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RESEARCH ARTICLE

Preformulation Study of Domperidone: An Insight for Formulation and Development of Nasal Formulation

Mansi M. Rathod, Disha D. Suthar, Hetal K. Patel, Pragna K. Shelat, Punit B. Parejiya

Department of Pharmaceutics, K. B. Institute of Pharmaceutical Education and Research, Kadi Sarva Vishwavidyalaya, Gandhinagar, Gujarat, India.

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ABSTRACT

Preformulation is a group of studies that focus on the physicochemical properties of a new drug candidate that could affect the drug performance and the development of a dosage form. This could provide important information for formulation design or support the need for molecular modification. So, in the present study preformulation studies were performed on Domperidone (DM) to assess its suitability for nasal formulation. Domperidone is a peripherally acting dopamine D2 receptor antagonist which has high first pass metabolism after oral administration. The authenticity of DM was established by DSC and FITR spectra. An UV spectrophotometric method and LC-MS method were employed for determination of DM in bulk and blood plasma respectively. Saturation solubility, micromeritical properties, melting point, pH, hygroscopicity, and stability profile were studied. The UV method was linear in the range of 5-50 µg/ml. The low % CV values of intra-day and inter-day variations revealed that the proposed method is robust. The retention time of DM in LC-MS method was found to be 2.6 min. The method was proven robust by obtaining very high regression coefficient value (0.999). The results of the physicochemical study of drug revealed suitability of DM for nasal route. Moreover, the drug was found stable in different conditions.

KEYWORDS

Preformulation, Domperidone, Nasal formulation, Bioavailability, Stability

INTRODUCTION

Delivery of any drug requires a stable dosage form to achieve optimum efficacy. For the development of dosage forms, study of fundamental properties of drug molecule is required.

Preformulation studies provide the understanding of the degradation process, any adverse conditions relevant to the drug, bioavailability, pharmacokinetics and formulation of similar compound and toxicity.[1] Preformulation influence a selection of the drug candidate, selection of formulation components, API & drug product manufacturing processes, determination of the most appropriate container closure system, analytical method development and toxicological strategy.[2] Preformulation studies strengthen the scientific foundation of the guidance, improve public safety standards, enhancement of the product quality and implementation of new technology.

The objective of preformulation study is to generate useful information for the formulator

*Address for Correspondence:
Mansi Rathod,
Department of Pharmaceutics,
K.B. Institute of Pharmaceutical Education and Research,
Gandhinagar 382023, India.
E mail ID: mansirathod18@yahoo.in

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to develop a stable and effective dosage form. The classic preformulation study requires drug characterization in solid as well as liquid phase. Preformulation can help in cost cutting for effective therapeutic development of the product.

The therapeutic efficacy of drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it is need to be solubilized. Majority of new chemical entities as well as classical molecules are found to be poorly water soluble in nature. To deliver such drugs in a better way, the issue of poor aqueous solubility needs to be addressed by formulation scientist. Domperidone is a dopamine-2 receptor antagonist. It acts as an antiemetic and a prokinetic agent through its effects on the chemoreceptor trigger zone and motor function of the stomach and small intestine. Unlike metoclopramide, it does not cause any adverse neurological symptoms as it has minimal penetration through the blood-brain barrier. It thus provides an excellent safety profile for long-term administration orally in the recommended doses.[3] Domperidone is a biopharmaceutics classification system (BCS) class II drug, which possesses very low aqueous solubility and poor permeation profile.

In present investigation, domperidone, a well-known anti-emetic drug with low oral bioavailability (about 15%) has been taken as a candidate drug. This is due to poor solubility and extensive first pass metabolism in the gut wall and liver.[4] Furthermore, it is reported that, the bioavailability of domperidone is enhanced in normal subjects when taken after meal, which indicates that fat may enhance absorption through lymphatic system and thus increase bioavailability.[5] To provide quick onset of action in emesis, route by which drug can directly goes into systemic circulation need to be chosen.

Nasal route as an alternative to oral route has recently gained much importance due to its advantages like; ease of administration, improved patience compliance, higher effective surface area and rapid onset of action.[6] Despite of such advantages, nasal route possess several limitations like; limited nasal delivery volume (≤ 300µl) only single space between ≤ and 300, nasal irritation due to pH of developed formulation, solubility of drug component in limited nasal delivery volume and molecular weight of the drug molecule.[7] Hence, preformulation study is necessary to check the suitability of drug candidate for nasal formulation which is stable, safe and effective.

MATERIALS AND METHODS

Domperidone (DM) was obtained *ex gratis* from M/s Torrent Research Centre, Ahmedabad, India. Methanol was purchased from M/s Finar Limited, Ahmedabad, India. Phosphate buffer pH 6.8 and double distilled water were prepared in laboratory.

Methods

Preformulation study is the mandatory step in formulation and development of pharmaceutical products for best selection of appropriate dosage form and choice of excipients. In the drug Preformulation studies, DM was tested for following parameters:

Analytical Preformulation

Quantification of Drug in Bulk

Quantification of domperidone in bulk was done by UV spectroscopic method which is mentioned below[8]:

Apparatus

An UV spectrophotometric analysis was performed on a double beam ultraviolet spectrophotometer (Shimadzu-1800, Japan), with a 1.00 cm quartz cells. The instrument settings were optimized to produce a spectrum with about 80% full-scale deflection and acceptable noise level. Each spectrum was recorded in triplicate. For each replicate measurement the cell was refilled with fresh solution.

Preparation of Phosphate Buffer pH 6.8

Dissolve 28.80g of di-sodium hydrogen phosphate and 11.45g of potassium dihydrogen

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phosphate in sufficient water to produce 1000 ml. Ultraviolet absorption in the range 200 to 400 nm of 10µg/ml solution in phosphate buffer (pH 6.8) was measured by UV spectrophotometer.

Preparation of DM Standard Solution

A stock solution containing 1000 µg/ml DM was prepared by dissolving 25 mg DM in 5 ml of methanol in a 25 ml of volumetric flask and volume was made up to 25 ml with the methanol. The same has been repeated for phosphate buffer pH 6.8. From these stock solutions, suitable aliquots were taken and diluted using appropriate solvent to get dilutions of 5-50 µg/ml. The determinations were conducted in triplicate and studied for three days to check intra and inter day variations.

Preparation of Calibration Curve

Calibration curve was constructed a concentrations range 5-50 µg/ml. Absorbance of each solution was measured at the wavelength of 287 nm. Calibration curve was constructed for domperidone by plotting absorbance versus concentration at 287 nm wavelength. The determination was conducted in triplicate.

Quantification of Drug in Plasma

LC-MS method was employed for determination of DM in human plasma is as described below[9]:

Instrument and Reagents

HP1100 LC-MS system (Hewllet Packard Company, USA) equipped with binary pump, on-line vacuum degasser, autosampler, column compartment, diod array detector, mass spectrometry detector of electrospray interface and HP ChemStation Review. Cisapride was used as an internal standard. Methanol was of HPLC grade and double distilled water was prepared in laboratory.

Preparation of Stock Solution

The stock solution of DM and cisapride were prepared by dissolving 20 mg each into 100 ml methanol separately. Aliquots were subsequently diluted with methanol to yield stock solutions 0.1 g/l. All prepared stock solutions were stored at 4° C and also checked for intra and inter day variations.

Liquid Chromatographic Conditions

Mobile phase: 0.5% acetic acid-methanol (60:40, v/v), column: Shimadzu VP-ODS, 5µm, 150 mm x 4.6 mm internal diameter maintained at 25° C and flow rate: 1.0 ml/min.

Extraction Procedure

Plasma sample (1 ml), working internal standard (10 µl) and NaOH solution (0.1 ml) were added to a test tube. The samples were mixed and then extracted with 5 ml ethyl acetate using vortex (Remi Instruments, Mumbai, India) for 3 min and centrifuged (Remi Centrifuge, Mumbai, India) at 25000 rpm for 5 min. The top organic layer (4 ml) was transferred to another tube and evaporated to dryness at 50° C under a gentle steam of nitrogen. The residue was reconstituted in 0.1 ml of mobile phase, centrifuged at 10000 rpm at 4° C for 10 min and then upper aliquot of this (20 µl) was injected in LC-MS for analysis.

Physicochemical and Micromeritical Preformulation

Saturation Solubility Study

Domperidone was taken in excess amount in clean and dry volumetric flask and dispersed in 50 ml purified water. The dispersion was shaken well and volume was adjusted to 100 ml followed by 10 min of shaking using flask shaker orbital shaker (CIS-24 Remi, India). The solution was kept aside for 15 min and 5 ml aliquot was withdrawn from supernatant and analysed using standardized analytical method. The procedure was repeated for different solvent (phosphate buffer pH 6.8, methanol, ethanol).

Melting Point

Melting point was determined by capillary fusion method in melting point apparatus. A capillary was sealed at one end filled with a small amount of domperidone and the capillary

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was kept inverted i.e. sealed end downwards into the melting point apparatus.

pH of 10% DM Solution

The pH of 10% DM solution (10 mg/100 ml) was determined using digital pH meter.

Hygroscopicity

Different samples of 25 mg of DM was placed in glass petri dishes and exposed to different humidity conditions in desiccators (previously calibrated) for a specific time period. The amount of moisture absorbed was determined by gravimetric analysis.

Aqueous State Stability Study

DM was accurately weighed and made into dispersion in distilled water. The solution was exposed to various conditions for specific time and checked for DM content periodically. The stability of drug in presence of light, oxygen, moisture, pH and ionic strength was also tested.

Differential Scanning Calorimetry (DSC)[10]

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The Samples were heated in an open aluminium pans at a rate of 100 per min^{-1} in a 30 to 300° C temperature range under a nitrogen flow of 40 ml/min.

Fourier Transform Infrared (FTIR) Spectroscopy[11]

FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The spectra was recorded as a dispersion of the sample in potassium bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm^{-1} and the resolution was 1 cm^{-1}.

Micromeritical Properties

Particle size and particle size distribution was determined by calibrated microscope. Bulk density and angle of repose were determined by standard procedure using standard density apparatus and fixed funnel method respectively. The Carr's index (%) and the Hausner's ratio were calculated using following equations:

Carr's index (%) = TBD - LBD / TBD × 100

Hausner's ratio = TBD / LBD

RESULTS AND DISCUSSION

Analytical Methods

The development of spectrophotometry methods for the determination of drugs has increased considerable in recent years because of their importance in pharmaceutical analysis. Based on the experimental data the standard calibration curves were plotted. The regression analysis showed very good correlation (r^2=0.987 in methanol and 0.998 in phoshphate buffer). The method was linear in the range of 5-50 µg/ml. These solutions obeyed Beer-Lambert's law in concentration range of 5-50 µg/mL in methanol and phosphate buffer with regression of 0.987 and 0.998 respectively. The overlaid spectrum of DM is shown in Figure 1.

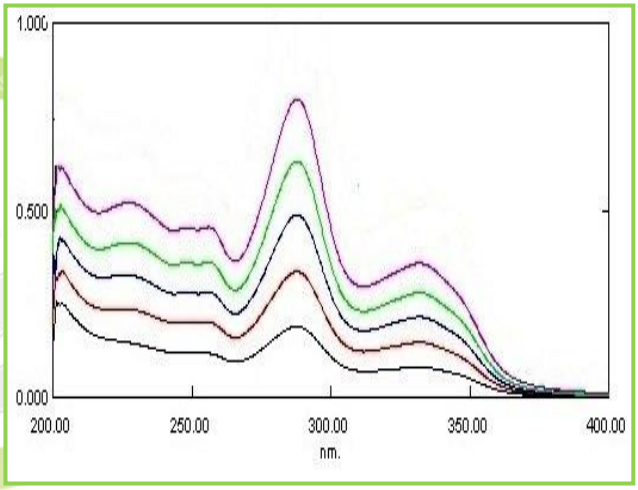

Figure 1: The overlaid UV spectra of DM in phosphate buffer

Figure 2 (a) shows calibration curve in methanol and (b) shows in phosphate buffer 6.8. The accuracy of analytical method is the closeness of test results obtained from that method to the true value. Accuracy is the measure of exactness of analytical method. Accuracy of the assay method was evaluated in triplicate at three concentration levels (5, 15, 25 µg/ml) and showed minor variation in concentration data. Result of intra-day and inter-day precision is expressed in % RSD. UV spectra of three different concentrations (5, 15, 25 µg/ml) were taken on the same day and the values of the relative standard deviation were calculated to determine intra-day precision. Percent RSD for Intraday assay precision was

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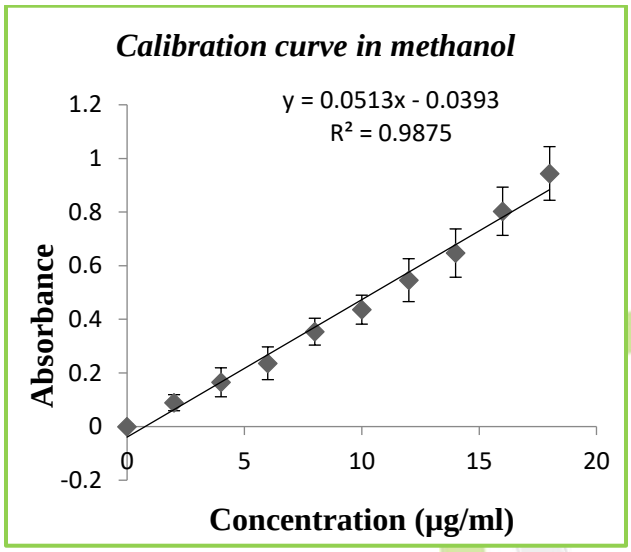
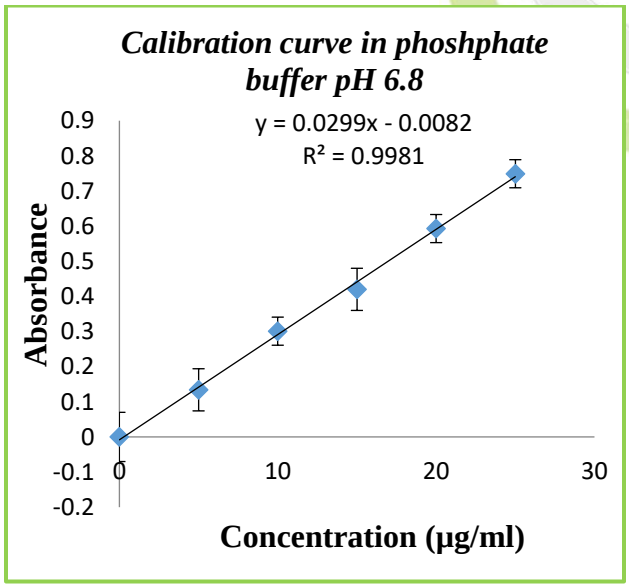
found to be 0.0501. Inter-day assay precision was found to be 0.0910. The low % CV values of intra-day and inter-day variations revealed that the proposed method is robust. According to the equation, the LOD was found be 0.27 and 0.24 for methanol and phosphate buffer respectively. LOQ was found to be 0.82 and 0.85 µg/ml for methanol and phosphate buffer respectively. This data shows that this method is sensitive for the determination of DM.



(a)



(b)

Figure 2: (a) calibration curve in methanol (b) calibration curve in phosphate buffer pH 6.8

The reliability of analytical findings is a matter of great importance in forensic and clinical toxicology, as it is of course a prerequisite for correct interpretation of pharmacokinetics and toxicological findings. LC-MS analysis of biological samples, such as plasma, requires sample preparation or clean-up prior to injecting into the LC-MS system. The mobile phase in developed LC-MS method was optimized and selected by taking different proportions of acetic acid and methanol which resulted acceptable asymmetry and theoretical plates. The LC-MS system was equilibrated with the initial mobile phase composition, followed by 10 injections of the same standard. These 10 consecutive injections were used to evaluate the system suitability on each day of method validation. The retention time of DM was found to be 2.6 min. The method was proven robust by obtaining very high regression coefficient value (0.999). The sensitivity and selectivity of method was proven by value of LOD and LOQ which are 0.001342 and 0.004067 respectively. Figure 3 shows linearity curve of DM by LC-MS method.

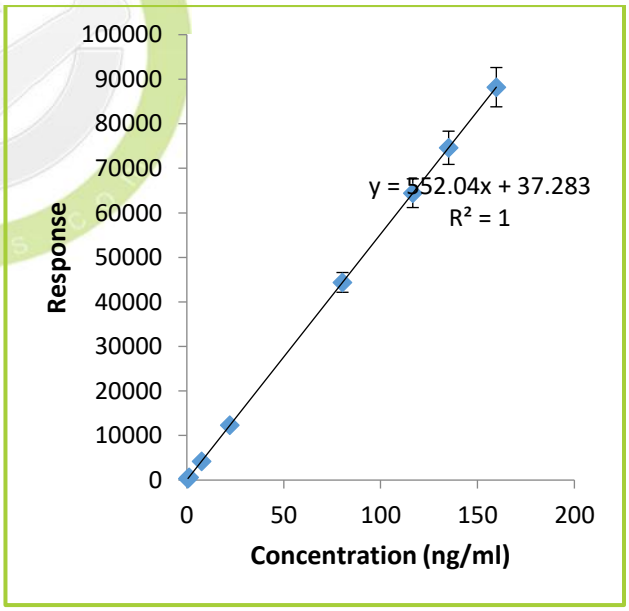


Figure 3: Linearity curve of DM by LC-MS method

Physicochemical and Micromeritical Preformulation

The results of physicochemical and micromeritical studies are depicted in Table 1. Various pharmacokinetics parameters were collected from literature. Acceptable

Organoleptic properties, solubility profile and physicochemical properties of domperidone establish its nasal administration profile. DSC thermogram of domperidone is shown in Figure 4. The thermogram of domperidone is showing an endothermic peak at 50.28°C. The characteristic absorption peaks of domperidone in FT-IR spectra as shown in Figure 5 proves stable and pure drug profile. Further, stability of domperidone has been also assessed at various temperatures, moisture, light, oxidation and pH condition. The results obtained from stability study under preformulation exhibited stable characteristics of drug at different storage conditions which are shown in Table 2.

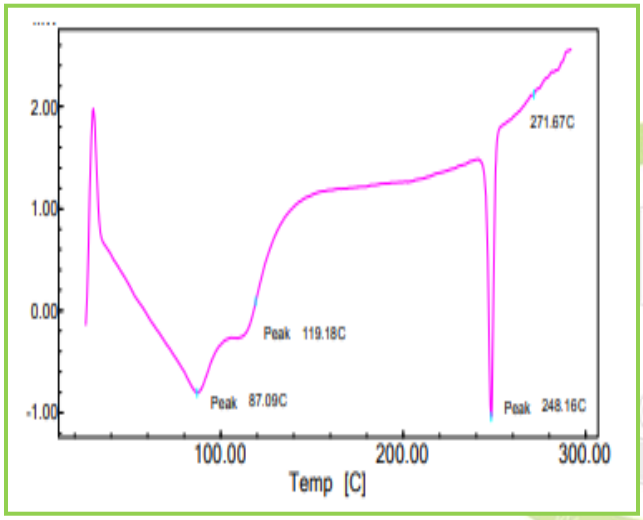


Figure 4: DSC thermogram of dompridone

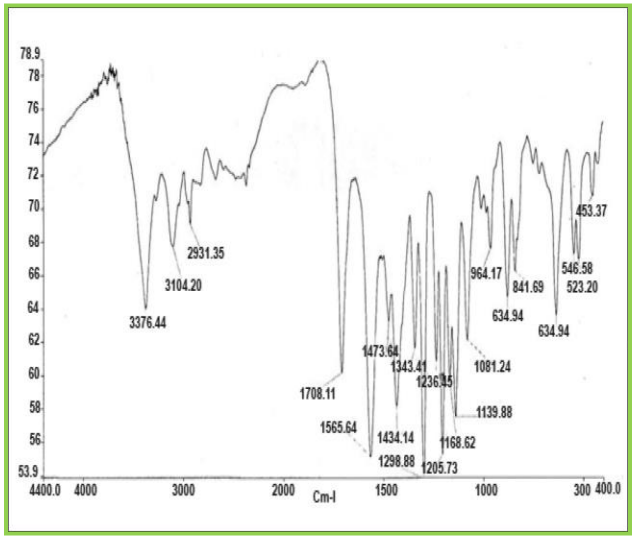


Figure 5: FT-IR spectra of domperidone

Table 1: Physiochemical, derived and pharmacokinetics data for DM

Sr. no.	Parameter	Observation
1. Organoleptic properties		
1.1	Colour	White fine powder
1.2	Odour	Odourless
1.3	Taste	Unpleasant, slightly bitter
2. Solubility		
2.1	Aqueous solubility	0.986 mg/L
2.2	pKa	13.14
2.3	Partition co efficient (Octanol-water, 25 °C)	308±40mg/L
3. Physicochemical property		
3.1	Melting point (˚C)	236-239
3.2	pH	6.4
3.3	Molecular weight	425.91
3.4	Purity (%)	99.97
4. Derived property		
4.1	Bulk density	0.545±0.047
4.2	Tapped density	0.555±0.043
4.3	Carr's index	17.56
4.4	Hausner's ratio	1.25
4.5	Angle of repose	23.22˚±1.44
5. Pharmacokinetic parameters (Reported)		
5.1	Half life (h)	7.2
5.2	Protein binging	~ 92%
5.3	Cmax (µg/L)	55.00
5.4	Tmax (h)	3-6
5.5	Bioavailability (%)	13-15 %

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Table 2: Drug stability under preformulation study at different conditions

No.	Influencing factor	Test sample	Packing material	Storage condition	Storage time (weeks)	Physical degradation	Drug content
1	Moisture	Pure drug	Open container	25˚C/75 % R.H.	0	No	98.99 ± 0.32
					1	No	98.79 ± 0.29
2	Temperature	Pure drug	50 ml glass container with twist-off closure	70˚C	0	No	99 ± 0.74
					2	No	100.43 ± 0.82
					4	No	98.45 ± 0.45
3	Temperature + Moisture	Pure drug substance with absorbed water at 25˚c/75 % RH	50 ml glass container with twist-off closure	70˚C	0	No	99.24 ± 0.34
					2	No	100.23 ± 0.11
					4	No	99.31 ± 0.58
4	Oxidation	1% aqueous solution in 0.35 H_2O_2 solution	25 mL glass flask with glass stopper	50˚C	0	No	99.12 ± 0.63
					1	No	100.66 ± 0.31
					3	No	98.78 ± 0.38
5	Light	Pure drug substance 1% aqueous solution	Open petridish	Xenon lamp	24 hrs	No	99.45 ± 0.33
					48 hrs	No	101.34 ± 0.68
			Brown glass flask	Xenon lamp	24 hrs	No	97.87 ± 0.35
					48 hrs	No	98.94 ± 0.23
			Open petridish	Xenon lamp	24 hrs	No	99.45 ± 0.89
					48 hrs	No	98.87 ± 0.54
			Brown glass flask	Xenon lamp	24 hrs	No	99.34 ± 0.92
					48 hrs	No	98.56 ± 0.78
6	pH	1% aqueous solution pH 1, 2, 3, 4, 5, 6, 7, and 8	25 ml glass flask with glass stopper	60˚C	0	No	98.34 ± 0.32
					1	No	98.24 ± 0.73
					3	No	100.89 ± 0.81

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CONCLUSION

From the results of the different preformulation study, it can be concluded that DM is suitable for nasal formulation. The pH of DM was found to be 6.4 proving no irritancy on nasal mucosa. Stability study under preformulation revealed stable characteristics of drug in both solid and aqueous state confirming final stability of formulation. So, in a nut shell it can be concluded that, due to high first pass metabolism of DM, the later can be administered via nasal route to achieve improved bioavailability. This study also suggests that DM can be delivered in nasal spray.

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