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Research Article

Formulation and characterization of Solid dispersion of Nisoldipine by Solvent Evaporation Method

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Abstract

The aim of this study is to improve the solubility of poorly water soluble drug Nisoldipine by formulating the solid dispersion with different water soluble carriers. This will improve the dissolution rate of antihypertensive drug, Nisoldipine. For this purpose, polyvinyl pyrrolidone (PVP) k-25and polyethylene glycol (PEG) 4000 were used as carriers and dispersion was carried out by solvent evaporation technique. Formulations were characterized by particle size analysis, fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), drug content determination and dissolution studies. The particle size was found in range of 43.52 - 45.12 µm. FTIR studies showed the compatibility between drug and polymers. DSC study indicated that the drug was in amorphous form which results in better dissolution of the drug from the solid dispersion as compared to the pure drug and physical mixture. Dissolution studies indicated better release for solid dispersions and solubility was also increased 15 folds than pure drug. This could provide the formulation technology with a potential of increased bioavailability of poorly water soluble drug by increasing its dissolution rate.

Keywords: Solid Dispersion, nisoldipine, solvent evaporation, PVP k-25, PEG-4000

1. Introduction

The bioavailability of poorly water soluble drugs is the main focus of research these days. For this purpose, numbers of technologies are developed including solid dispersion technique (Chiou and Riegelman, 1971; Leuner and Dressman, 2000; Ryan et al., 2005). The solid dispersion technique resulted in improved bioavailability of many drugs which are now commercially available (Sethia and Squillante, 2003). In this technique, drug crystals are very finely divided and dispersed in water soluble carrier. Many carries are used in this formulation technique but mainly polyvinyl pyrrolidone (Hirasawa et al., 2003) and polyethylene glycol (Verheyen et al., 2002) can easily be utilized. Many methods are employed for the formulation of solid dispersions but solvent evaporation technique offer more potential and circumvents the difficulties faced in other methods. Nisoldipine, an anti-hypertensive drug, is a calcium channel blocking agent included in dihydropyridine family. Nisoldipine is (9/)3-isobutyl-5-methyl-1,4-dihydro-2,6-dimethyl-4-(2-nitrophenyl)-pyridine-3,5-dicarboxylate. It is

mainly indicated for hypertension, angina pectoris and heart failure (Vogt and Kreuzer, 1983). This drug has poor water solubility and high hepatic metabolism. Nisoldipine is Class II drug of Biopharmaceutical system (BCS) with low bioavailability. This makes nisoldipine a potential drug of choice for solid dispersion formulation which will result in improved solubility, dissolution and ultimately bioavailability.

Solid dispersions of nisoldipine were characterized by particles size analysis, fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Drug content determination and dissolution studies were carried out for further analysis.

2. Materials and Methods

2.1. Materials

Nisoldipine was purchased from Sigma Chemical Co. (USA). Polyvinyl pyrrolidone k-25 (PVP k-25) was purchased from Riedel-deHaen. Sodium lauryl sulphate (SLS) and Polyethylene glycol 4000 (PEG 4000) was purchased from Merck. All other chemicals and reagents used were of analytical grade.

2.2. Method

Nisoldipine is a light sensitive drug so all the experiments were carried out in light protected environment.

2.2.1. Preparation of physical mixtures

Physical mixtures were prepared by mixing of Nisoldipine and polymers in mortar and pestle by geometrical dilution method. This mixture is then passed through sieve (335 μm) (Six et al., 2004). All physical mixtures were prepared by same process and their composition is shown in table 1.

2.2.2. Preparation of solid dispersions

Solid dispersions were prepared by solvent evaporation method. The composition of all formulations is presented in table 1. Polyvinyl pyrrolidone k-25 and polyethylene glycol 4000 were dissolved in ethanol with continuous stirring until clear solution is obtained. Nisoldipine was then added to above said mixture with continuous stirring for 45 minutes. The solvent was removed under reduced pressure and the resulting solid dispersions were kept at room temperature in a dessicator, whch is then subjected to pulverization and sieving (Lingam and Venkateswarlu, 2009).

Table 1: Composition of formulations of physical mixtures (PM) and solid dispersions (SD)

Formulation	Nisoldipine	PVP k-25	PEG 4000
PM1	1	2	
PM2	1	4	
PM3	1	6	
PM4	1		2
PM5	1		4
PM6	1		6
SD1	1	2	
SD2	1	4	
SD3	1	6	
SD4	1		2
SD5	1		4
SD6	1		6

2.3. Characterization of Nisoldipine solid dispersions

2.3.1. Particle size analysis

Particle size analysis was carried out by laser diffraction size analyzer (LS 13 320, Beckman Coulter, CA). For this purpose, the samples were ultrasonicated for a minute after suspending in silicone oil. Then these

samples were analysed by laser diffraction analyser.

2.3.2. FTIR spectroscopy

The FTIR spectra for all the formulations were collected on FTIR spectrometer Pristige-21 (Shimadzu-Japan). KBr discs were prepared by mixing the samples with potassium bromide before analysis. Samples were analyzed over the range of 4000-400 cm-1 at the resolution of 2 cm-1.

2.3.3. Differential scanning calorimetry (DSC)

DSC was performed for pure drug, polymers and all the formulations using DSC (DT-60, Shimadzu, Japan). Samples equivalent to 4-5mg of drug were sealed in aluminum pans and then heated. Temperature range was 50-300 0C at a rate of 20 0C per minute.

2.3.4. X-ray powder diffraction (XRD)

X-ray diffraction of nisoldipine and the formulations was carried out by diffractometer. This was done to determine the polymorphic state of nisoldipine. Recording was made form 3 to 1500 in Si (Li) PSD detector with scanning speed of 30 per minute. All the process was operated at 40kV and 35mA.

2.3.5. Drug content determination

All the samples of various formulations were placed in 25 ml volumetric flask (equivalent to 20 mg of drug). 10 ml methanol was added to the each sample mixture and sonicated for 10 minutes. Methanol was used to make the final volume. This solution is then diluted by methanol up to certain extent so that it can easily be analyzed spectrophotometrically at λ = 238 nm (Swami et al., 2010).

2.3.6. Dissolution studies

Dissolution studies were performed using Type II paddle apparatus. The dissolution medium consisted of 900 ml phosphate buffer solution with pH 6.8 containing 1 % sodium lauryl sulphate (SLS). The temperature was maintained at 37 ± 0.5 ˚C and stirring speed of 60 rpm.

Samples (equivalent to 10 mg of nisoldipine) were spread on the surface of dissolution medium. 5 ml of aliquots were withdrawn at specific intervals and measured spectorphotometrically for nisoldipine content at wavelength 238 nm. The volume of dissolution medium was kept constant by adding same amount of fresh medium.

Drug dissolution was determined by plotting a graph between drug dissolved and time interval.

2.3.7. Solubility studies

Solubility studies were carried out for pure nisoldipine and all the formulations by placing them in medium of pH 6.8. All the samples were shaken for 48 hours in an orbital shaker by keeping temperature at 37 ˚C. This solution is then filtered by whatmann filter paper and filtrate was further diluted and measured spectrophotometrically at 238 nm

3. Results and Discussion

3.1. Particle size analysis

Particles size analysis was carried out for all the solid dispersion formulations as it plays an important role in drug release. Smaller the size more will be the release. The particle size for all solid dispersion formulations was found to be in range of 43.52 - 45.12 μm as shown in table 2

3.2. FTIR spectroscopy

FTIR spectroscopy was carried out for determination of any polymorphic alteration in complexes and to check interaction between drug and polymers. FTIR of pure nisoldipine showed characteristic peaks at wave number 3320 cm-1 indicating N-H stretching. Peak at 3001 cm-1 indicated C-H stretching and peak at 1701 cm-1 showed the presence of C=O stretch. There was also peak at 1555 cm-1 indicated the presence of nitro group and at 1230 cm-1 for ether absorption.

All the formulations i.e. physical mixtures and solid dispersions showed principle peaks of nisoldipine but the peak at 3320 cm-1 of N-H stretching was not observed in case of solid dispersion of nisoldipine with

both PVP k-25 and PEG 4000 showing functional group interaction between drug and polymer. All other peaks were observed with less intensity. The spectra of solid dispersions with polymers showed all the characteristic peaks but with less intensity than pure nisoldipine as shown in Fig.1.

Table 2: Particle size analysis of solid dispersion formulations

Formulation	Particle Size (µm)
SD1	43.52
SD2	43.96
SD3	44.69
SD4	43.72
SD5	44.56
SD6	45.12

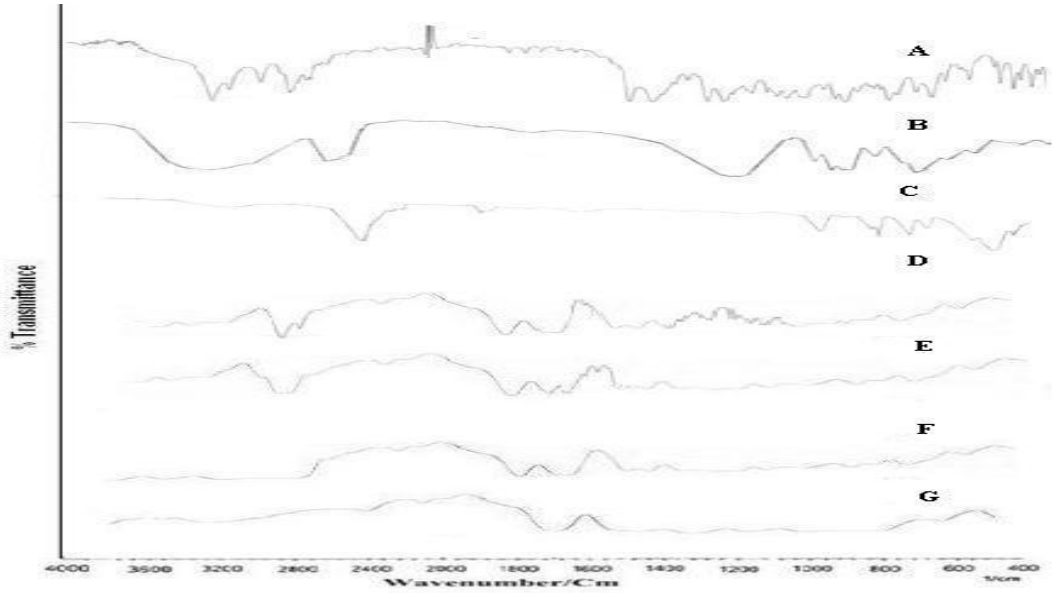

Fig: 1. FTIR Spectra of A: Nisoldipine, B: PVP k-25, C: PEG 4000, D: PM3, E: PM6, F: SD3, G: SD6

3.3. Differential scanning calorimetry (DSC)

DSC was carried out for thermal analysis of drug and polymer after formulation. This is very helpful tool in evaluation of physicochemical properties of drug. All thermal curves are shown in Fig. 2. Pure nisoldipine showed a sharp endothermic peak at 151 oC (Melting point range of Nisoldipine = 150-155 oC). Thermal Peak of PVP k25 was at 112 oC and that of PEG 4000 was at 55 oC. The thermograms of all the formulations showed peaks shifted to slightly lower melting point as shown in Fig. 2. This can be attributed to change in physical state of nisoldipine from crystal to amorphous during the preparation of solid dispersion. As amorphous state has high disorder and high energy state so the solid dispersions had enhanced solubility and higher dissolution rates.

3.4. X-ray powder diffraction (XRD)

XRD studies were carried out for confirmation of results obtained from DSC studies to evaluate the physicochemical properties of active drug. The XRD of pure nisoldipine showed sharp peaks whereas the diffractogram of the complex showed reduction in peak intensity as shown in Fig. 3.

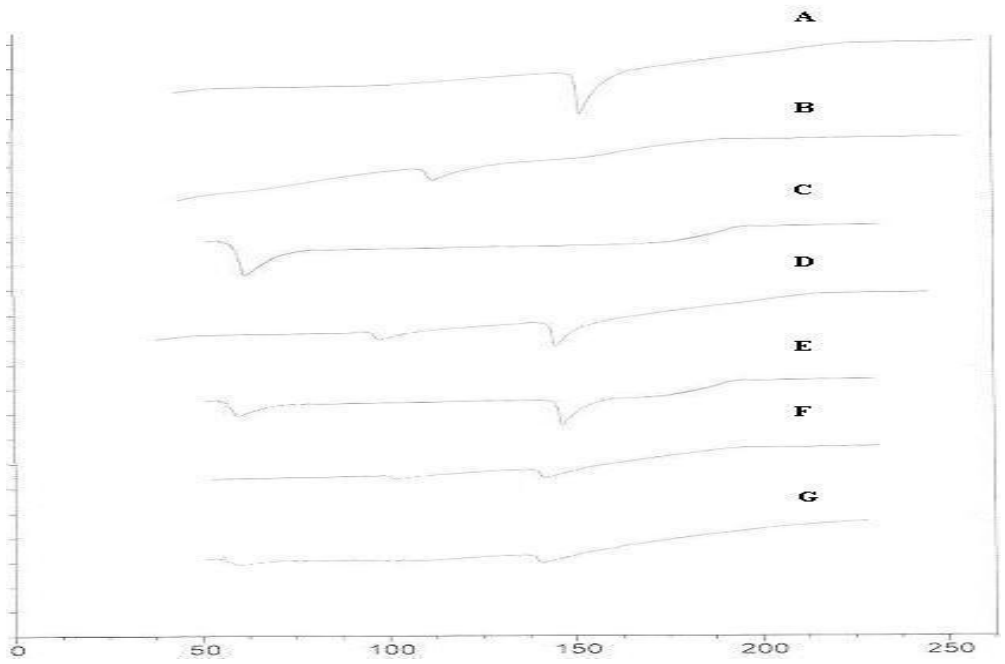

Fig: 2. DSC of A: Nisoldipine, B: PVP k-25, C: PEG 4000, D: PM3, E: PM6, F: SD3, G: SD6

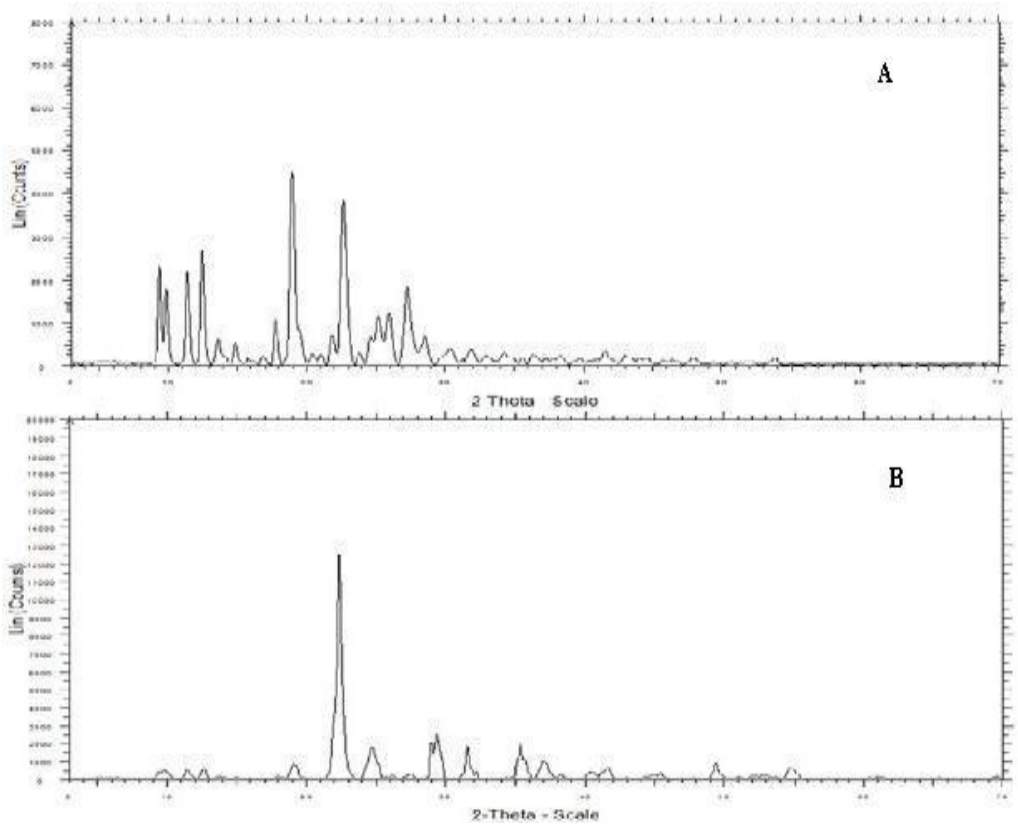

Fig 3. XRD of A: Nisoldipine, B: Complex

3.5. Drug content determination

Drug content determination was carried out for control of drug quality and effectiveness of process for preparation of formulation. The drug content of various formulations was in range of 79.9 to 87.5 % w/w. The results confirmed the homogeneous distribution of drug within complexes.

3.6. Dissolution studies

Dissolution studies were carried out to determine the release properties of drug from the formulations. Dissolution rates can be increased by reducing particle size and absence of crystallinity of drug. Table 3 and Fig. 4 showed the dissolution profile of pure nisoldipine, physical mixture and solid dispersion prepared by PVP k25 and table 4 and Fig. 5 showed the dissolution profile of formulations using PEG 4000 as polymer. Solid dispersion complex showed maximum dissolution rates in 90 minutes followed by the dissolution rate of physical mixtures and pure nisoldipine in formulations of both polymers.

Increased dissolution rates for physical mixtures can be attributed to increased surface area of drug and solubility of drug when come in contact with dissolution medium as carrier dissolves resulting in enhanced wettability of drug (Liu et al., 2006). In case of solid dispersion complexes, increased dissolution rates can be attributed to reduced particle size and reduction in crystallinity resulting in increased wettability (Muralidhar et al., 2011; Sharma and Jain, 2010). Reduction in crystallinity was also confirmed by DSC studies.

Overall result of dissolution studies showed that PVP had improved drug release than PEG 4000 for nisoldipine solid dispersion. These results were in accordance with Lingam and Venkateswarlu, (2009).

Table 3: Dissolution Study of various formulations by PVP k-25

Sr. No.	Time (min)	NSD	PM1	PM2	PM3	SD1	SD2	SD3
1	0	0	0	0	0	0	0	0
2	15	6.3	8.3	9.1	9.8	18.3	19.9	20.5
3	30	17.8	19.1	20.8	21.3	36.9	37.5	38.4
4	45	29.1	32.6	33.4	35.2	55.4	56.1	57.8
5	60	43.6	47.2	48.5	49.7	68.8	69.7	71.3
6	75	58.2	64.3	66.1	66.3	79.2	80.6	83.1
7	90	61.5	72.8	74.1	74.6	87.8	92.1	94.6

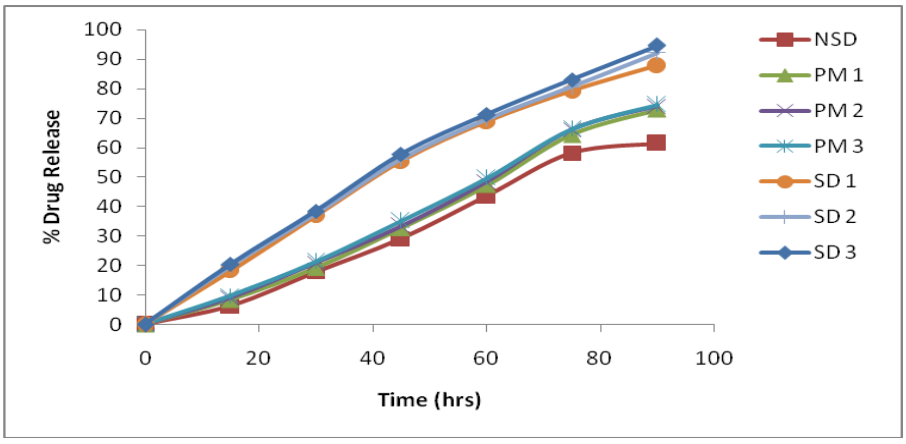

Fig 4. Dissolution of Pure Nisoldipine, PM and SD with PVP k-25

Table 4: Dissolution Study of various formulations by PEG 4000

Sr. No.	Time (min)	NSD	PM4	PM5	PM6	SD4	SD5	SD6
1	0	0	0	0	0	0	0	0
2	15	6.3	7.4	8.2	9.8	17.2	18.7	19.3
3	30	17.8	18.2	19.6	24.6	35.3	36.5	38.7
4	45	29.1	30.9	31.4	39.2	54.6	55.8	58.6
5	60	43.6	45.7	46.8	51.4	67.9	69.1	72.2
6	75	58.2	62.8	64.1	66.3	76.8	78.9	83.1
7	90	61.5	70.6	72.3	74.8	81.3	86.7	88.1

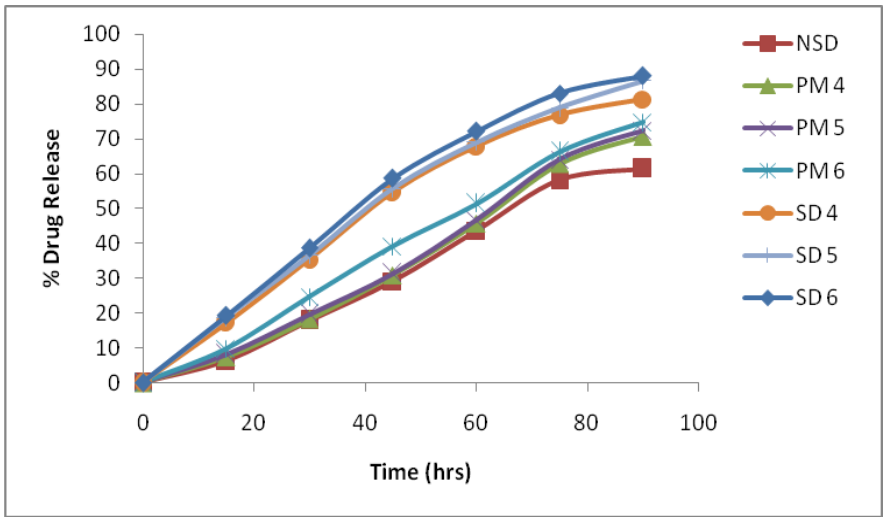

Fig 5. Dissolution of Pure Nisoldipine, PM and SD with PEG 4000

3.7. Solubility studies

Solubility studies were carried out to estimate the bioavailability of the drug. The solubility of pure nisoldipine was found to be 0.0246 mg/ml but after its formulation in solid dispersion complex the solubility of nisoldipine increased about 15 folds. The pH solubility profile of nisoldipine does not alter over the pH range of 1-8 which proved that the solubility of nisodipine is independent to pH..

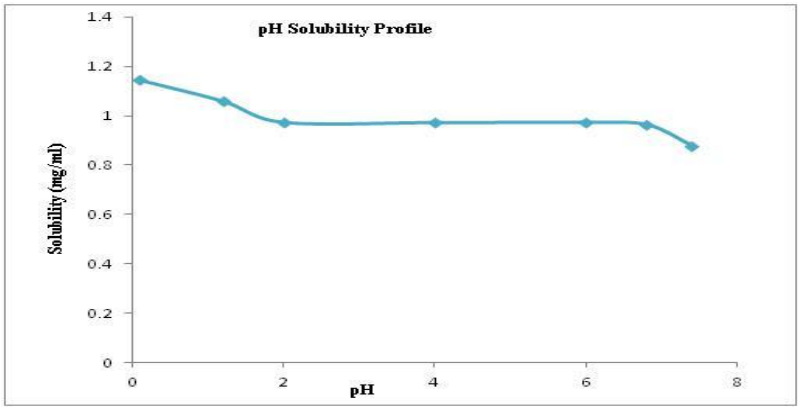

Fig 6. pH Solubility Profile of Nisoldipine

4. Conclusion

Solid dispersion of nisoldipine was prepared by solvent evaporation method, a simple and easily reproducible method. The evaluation of all the formulations was carried out by various parameters. FTIR studies showed the adequate behavior of drug. DSC and XRD studies showed reduction in crystallinity of nisoldipine. Drug content was also found to be adequate. Dissolution was carried out with all the formulations and SD3 showed highest release and found to be the best formulation. Solubility of nisoldipine was also increased to 15 folds in solid dispersion formulation. Therefore, it can be assessed that improvement in dissolution rate of hydrophobic nisoldipine was achieved.

These formulations can also be used further for buccal tablets to avoid systemic metabolism but this formulation provided a potential for increased bioavailability of drug to the body.

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