Original Article

Solvent Drop Grinding Approach Assisted Development of Glimepiride Co-crystals: Solubility Enhancement Journey of BCS Class-II Product

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ABSTRACT

Background: Glimepiride has limited aqueous solubility and majorly suffers from bioavailability issues that eventually reduce the pharmacotherapeutic potentials of the moiety. **Materials and Methods:** For the possible augmentation of all the crucial factors, co-crystals were developed using a Generally Recognized As Safe (GRAS) co-former (caffeine) in the presence of few drops of solvent (acetone) by employing a very simple green approach (solvent drop grinding method). The pharmacokinetic study of the co-crystals was performed in Wistar albino rats, the data was compared with free drug form and pharmacokinetic parameters were determined. The fabricated co-crystal product was comprehensively characterized through sophisticated analytical techniques that ascertained the complete product formation. **Results:** The formation of the glimepiride crystal with the co-former was confirmed through FTIR, DSC, XRD and SEM. From the pharmacokinetic study in rats, the procured data expressed several-folds higher plasma drug concentration which can be correlated with increased bioavailability of glimepiride. **Conclusion:** This study will positively inspire researchers working in the field of solubility/ bioavailability enhancement due to the simplicity of the method, green approach and positive results which will open several future avenues of drug applications.

Key words: Glimepiride, Caffeine, Co-crystal, Bioavailability, Solubility, Green technique.

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INTRODUCTION

The concept of solubility enhancement of a therapeutically active moiety is essentially required in the modern days as it directly influences the drug bioavailability profile.[1] In general, the United States Food and Drug Administration (USFDA) approved drug molecules belonging to the Class-II (low solubility, high permeability) and Class-IV (low solubility, low permeability) of Biopharmaceutics Classification System (BCS) exclusively suffers from this phenomenon.[2] At present, several methods and techniques are available for the solubility enhancement of which solid dispersion, inclusion particle size reduction,[3-6] complex formation, micellar solubilization, hydrotrophy, cryogenic techniques, crystal engineering, supercritical fluid process, nanosuspensions, etc. are the most prominent one.[7]

Glimepiride (Figure 1A) is a second-generation, BCS Class-II, once-daily orally administered sulfonylurea class of drug that is recommended primarily for treating Type-2 diabetes mellitus (T2DM).[8] This insulin secretagogue directly stimulates the release of insulin (by depolarization of ATP-sensitive potassium channels) from

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the β-cells of the pancreas and may also act by extra-pancreatic mechanisms.[9] It is often recommended in therapy along with metformin or insulin, however, limited solubility and compromised pharmacokinetic properties result in a quite limited diabetotherapeutic advantage.[10]

Crystal engineering is one of the most emerging areas of modern pharmaceutics for solubility enhancement and increasing the bioavailability.[11] The crystal forms of drugs have been traditionally restricted to salts, hydrates solvates and polymorphs which impart a direct role in bioavailability, stability, solubility, manufacturability, performance and purification attributes.[12] Therefore, the selection of the most proper crystal or co-crystal form(s) is essential for pharmaceutical scientists.

While looking at other most popular methods for the formation of co−crystals such as solvent evaporation method, it often results in undesirable solvates or hydrates or homomeric molecules formation.[13] In contrast to the above, the use of solvent drop grinding method provides several distinct advantages such as addition of only few drops of solvent (environmentally friendly green approach), does not engross evaporation of huge amounts of solvent, a much shorter duration of co-crystal phase formation, compatible constituents for the co-crystal in an equimolar ratio, improves the formation of co-crystal and prospect of acquiring pure co-crystals.[14,15]

After studying the fact that glimepiride has limited aqueous solubility and majorly suffers from bioavailability issues that eventually reduce the pharmacotherapeutic potentials of the moiety, for the possible augmentation of all the crucial factors, co-crystals were developed using a Generally Recognized As Safe (GRAS) caffeine (Figure 1B), a co-former in the presence of few drops of solvent (acetone) by employing a very simple green approach (solvent drop grinding method). The pharmacokinetic study of the co-crystals was performed in Wistar albino rats, the data was compared with free drug form and pharmacokinetic parameters were determined.

MATERIALS AND METHODS

Materials

Glimepiride was obtained as a generous gift from Bluecross Pharmaceutical Ltd., Nashik, Maharashtra. Caffeine was procured from Sigma Aldrich Ltd., Germany through a local vendor at Nashik. All other analytical grade reagents, solvents and chemicals were utilized in the study were procured from Hi Media Ltd., India. Double distilled water (Borosil®) was employed during this study.

Synthesis of co-crystals

The co-crystals of glimepiride were prepared by a viable and green chemistry approach (solvent drop grinding method). GRAS co-former containing complementary functional groups such as caffeine was taken with the glimepiride in a stoichiometric ratio of 1:1 in a mortar and neatly grounded with the pestle in for 2 hr duration in presence of a solvent (acetone). The re-crystallization of the prepared co-crystals from the various solvents was also done (Figure 2).

Animals

The pharmacokinetic profile of glimepiride co-crystals was screened in Wistar albino rats of age 5-6 weeks, 160-230 g weight after obtaining permission from Institutional Animal Ethics committee (IAEC) and CPCSEA. The experimental animals were kept in the animal house at a controlled environment of temperature (24–25°C), humidity (50–60%) and diurnal cycles (12 hr light / 12 hr dark) along with good hygienic conditions. The rodents were caged in polypropylene cages (three in each cage), fed with standard pellets and allowed free access to water.

Characterization of co-crystals

Fourier-transformed Infrared Spectroscopy (FT-IR)

The FT-IR spectra of the developed product were recorded on a FTIR spectrophotometer (Perkin Elmer® GX-FT-IR, USA) by employing the potassium bromide technique in the range of 4000 cm^{-1} to 400 cm^{-1}. The products were scanned at 0.15 cm^{-1} resolution and 20 scan/sec scan speed.[16]

Differential Scanning Calorimetry (DSC)

The thermogram of the product was determined by DSC thermogram analysis on a Perkin Elmer® Pyris Diamond TG/DTA, USA. The product was heated gradually on a platinum crucible in the range 30-300°C along with the reference alumina powder at a rate of 10°C/min under inert nitrogen environment (150 mL/

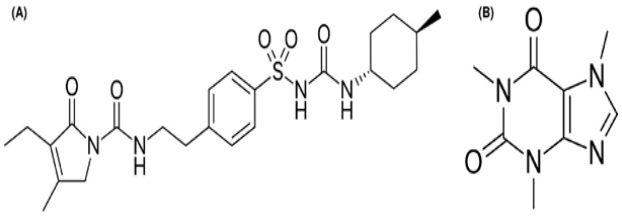

Figure 1: Structure of drug and co-former: (A) Glimepiride and (B) Caffeine.

min). Indium was employed as the standard material for periodical temperature calibration.[17]

Powder X-ray Diffraction (XRD)

The products were packed compactly in an aluminum sample holder by using a glass slide and characterized for their physical state by utilizing an X-ray powder diffractometer (Rigaku® Ultima-III, Japan). The scattering measurement was performed employing a monochromatic CuK- radiation (Cu target, 40 KV, slit 10 mm) at room temperature in the range of 5° to 80° at 4°/min scanning speed.[18]

Scanning Electron Microscopy (SEM)

The external morphology of co-crystals of glimepiride was determined by SEM (Jeol® JSM-6360A, Japan) technique. The product for analysis was sprinkled over the double adhesive tape attached with an aluminum stub and finally, the stub containing the product was placed in the chamber. The product was scanned randomly at 10 kV acceleration voltage and the photomicrographs were taken.[19]

Physicochemical studies

Solubility study

An excess quantity of glimepiride was added to double-distilled water (5 mL) containing caffeine in a 15 mL screw-capped plastic tube and the mixture was rotated on a test tube rotator at 45° angle, 150 rpm for the duration of 6 hr at room temperature. The sample was set aside for 24 hr duration to attain equilibrium and the content was assayed by using a UV-Vis spectrophotometer.[20]

Dissolution study

With compliance to the USP guidelines 30, the dissolution was performed with several modifications. 500 mg of the pure drug and co-crystal were individually compressed into pellet forms using CadMach Tablet punching machine. The dissolution of both the products was determined using a USP dissolution TDT-08 apparatus (Electrolab®, India) where phosphate buffer pH 6.8 medium was employed at 37±1°C temperature and 50 rpm rotation in 900 mL volume. Sample (5 mL) was withdrawn at time intervals of 5 min, 25 min, 40 min, 50 min, 75 min, 100 min, 125 min and 150 min to determine the cumulative glimepiride concentration at each endpoint. The sink condition was maintained. A graph was plotted for the cumulative amount dissolved from the pellet against time employing the linear regression on various data points. The dissolution rate was estimated from the slope of the regression plot.[21]

Pharmacokinetic study

Wistar albino rats were fastened for 6 hr duration before the administration of the drug product. The rats were divided into two groups, each comprising of 6 rats. Group-A was administered with glimepiride (6 mg/kg b.w.) orally using an animal feeding needle whereas Group-B was administered with co-crystals in a similar manner. After the drug administration, 0.7 mL of blood was withdrawn from retro-orbital plexus of the rats at pre-determined points; 1 hr, 2 hr, 4 hr, 8 hr, 12 hr and 24 hr. The blood was collected in heparinized tubes and centrifuged at 3000 rpm for 10 min at 4°C temperature to obtain the plasma. The concentration of the drug in pure form and in co-crystal forms were measured employing the RP-HPLC method of analysis.[22]

RESULTS AND DISCUSSION

Characterization of co-crystals

Fourier-transformed Infrared Spectroscopy (FT-IR)

The pure drug glimepiride showed characteristic absorption peaks (cm^{-1}) at 3369 (amide, -NH stretching), 3289 (aromatic C-H stretching), 2794, 1728 (carbonyl, C=O stretching), 1703, 1611 (amide, -NH bending), 1482 (aromatic C=C stretching), 1426 ($-CH_3$ bending), 1213 (C-N stretching), 1187, 1098 ($-SO_2-$ stretching), 964, 839 (aromatic C-H bending), 791 and 698. Caffeine featured absorption peaks (cm^{-1}) at 3203, 2963, 1741 (carbonyl, C=O stretching), 1682 (C=N stretching), 1547, 1520, 1439 ($-CH_3$ bending), 1283 (C-N stretching), 1117, 1044, 815, 771, 668 and 542 in FT-IR spectrum (Figure 3). In contrast to both of the above compounds, the FT-IR spectrum of the co-crystal presented the emergence of a different set of absorption peaks

Figure 2: Schematic representation of co-crystal formation process.

(cm^{-1}) at 3374 (amide, -NH stretching), 3290 (aromatic C-H stretching), 2997, 2894, 1769, 1755 (carbonyl, C=O stretching), 1553 (amide, -NH bending), 1519, 1337, 1228 (C-N stretching), 1204, 1167, 1044 ($-SO_2-$ stretching), 946 (aromatic C-H bending), 759 and 681 that eventually concluded the formation of the co-crystal product. Although few peaks indicating the amide (-NH-) and carbonyl (-C=O-) components remained fairly in a close agreement in the spectrum.

Differential Scanning Calorimetry (DSC)

The DSC thermograms of glimepiride and caffeine demonstrated sharp characteristic peaks corresponding to their melting point at 212.39°C and 236.08°C, respectively (Figure 4). The formed product in the 1:1 stoichiometric ratio showed an endothermic peak at its melting point 192.80°C. The reduction in the thermal characteristics of the product in comparison to the individual components indicated towards the formation of a new phase (either a co-crystal or possibly a eutectic). The new peak at 192.80°C with a reduced melting point indicated towards the formation of new H-bond(s) and the prospect of formation of a new crystal lattice among glimepiride and the co-former (caffeine).[23]

Powder X-ray Diffraction (XRD)

PXRD technique helped in differentiating the diverse crystalline phases. The pure drug glimepiride displayed several crystalline peaks (2θ) at 6.63°, 13.63°, 15.55°, 15.93°, 20.85°, 23.35°, 23.89°, 24.88°, 25.46°, 26.01°, 26.57°, 26.88°, 27.81°, 28.11°, 29.61° and 30.46°. Caffeine presented limited imperative crystalline peaks (2θ) at 14.71°, 16.05°, 20.03°, 20.86°, 23.93°, 24.36°, 26.27°, 26.72°, 27.39° and 29.94° (Figure 5). In contrast to them, the fabricated co-crystals demonstrated characteristic peaks (2θ) at 6.79°, 13.77°, 15.77°, 17.02°, 36.67°, 23.95°, 24.32°, 25.58°, 26.71°, 27.31°, 29.71°, 30.58°, 37.61° and 38.46° which indicated the formation of co-crystals owing to the disappearance of important peaks of both the drug and the co-former as well as reappearance of new peaks.

Scanning Electron Microscopy (SEM)

The microscopic particles of glimepiride were big stone-liked, irregularly shaped (~10 µm size), smooth hard solid and have no pores or crevices (Figure 6A). The photomicrograph of caffeine showed a long smooth needle-like crystalline feature of varied sizes and shapes (averagely 400 µm size) (Figure 6B). In contrast to the above observations, the formed co-crystals had small stone-liked solid irregularly shaped morphology with an extremely rough surface (~1 µm size) which confirmed the formation of a new co-crystal phase owing to the formation of hydrogen bonding between the drug and the co-former (Figure 6C).

Solubility and Dissolution Characteristics

The aqueous solubility of the pure drug was found to be 12.79 mg/25 mL (0.5116 mg/mL) whereas the co-crystals expressed a higher (6-folds) solubility profile of 72.56 mg/25 mL (2.9024 mg/mL). The dissolution profile of the drug pellet and co-crystal pellet revealed that the co-crystal formulation exhibited a higher release rate of glimepiride as compared to the free drug form till 150 min of study in the phosphate buffer pH 6.8 (Figure 7). Both solubility and dissolution studies ultimately concluded the fact that enhancement in the solubility profile leads to enhancement in the drug dissolution attribute that eventually leads to higher bioavailability characteristics.[24]

Pharmacokinetic profiling

The *in vivo* pharmacokinetic profiling in Wistar rats was performed using the HPLC method where the retention of the drug (glimepiride) was found exclusively at

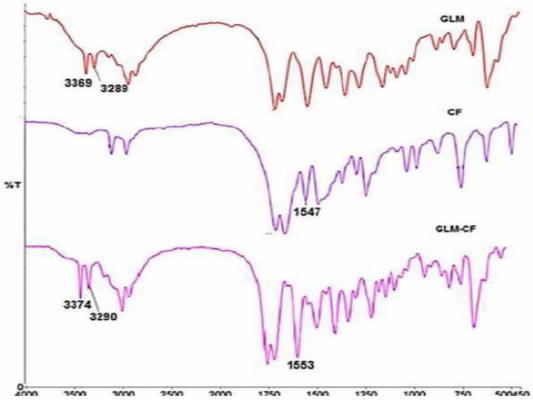

Figure 3: FT-IR spectra of drug, co-former and co-crystal.

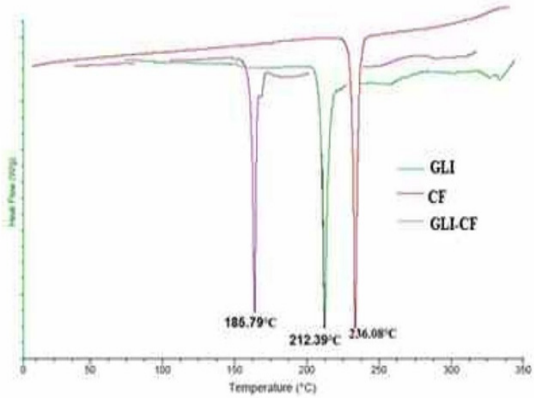

Figure 4: DSC Thermograms of drug, co-former and co-crystal.

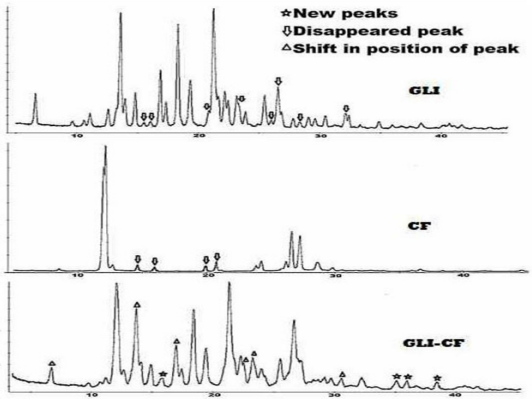

Figure 5: X-Ray Diffractogram of drug, co-former and co-crystal.

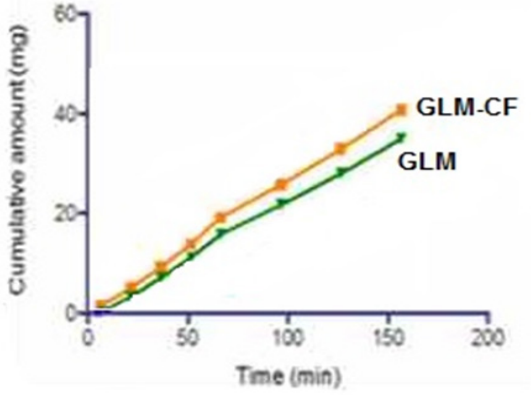

Figure 7: Cumulative drug release profile of glimepiride crystals and its comparison with normal glimepiride.

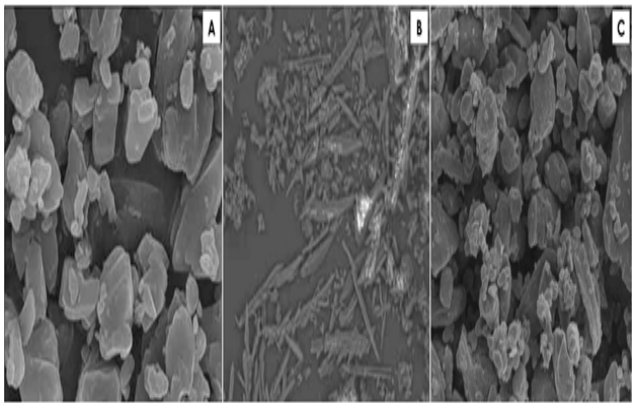

Figure 6: Photomicrographs of (A) glimepiride, (B) caffeine and (C) co-crystal.

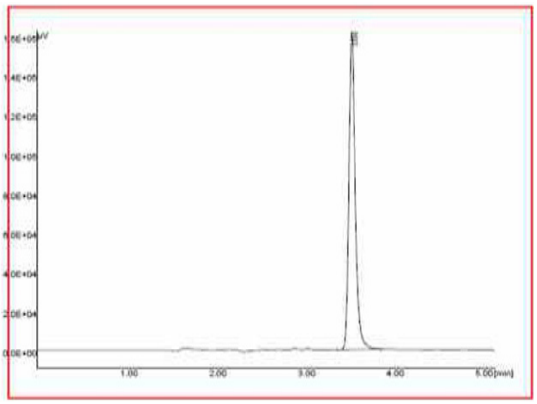

Figure 8: RP-HPLC chromatogram depicting the glimepiride peak in rat plasma sample.

Table 1: *In vivo* drug levels of glimepiride from normal product and co-crystal product.

Time (hrs)	Glimepiride normal product (ng/mL)	Glimepiride co-crystal product (ng/mL)
1	1378.56 ± 24.3	1430.25 ± 29.4
2	1420.36 ± 44.7	1560.23 ± 23.8
4	1498.36 ± 52.8	1688.23 ± 17.6
8	1449.26 ± 39.6	1565.23 ± 41.6
12	1409.36 ± 41.1	1468.56 ± 48.3
24	1374.23 ± 30.4	1420.15 ± 51.7

n = 6; standard error of the mean (SEM); *p = <0.05

3.611 min in the plasma samples (Figure 8). The study revealed that the co-crystals exhibited release of a higher amount of glimepiride in the plasma of the subjects (n=6) as compared to simple administration of the drug which indicated the significance of co-crystals in the bioavailability enhancement of drugs, particularly belonging to BCS Class-II. The pharmacokinetic parameters of co-crystal administered subjects were recorded as following; C_{max} = 1688.23 ng/mL and T_{max} = 4 hr in contrast to the administration of the simple drug which showed C_{max} = 1498.36 ng/mL and T_{max} = 4 hr, respectively (Table 1). The amount of glimepiride release from the fabricated co-crystals was found to be higher in the first 6 hr phase with approximately 1.25 times higher plasma levels, which later declined gradually in the rat plasma as a result of the various CYP_{450}-oriented liver-based metabolism process and concurrent time-bound elimination process of the body.[25]

CONCLUSION

The present study represented an effort towards the plausible enhancement of bioavailability of glimepiride, a BCS Class-II drug belonging to an anti-diabetic group. Caffeine, a simple chemical constituent was taken into account as a co-former for preparing the co-crystals through the solvent drop grinding method (a green approach). The fabricated co-crystal product was comprehensively characterized through sophisticated analytical techniques that ascertained the complete product formation. From the pharmacokinetic study in rats, the procured data expressed several-folds higher

plasma drug concentration which can be correlated with increased bioavailability of glimepiride. This study will positively inspire researchers working in the field of solubility/bioavailability enhancement due to the simplicity of the method, green approach and positive results which will open several future avenues of drug applications.

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CONFLICT OF INTEREST

Authors have no conflict of interest with the content and publication of this article.

ABBREVIATIONS

GRAS: Generally Recognized as Safe; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier-transformed Infrared Spectroscopy; **XRD:** Powder X-ray Diffraction; **SEM:** Scanning Electron Microscopy; **USFDA:** United States Food and Drug Administration; **BCS:** Biopharmaceutics Classification System; **T2DM:** Type-2 diabetes mellitus.

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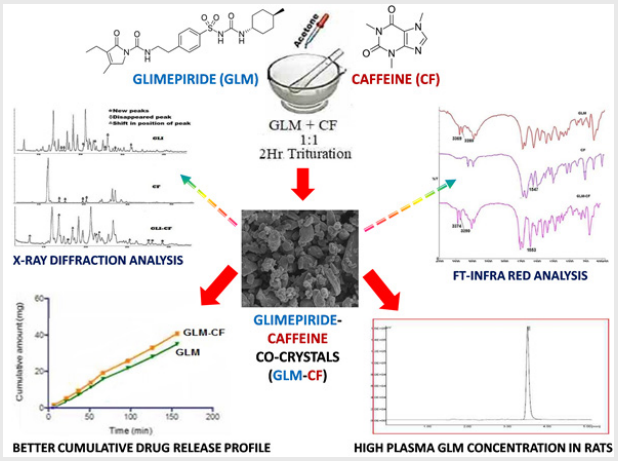
PICTORIAL ABSTRACT



SUMMARY

- The present study represented an effort towards the plausible enhancement of bioavailability of glimepiride, a BCS Class-II drug belonging to an anti-diabetic group.
- Caffeine, a simple chemical constituent was taken into account as a co-former for preparing the co-crystals through the solvent drop grinding method (a green approach).
- The fabricated co-crystal product was comprehensively characterized through sophisticated analytical techniques that ascertained the complete product formation.
- From the pharmacokinetic study in rats, the procured data expressed several-folds higher plasma drug concentration which can be correlated with increased bioavailability of glimepiride.

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Dr. Santosh S. Chhajed is working as Associate Professor at Mumbai Education Trust's Institute of Pharmacy, Adgaon, Nashik. Dr. Santosh is having teaching experience of 12 years of various Pharmaceutical Chemistry subjects at undergraduate as well postgraduate level. Dr. Chhajed has guided 20 scholars for their M. Pharm. Professor Chhajed has to his credit nine books in subjects like pharmaceutical chemistry, medicinal chemistry and pharmaceutical analysis and has published 40 papers in national and international journal of repute. Professor Chhajed was awarded with Best Research Guide Award in State Level Conference held in 2017 and he was conferred with Best Teacher Award 2018 from Mahavir International, Nashik chapter. His research area is computational approaches for design of drugs, synthesis of small molecule heterocycles, bioanalytical method development, synthesis and analysis of drug impurities, toxicity predictions of new chemical entities and drug impurities. Dr Chhajed is Nominated as FOCAL POINT by European commission for HORIZON2020 projects. He has worked as External Reviewer for major project competition held at Chile National Institute of Technology Chile in 2017.

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