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Preparation and Evaluation of Diltiazem Hydrochloride-Gelucire 43/01 Floating Granules Prepared by Melt Granulation

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ABSTRACT

The basic objective of this study was to explore the application of Gelucire 43/01 for the design of multi-unit floating systems of a highly water-soluble drug diltiazem HCl. Diltiazem HCl-Gelucire 43/01 granules were prepared by melt granulation technique. The granules were evaluated for in vitro and in vivo floating ability, surface topography, and in vitro drug release. Aging effect on storage was evaluated using scanning electron microscopy, hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), and in vitro drug release. Granules were retained in stomach at least for 6 hours. Approximately 65% to 80% drug was released over 6 hours with initial fast release from the surface. Surface topography, HSPM, DSC study of the aged samples showed phase transformation of Gelucire. The phase transformation also caused significant increase in drug release. In conclusion, hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for design of a multi-unit floating drug delivery system of highly water-soluble drugs such as diltiazem HCl.

KEYWORDS: multi-unit lipid granules, floating, diltiazem hydrochloride, Gelucire, aging.

INTRODUCTION

Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose.[1] Therefore different approaches have been proposed to retain the dosage form in the stomach. These include bioadhesive systems,[2] swelling and expanding systems,[3,4] and floating systems.[5,6] Large single-unit dosage forms undergo significant swelling after oral administration, and the swollen matrix inhibits the gastric emptying even at an uncontractile state of the pyloric sphincter. Park and Park reported medicated polymeric sheets and swelling of balloon hydrogels.[7] But the swelling and expanding systems may show hazard of permanent retention. Bioadhesive systems may cause problems such as irritation of the mucous layer owing to high localized concentration of the drug.[8] Hydrodynamically balanced systems, designed using effervescent mixtures, have achieved commercial success but require a high drug:excipient ratio, have unpredictable bioavailability, and are unsuitable for drugs degrading in basic pH due to the alkaline microenvironment. The single-unit systems such as tablet or capsule may exhibit the all-or-none emptying phenomenon, which may be overcome by the design of multi-unit systems.[9] The multi-unit dosage forms such as pellets and granules may be more suitable because they claim to reduce the intersubject variability in absorption and lower the probability of dose dumping.[10] Many lipid-based sustained release matrix systems are reported in literature.[11-14] Recently, Kiran Kumar et al reported floating glycerol monooleate (GMO) single-unit lipid matrix containing high drug:excipient ratio (1:30) to achieve sustained drug release.[15]

Gelucires are a family of vehicles derived from mixtures of mono-,di-, and triglycerides with polyethylene glycol (PEG) esters of fatty acids. Gelucires are available with a range of properties depending on their Hydrophilic Lipophilic Balance (HLB 1-18) and melting point (33°C-65°C) range.[16,17] The Gelucires containing only PEG esters (Gelucire 55/18) are generally used in preparation of fast release formulations, while Gelucires containing only glycerides or a mixture of glycerides and PEG esters (Gelucire 54/02, 50/13, 43/01) are used in preparation of sustained release formulations.[11,18] Sutananta et al reported sustained release single unit matrices using Gelucire 43/01, where only 1.7% theophylline was released over a period of 20 hours.[19]

Thus, the major objective of the present study was to design floating sustained release granules with a low drug:lipid ratio. In order to achieve lower drug to excipient proportion and floating ability, the hydrophobic grade of lipid excipient Gelucire (Gelucire 43/01) was selected. Diltiazem HCl (DTZ), a model drug for this study, is a calcium antagonist used in the treatment of chronic heart diseases such as angina and hypertension. It has elimination half-life of 3.5 hours. Therefore, it is a suitable model candidate for gastro-retentive formulation. High solubility of DTZ is a major challenge in designing its controlled drug delivery system. The extreme

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release retarding ability of Gelucire 43/01 may be exploited to overcome this problem. In the present study, DTZ-Gelucire 43/01 floating granules were prepared by melt granulation and were evaluated with respect to in vitro and in vivo floating ability, drug content, surface topography, and in vitro drug release. Effect of aging on the granules was studied using hot stage polarizing microscopy (HSPM), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and in vitro drug release.

Materials and Methods

Materials

Gelucire 43/01 (waxy solid, melting point (mp) 43°C, HLB = 01, lot no. 0E4404–2) was a generous gift from Gattefosse (St Priest, Cedex, France). Glyceryl monosterate (GMS, MGS-F 75, white to yellow beads, mp 64°C, HLB = 1.5, lot no. 2054) was kindly supplied by Nikko Chemical Co Ltd (Tokyo, Japan). Methocel K4M (HPMC, lot no. 0G08012N31) and Ethocel 20 FP (EC) were kindly supplied by Colorcon Asia Pvt Ltd (Mumbai, India). Sterotex NF (hydrogenated cotton seed oil, white solid powder, mp 61.4°C, HLB = 1.5, lot no. 065M3NF) was supplied by Abitec Corp (Jenesville, WI). Diltiazem HCl was a kind gift from Sun Pharmaceuticals Ltd (Mumbai, India). All other chemicals were of analytical grade.

Methods

Preparation of Floating Granules

Floating granules containing DTZ were prepared using the melt granulation technique. The drug:lipid ratios used to prepare the different formulations were 1:1, 1:1.3, and 1:1.5. To study the effect of additives of different sustaining agents such as HPMC, EC, Sterotex, and GMS were added separately to the formulations. The proportion of additives was 0.5 parts for HPMC and EC, whereas it was 0.25 parts for Sterotex and GMS. Lipid was melted at 50°C, and the drug or drug and additives mixture was added, mixed well, and cooled to room temperature. The mass was passed through a 510-µm sieve to obtain uniform-sized granules.

Drug Content and Percentage Yield

Ten milligrams of floating granules were added to 10 mL of distilled water, heated to 60°C to 70°C, and allowed to cool to room temperature. The lipid was solidified and the drug solution was filtered through Whatman No. 1 paper (Whatman plc, Middlesex, UK). The sample was analyzed for drug content by UV spectrophotometry (Jasco V530, Tokyo, Japan) at 236.4 nm after suitable dilutions. Drug stability in the dissolution medium and distilled water was checked for a period of 8 hours. Determinations were performed in triplicate. Percentage yield of each formulation was calculated.

Surface Topography

The surface of the drug and granules were coated with a thin gold-palladium layer by sputter coater unit (VG-Microtech, Uckfield, East Sussex, UK) and the surface topography was analyzed with a Cambridge Stereoscan S120 SEM (Cambridge, UK) operated at an acceleration voltage of 5 kV.

Floating Characteristics

In Vitro Evaluation of Floating Ability

Fifty unit granules were placed in 900 mL of distilled water and United States Pharmacopeia (USP) simulated gastric fluid (pH 1.2) in a vessel maintained at 37°C ± 0.2°C and stirred at 50 and 100 rpm in a USP 24 type II dissolution test apparatus (Electrolab TDT-06P, Mumbai, India). The percentage of floating granules up to 6 hours was determined, and the floating times were measured by visual observation.[1]

γ-Scintigraphy

In vivo floating ability was studied by γ-scintigraphy in 6 healthy human volunteers of aged 25 to 30 years and having 55 to 65 kg total body weight. They were nonalcoholic, nonsmokers, and were not taking any other medication. The volunteers were asked to swallow the capsules filled with granules (drug:lipid, 1:1.5) containing radiolabeled tecnicium (^{99m}Tc) along with 100 mL water after taking a light breakfast in the morning. The dosage form was visualized using a gamma camera (GE Millennium MPR Gamma Camera, Israel). Images were taken at 0 hours, 1 hour, 2 hours, 4 hours, and 6 hours. Volunteers were in supine position during imaging.

In Vitro Release Studies

The release of drug from the granules containing different drug to lipid proportions (1:1, 1:1.3, and 1:1.5) was investigated in triplicate. Studies were performed in USP 24 type II dissolution test apparatus with the agitation speed of 100 rpm in USP simulated gastric fluid (pH 1.2) maintained at 37°C ± 0.2°C. At appropriate time intervals, samples were withdrawn and assayed spectrophotometrically at 236.4 nm with suitable dilutions. Analysis of data was done using PCP Disso v 2.08 software (Pune, India).[20]

Effect of Aging

Effect of aging was studied by HSPM, SEM, DSC, and in vitro drug release.

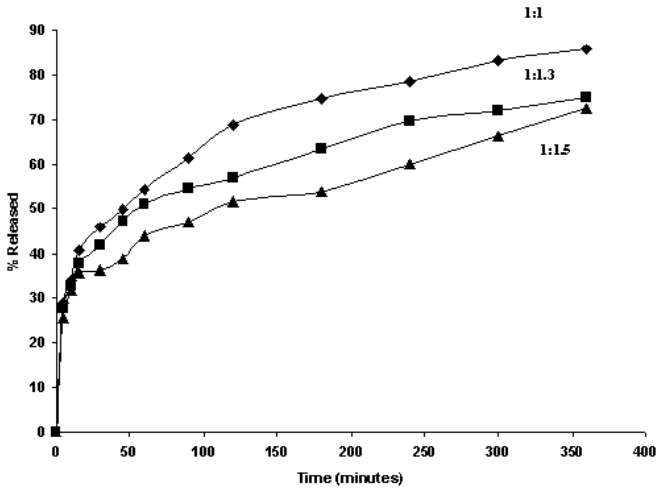

Figure 1. Release profiles of diltiazem hydrochloride from the granules showing the effect of increasing the drug:Gelucire ratios.

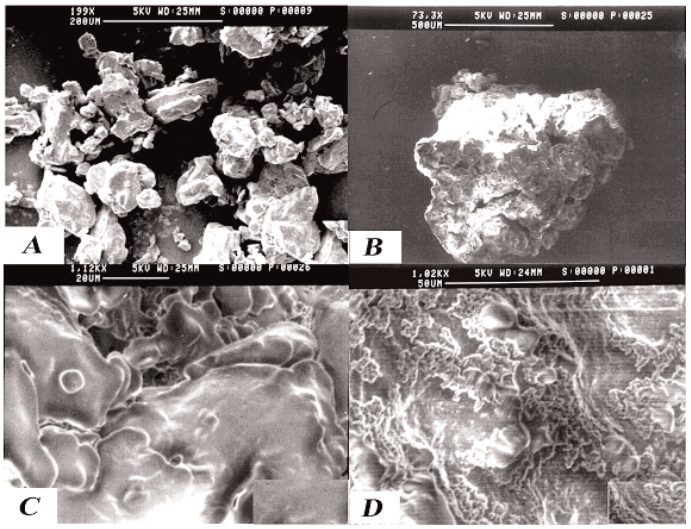

Figure 2. SEM images of (A) diltiazem hydrochloride, original magnification × 199; (B) melt granules, × 73; (C) fresh sample, × 1120; and (D) aged sample, × 1020.

Hot Stage Polarizing Microscopy

HSPM was conducted using Mettler Toledo FP82HT hot stage (Greifensee, Switzerland) assembled on Leica DMLP polarizing microscope equipped with Leica MPS-30 camera (Leica, Bensheim, Germany). Untreated, freshly prepared and aged samples were observed under the microscope at scanning speed of 2°C/min. Changes in the samples morphology (melting-crystallization) were noted as a function of temperature. Three types of samples were prepared for the physical evaluation of granules.

1. Freshly solidified samples. Placebo granules were prepared and stored for 6 hours at room temperature in order to avoid effects due to the thermal history.
2. Aged samples. Placebo granules were stored up to 1 month at room temperature (25°C; 60% relative humidity) in order to detect any physical changes (structural or polymorphic) on aging associated with glyceride bases.
3. Untreated samples. Base without any special treatment (as received from supplier).

Differential Scanning Calorimetry

Thermograms of granules were obtained using a Mettler-Toledo DSC 821^e instrument equipped with an intracooler. Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The sample of granules were hermetically sealed in an aluminum pan and heated at a constant rate of 10°C/min, over a temperature range of 25°C to 65°C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 mL/min.

Scanning Electron Microscopy

Surface of the fresh and aged samples were observed by SEM to study the ageing effect.

In Vitro Release

Effect of aging on drug release was studied on samples aged for 10 days and 30 days by the in vitro release method described for fresh samples.

Results and Discussion

Yield and drug content of the granules were found to be in the range of 95% to 99% and 98% to 102% wt/wt, respectively. In all the formulations (without any additives), 94% to 98% granules were found to float up to 6 hours. No significant difference was observed in the floating ability of granules containing different proportions of Gelucire. But drug release was retarded significantly with increase in the amount of Gelucire (Figure 1). All 3 drug:lipid ratios showed burst release in the initial stage, but increase in lipid ratio above 1:1.5 caused significant retardation, making it unsuitable for gastroretentive release, where complete drug release is expected to occur within the gastric residence period of 6 to 8 hours. The granules containing drug to lipid ratio 1:2 parts by weight showed significant release retardation, as less than 50% drug was released in 6 hours. Hence, the higher level of lipid in this study was restricted to 1.5 parts, and granules containing drug:lipid 1:1.5 were used for further evaluation. The SEM photomicrograph of the granules showed presence of lipid on the surface (Figure 2A-C). There was no effect of agitation speed on floating ability (data not shown). All the formulations floated for more than 6 hours except the formulation containing GMS. The γ-scintigraphy study of the floating granules in

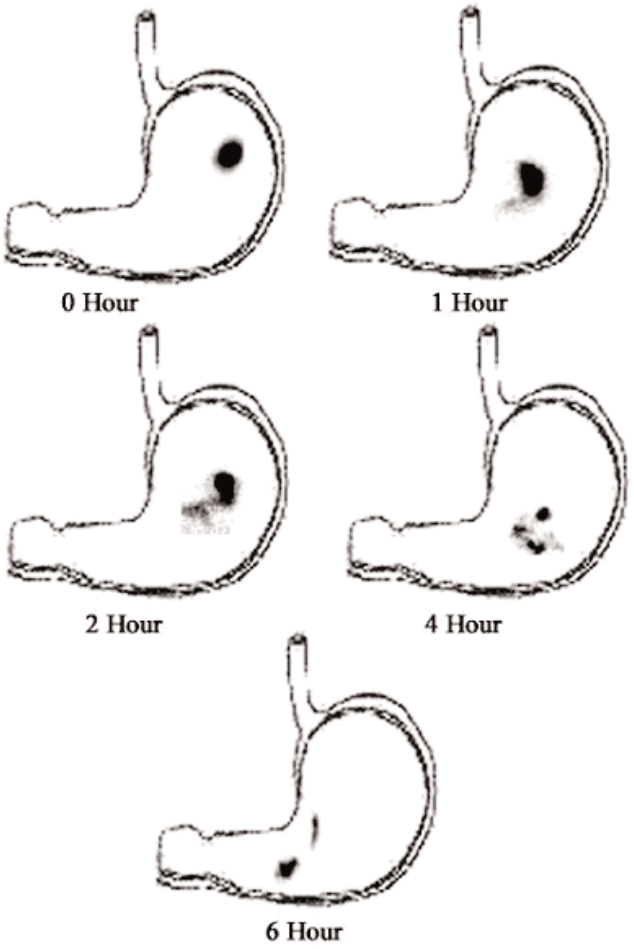

Figure 3. Gamma scintigraphs showing floating ability of diltiazem hydrochloride:lipid granules (1:1.5) in stomach.

human volunteer showed that the formulation remains in the stomach for ~6 hours (Figure 3). Drug release profiles in 0.1 N HCl are shown in Figure 1. It was observed that as the amount of lipid increased, the drug release decreased.

As an attempt to reduce initial drug release GMS, HPMC, EC, and Sterotex were evaluated as release-retardant additives. Surprisingly, the granules containing Gelucire:GMS (1:0.25) did not float despite low HLB of GMS. Whereas, granules containing Sterotex and HPMC floated but showed faster release of drug as compared with plain drug:Gelucire granules. Many workers have reported increased drug release owing to addition of hydrophilic excipient to lipid carriers.[21-23] Granules containing Gelucire:EC mixture (1:0.5) have shown significant retardation of drug release without hampering the floatability. The surface hydrophobicity imparted to the drug particle by the hydrophobic lipid coat was responsible for floating behavior. But all low HLB excipient did not ensure floating, as similar granules prepared using Compritol and GMS separately did not show floating property. Therefore, apart from hydrophobicity, density also plays an important role in design of floating granules using lipophilic excipient.

The SEM photomicrographs of fresh and aged granules are shown in Figure 2C and D. The SEM photomicrograph of

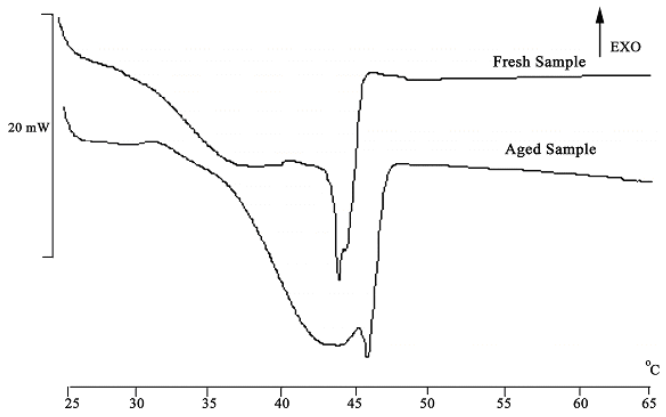

Figure 4. DSC thermograms of granules: fresh sample (0 day) and aged samples (30 days; Room Tempertaure).

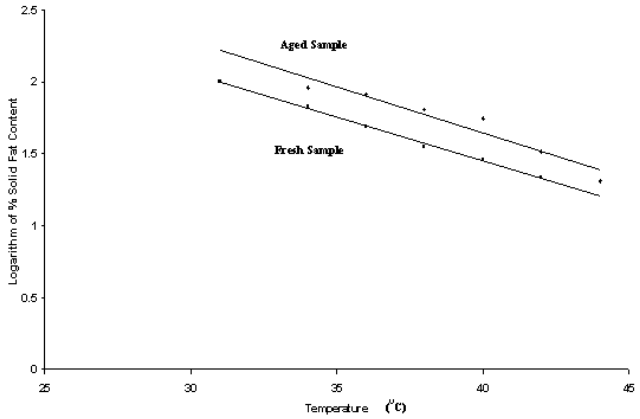

Figure 5. Semi-log solid fat content as a function of temperature of Gelucire 43/01.

surface of the fresh granules did not show any crystalline structure but showed smooth patches of lipid on the surface. After aging, sample showed significant change in the surface, possibly owing to phase transformation.

Thermograms of fresh and aged samples have shown significant difference. Enthalpy of fusion (ΔH_f) increased significantly upon aging (Figure 4). The average ΔH_f of fresh sample was 124.48 J/g, which increased to 130 J/g during aging. The glycerides melted over a narrow temperature range in the aged sample as compared with the fresh one. In the fresh sample, melting onset occurred at a temperature significantly lower than the aged sample, whereas end set temperature was slightly higher in aged sample. Aged sample showed a sharp shoulder at 45.6°C.

As the endotherm area is proportional to the solid content, DSC data was converted in terms of solid fat content. A semi-log plot of solid fat content versus temperature is shown in Figure 5. The data fitted well in following model

$$\% \text{ Solid content} = Me^{-Bt} \quad (1)$$

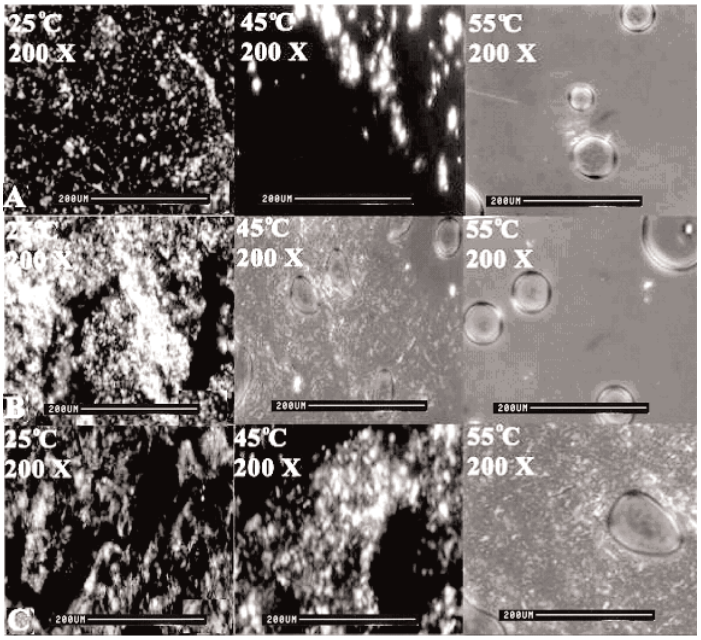

Figure 6. HSPM photomicrographs of Gelucire 43/01: (A) untreated samples; (B) freshly prepared placebo granules; and (C) aged placebo granules.

Where M and B are constant, M and B reflect initial solid content and rate of decrease in solid content respectively. Thus, logarithmic decrease occurred in the solid content in both the samples. Significant differences existed in the slopes of semi-log plots and were found to be 0.061 and 0.052 for fresh and aged samples, respectively. This finding indicated that rate of decrease in solid content was significantly higher in the fresh sample as compared with the aged sample. The similar observation was reported by Sutananta et al.[24]

HSPM photomicrographs of untreated, fresh and aged placebo samples are shown in Figure 6. It has been observed that complete melting of the Gelucire occurs at 45°C. HSPM photomicrograph showed presence of some unmelted portion even at 45°C in aged sample. Similarly, DSC data analysis showed that 71.5% glycerides melted up to 40°C in fresh samples as compared with 44.6% in aged samples (Figure 5). The energy required for melting increased with aging, which might be attributed to phase transformation due to crystallization of glycerides during aging. This slow crystallization of glycerides may be responsible for phase transformation, showing surface roughness.

Dissolution profiles of granules on aging (after 10 and 30 days) are shown in Figure 7. Drug release increased significantly on aging, which might be attributed to the phase transformation. About 94% to 98% of granules floated up to 6 hours; hence floating ability of the granules was not affected by aging. Initial fast release was owing to the dissolution of drug from the surface, after which release followed zero order kinetics, which may be owing to a noneroding lipid coat on the granule surface. Drug release kinetics were not

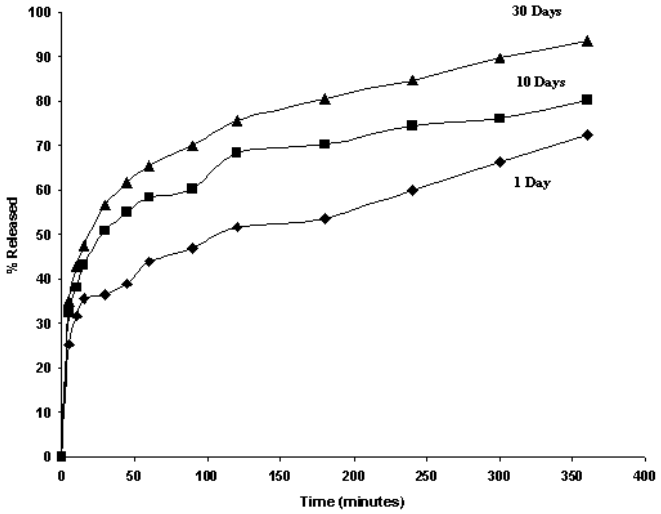

Figure 7. Release profiles of diltiazem hydrochloride from granules (1:1.5) showing effect of aging.

affected by aging. Studies using Gelucires 50/13 and 55/18 have shown similar effects on aging. Sutananta et al studied effect of preparation conditions, drug:Gelucire ratio, and storage on theophylline release from Gelucire 50/13 and 55/18 molded tablets and reported increase in drug release on aging.[25] It was attributed to changes in physical structure and chemical composition during aging. Roussin and Duddu attributed the increase in release to the development of surface cracks caused by phase transformation during aging.[26] The detailed study about mechanism of changes during aging and its stabilization may further widen the scope of this application.

CONCLUSION

It may be concluded that hydrophobic lipid, Gelucire 43/01, can be considered as an effective carrier for the design of a multi-unit floating drug delivery system of highly water-soluble drugs like diltiazem HCl.

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