	Higuchi's equation	Ritger-peppas
MHSRT	0.996	0.893	0.991	0.993
Fortamet®	0.996	0.910	0.989	0.991

Table 3. Correlation coefficients of kinetic models used for evaluate the *in vitro* release behavior of MHSRT and Fortamet® in 0.1 M HCl as dissolution medium.

Sample	Zero-order	First-order	Higuchi's equation	Ritger-peppas
MHSRT	0.987	0.853	0.996	0.998
Fortamet®	0.988	0.865	0.993	0.997

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Table 4. Correlation coefficients of kinetic models used for evaluate the *in vitro* release behavior of MHSRT and Fortamet® in pH 6.8 phosphate buffer as dissolution medium.

Sample	Zero-order	First-order	Higuchi's equation	Ritger-peppas
MHSRT	0.995	0.827	0.993	0.999
Fortamet®	0.994	0.834	0.982	0.996

and could be described by the following equation: Ln*Mt* = 0.801Ln*t* + 2.665 (R = 0.998) and Ln*Mt* = 0.857Ln*t* + 2.551 (R = 0.997); Ln*Mt* = 0.875Ln*t* + 2.471 (R = 0.999) and Ln*Mt* = 0.922Ln*t* + 2.354 (R = 0.996), respectively, which indicated that the drug release mechanisms of MHSRT and Fortamet® were similar in gastrointestinal tract. According the formulation composition MHSRT, it was obvious that drug diffusion and erosion were the main factor in controlling the drug release rate from MHSRT. This was also evidenced by the value of the release exponent *n* of 0.801 and 0.875, because when n ranged from 0.45 to 0.89, indicating that drug is released by the combination of diffusion and erosion mechanisms [15-16].

On the other hand, the similarity factor f_2 value between 50 and 100 shows that two release profiles are similar [17]. Therefore, in order to evaluate the *in vitro* release difference of MHSRT, when imported Fortamet® were chosen as reference, f_2 value was calculated. It was found that the dissolution profile of only MHSRT prepared in this study was similar to that of Fortamet®, because the f_2 values in water, 0.1 M HCl and pH 6.8 phosphate buffer were 82, 80 and 74, respectively, which were all greater than 50.

3.3. Test for Stability

It was known that the stability of preparation is an important factor to estimate the quality of pharmaceutical formulation. Thus, the acceleration stability test was performed to study the stability of MHSRT. It can be seen from **Figures 5-7** that good storage stability was observed and the *in vitro* release profiles had little change. And no significant difference in cumulative release percentage of drug in water, 0.1 M HCl and pH 6.8 phosphate buffer after 1, 2, 3 and 6 months was observed in comparison with MHSRT samples before storage ($n = 3$; $P > 0.05$). Therefore, MHSRT developed in this study were stable at least for 6 months under stress conditions.

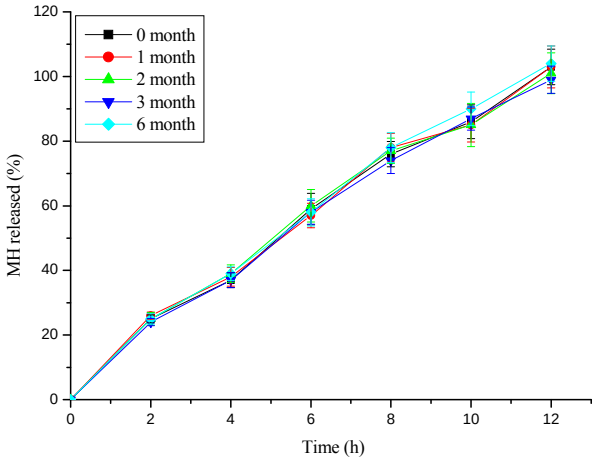

Figure 5. Drug release profiles of MHSRT developed in this study in water before and after 1, 2, 3 and 6 months of storage under stress conditions (40˚C ± 2˚C, RH 75% ± 5%).

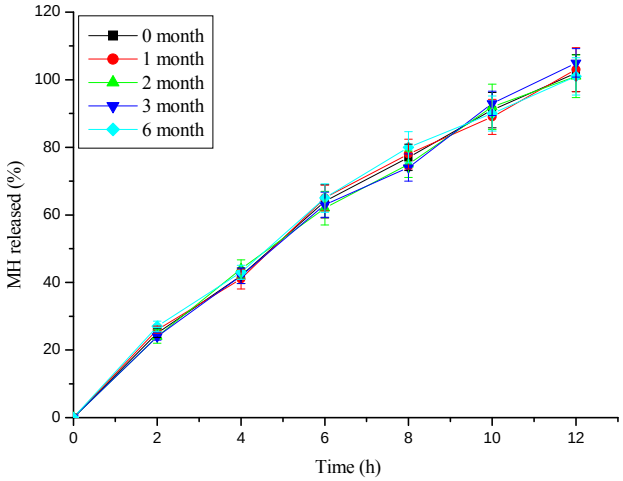

Figure 6. Drug release profiles of MHSRT developed in this study in 0.1 M HCl before and after 1, 2, 3 and 6 months of storage under stress conditions (40˚C ± 2˚C, RH 75% ± 5%).

4. Conclusion

In this study, once-daily metformin hydrochloride sustained-release tables (MHSRT) were successfully developed by the optimized formulation technologies that are suitable for mass produce at Chongqing Conquor Pharmaceutical Co., Ltd. The *in vitro* release behavior of MHSRT was almost similar to that of imported Fortamet®. Furthermore, MHSRT developed in this study were stable at least for 6 months under stress conditions.

5. Acknowledgements

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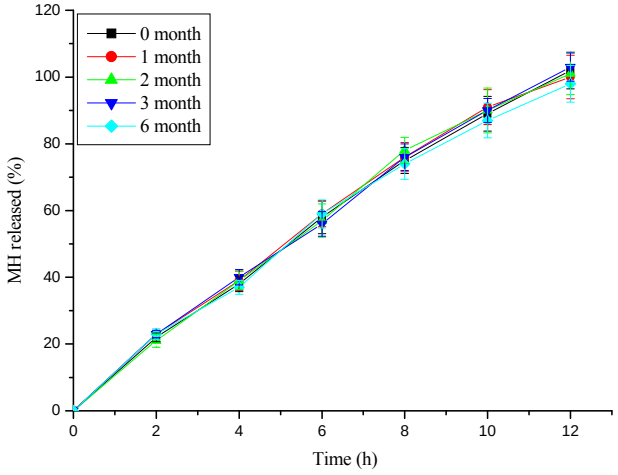

Figure 7. Drug release profiles of MHSRT developed in this study in pH 6.8 phosphate buffer before and after 1, 2, 3 and 6 months of storage under stress conditions (40˚C ± 2˚C, RH 75% ± 5%).

cation Department of Sichuan Province [09ZA049; 11ZZ024], the Scientific Research Foundation of the Health Bureau of Sichuan Province [100215; 100214]and the Key Program of the Scientific Research Foundation of Bureau of Science and Technology of luzhou Municipality [2011-S-32(1/4)].

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