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EVALUATION OF EFFECT OF MOISTURE ON NEOSTIGMINE METHYLSULFATE DRUG SUBSTANCE BY FTIR SPECTROSCOPY

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ABSTRACT

The intermolecular carbon and hydrogen bonding interaction with that of methylsulfate and counter ion of drug substance has been investigated by FTIR Spectroscopy. This article mainly reports the effect of moisture on Neostigmine methylsulfate drug substance by FTIR Spectroscopy. The spectroscopic characteristics of O----H complexes are specified. Neostigmine Methylsulfate is hygroscopic in nature, the water molecule reacts with methylsulfate ion to form O----H intramolecular hydrogen bonding, due to which IR spectra shows noise and chemical shift at region of wavenumber about 3020 cm^{-1} and 2900 cm^{-1}.

KEYWORDS: Intramolecular hydrogen bonding, Hygroscopic, FTIR spectroscopy, Neostigmine Methyl sulfate

INTRODUCTION

Neostigmine methylsulfate (Figure 1)[8,9,10] chemically known as [3-(dimethylcarbamoyloxy)phenyl]-trimethylazanium; methyl sulfate. Molecular formula $C_{13}H_{22}N_2O_6S$, molecular weight 334.40.[8,9,10] Neostigmine was first synthesized by Aeschlimann and Reinert in 1931[12] and was patented by Aeschliman in 1933.[13] Neostigmine is made by first reacting 3-dimethylaminophenol with N-dimethylcarbamoyl chloride, which forms a dimethylcarbamate. Next, that product is alkylated using dimethyl sulfate, which forms neostigmine.[13,16]

Neostigmine methylsulfate is approved for the treatment of myasthenia gravis and reversal of nondepolarizing muscle relaxants.[14] Neostigmine Methylsulfate is given by injection either into a vein, muscle, or under the skin.[15] Neostigmine methylsulfate injection is a

cholinesterase inhibitor indicated for the reversal of the effects of non depolarizing neuromuscular blocking agents after surgery.[17] Neostigmine is poorly absorbed when administered orally and does not cross the blood–brain or placental barriers, due to its quaternary amine structure.[18]

Literature survey was carried out for the effect of moisture on Neostigmine methylsulfate drug substance during IR analysis. However, no method has been published to check the effect of moisture on Neostigmine methylsulfate drug substances. In the present work, a procedure was proposed to avoid the noise and chemical shift in the IR pattern at region of wavenumber about 2900 cm^{-1} and 3020 cm^{-1} during Infra-red analysis. As per general chapter of IR-Spectroscopy in EP(2.2.24)[8] and USP (197)[9], if spectra of sample does not comply with that of standard, the same solvent treatment should be given to both sample and standard preparation and the analysis can be reperformed to match the spectra. There upon our studies resort on inspecting the solvent induced crystallization technique and to check the effect of moisture on Neostigmine drug substance by analyzing the sample and standard using infra-red spectroscopy.

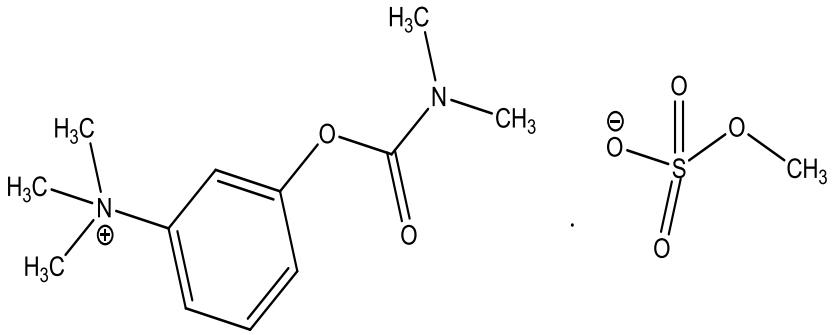

Figure 1: The structure of Neostigmine Methylsulfate.

METHODS

FTIR Spectroscopic analysis

FTIR Spectroscopy is an important analytical technique which detects various characteristic functional groups in molecules of any matter. On interaction of an infrared light with the matter, chemical bonds would stretch, contract and bend, and as a result each chemical functional group tends to absorb infrared radiation in a specific wavelength range regardless of the structure of the rest of the molecule. Based on the principle, functional groups present in composite materials are identified.

EXPERIMENTAL

1. Experiment (Standard moisture free and test sample which has absorbed Moisture)

1.1. Instrumentation

The FTIR Spectroscopy is of make Perkin Elmer, Model – Spectrum One. Hydraulic Press, Vacuum Oven, Mortar and Pestle.

1.2. Reagents and reference samples

Potassium bromide of Spectroscopic grade.

1.3. Standard preparation (Moisture free)

Weigh and Triturate about 2 mg of Standard with about 300 mg of finely powdered and dried potassium bromide and grind the mixture. Prepare the pellet and record IR absorption spectrum in the range of 3800cm^{-1} - 650cm^{-1}.

1.4. Sample preparation (Moisture absorbed)

Weigh and Triturate about 2 mg of Sample with about 300 mg of finely powdered and dried potassium bromide and grind the mixture. Prepare the pellet and record IR absorption spectrum in the range of 3800 cm^{-1} - 650 cm^{-1}.

1.5. Procedure

Prepared the pellets of Working standard and test sample as per mentioned in Standard and Sample preparation part and recorded the IR absorption spectrum in the range of 3800 cm^{-1} to 650 cm^{-1} and compared the test samples with that of working standard by overlapping.

FTIR Interpretation

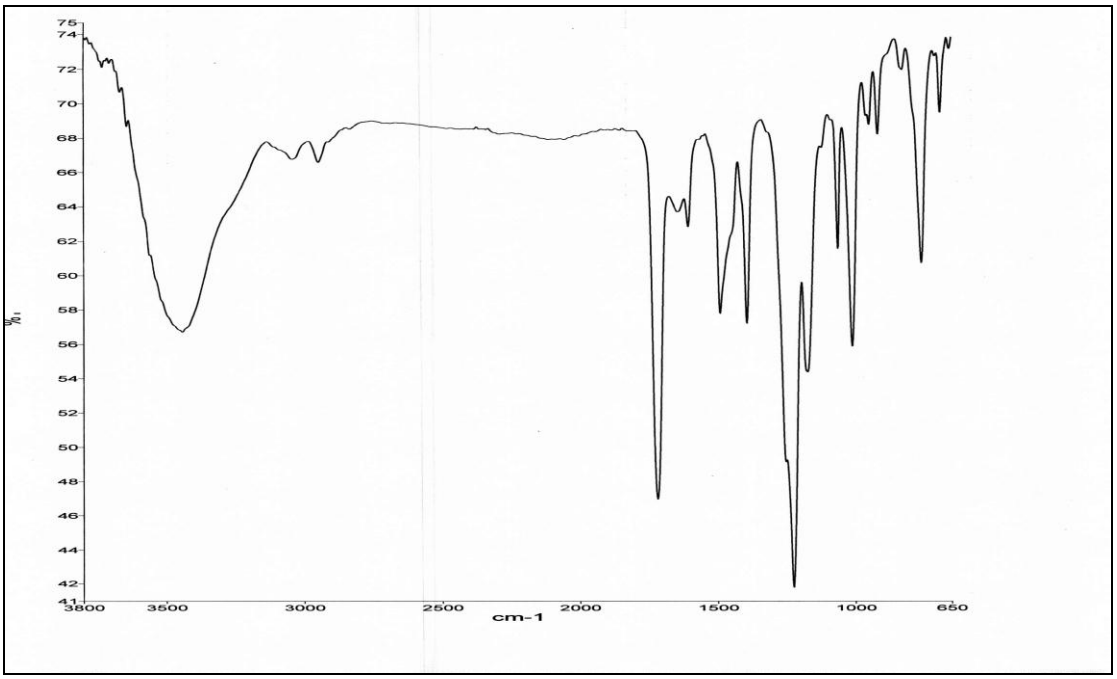

Figure 2: Standard Spectra (Moisture free).

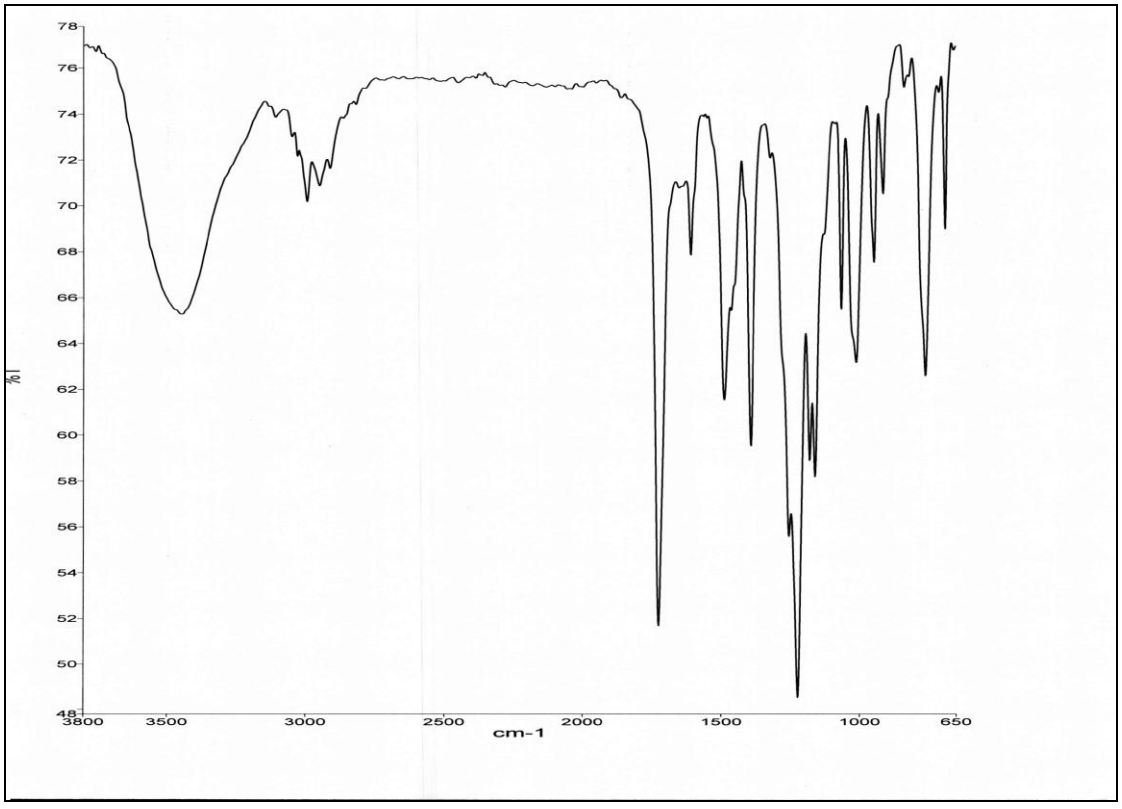

Figure 3: Sample Spectra (Moisture absorbed).

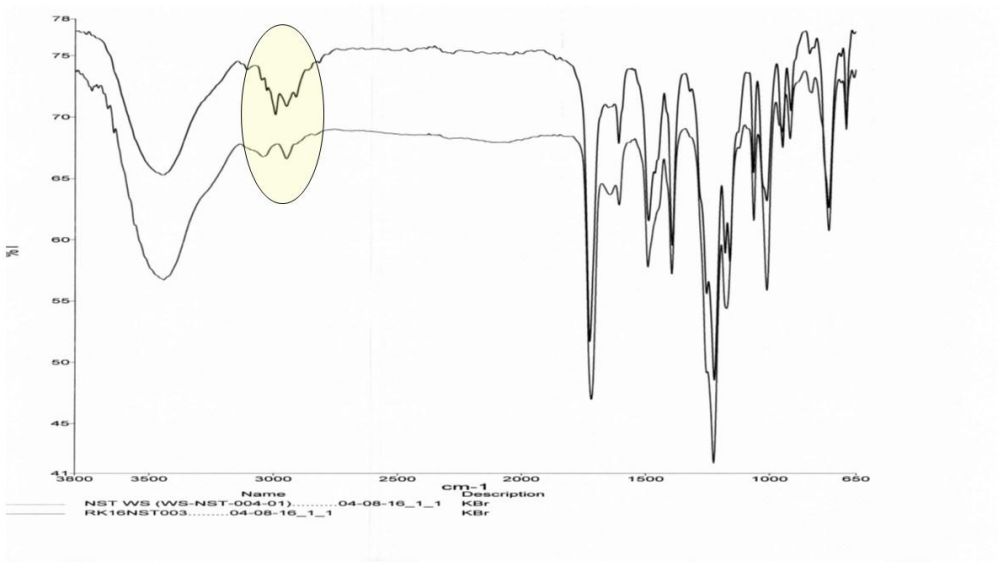

Figure 4: Sample overlay spectra with Standard – Noise in sample at Circled part.

2. Experimental (Moisture free – Sample and Standard)

2.1. Instrumentation

The FTIR Spectroscopy is of make Perkin Elmer, Model – Spectrum One. Hydraulic Press, Vacuum Oven, Mortar and Pestle.

2.2. Reagents and reference samples

Potassium bromide of Spectroscopic grade. Chloroform of AR grade.

2.3. Standard preparation

Weigh and transfer about 10 mg of working standard in petri dish. Add about 10 mL of chloroform to it, dissolve properly. Keep this petri dish in vacuum oven at 100°C for about 1 hour.

Triturate about 2 mg of above residue with about 300 mg of finely powdered and dried potassium bromide and grind the mixture. Prepare the pellet and record IR absorption spectrum in the range of 3800 cm^{-1} to 650 cm^{-1}.

2.4. Sample preparation

Weigh and transfer about 10 mg of sample in petri dish. Add about 10 mL of chloroform to it, dissolve properly. Keep this petri dish in vacuum oven at 100°C for about 1 hour.

Triturate about 2 mg of above residue with about 300 mg of finely powdered and dried potassium bromide and grind the mixture. Prepare the pellet and record IR absorption spectrum in the range of 3800 cm^{-1} to 650 cm^{-1}.

2.5. Procedure

Prepared the pellets of working standard and test sample as per mentioned in Sample preparation part and recorded the IR absorption spectrum in the range of 3800 cm^{-1} to 650 cm^{-1} and compared the test samples with that of working standard by overlapping.

FTIR Interpretation:

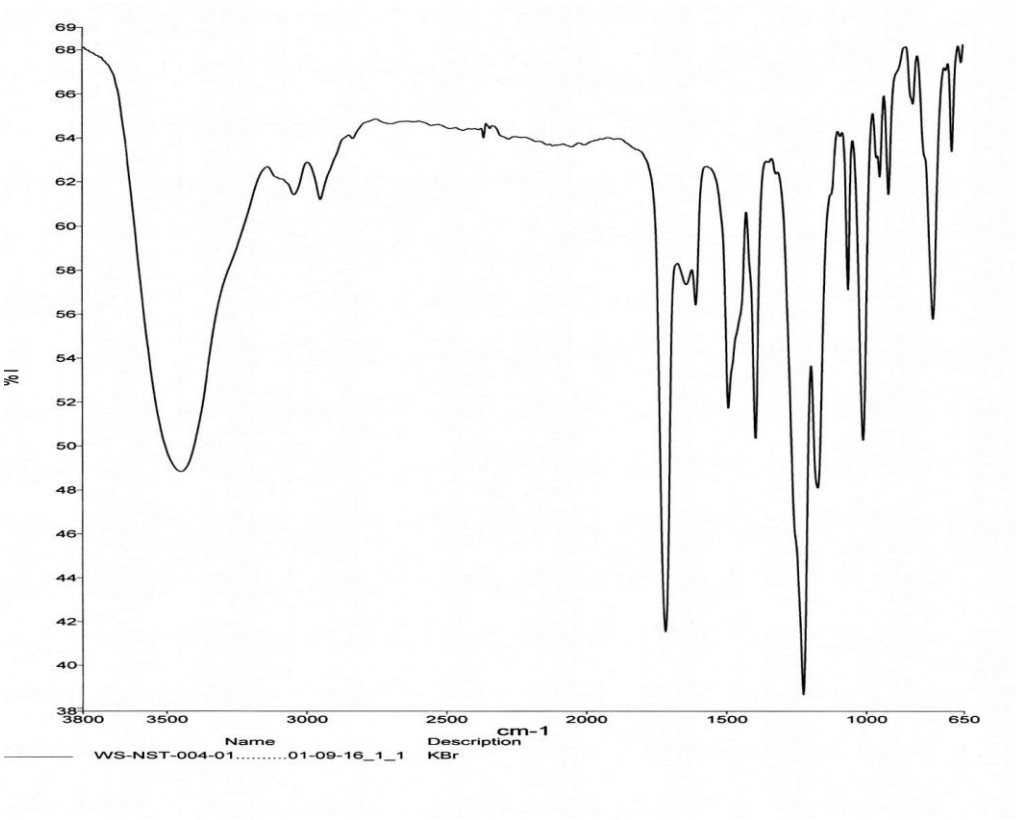

Figure 5: Working Standard IR Spectra.

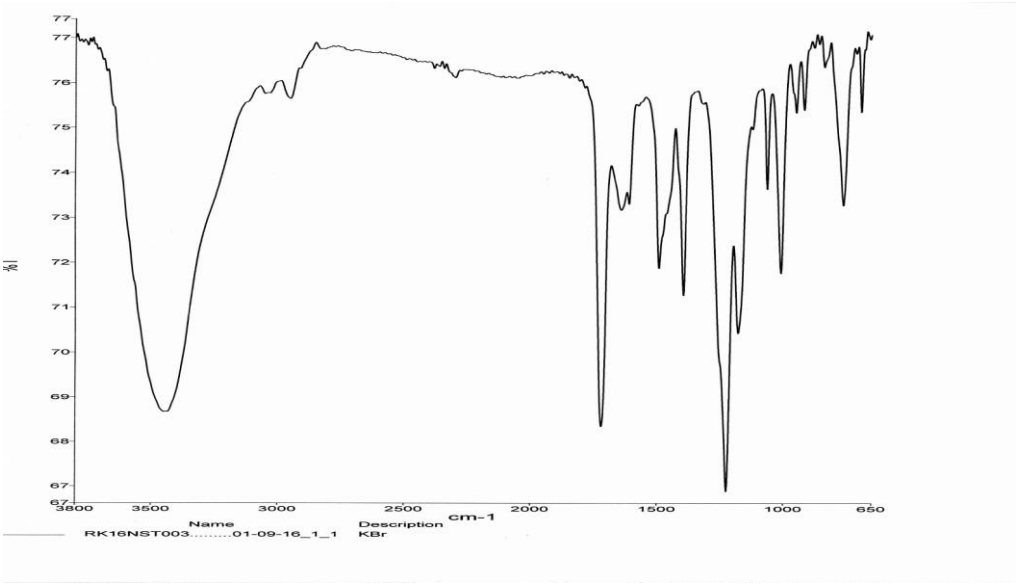

Figure 6: Test Sample (1) IR Spectra.

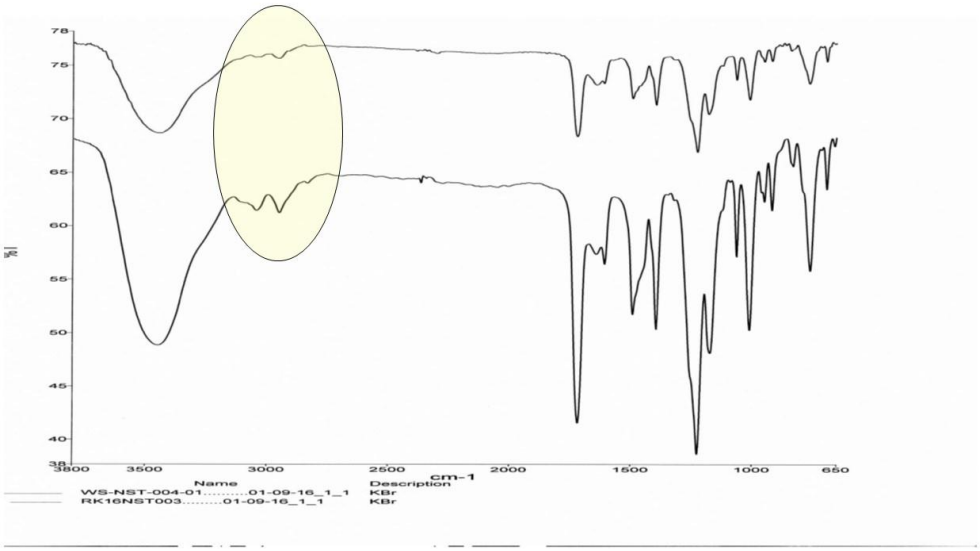

Figure 7: Overlay Spectra - Test Sample (1) vs Working Standard.

RESULTS AND DISCUSSION

Infrared (IR) spectroscopy is one of the most common and widely used spectroscopic techniques. Absorbing groups in the infrared region absorb within a certain wavelength region. The absorption peaks within this region are usually sharper when compared with absorption peaks from the ultraviolet and visible regions. In this way, IR spectroscopy can be very sensitive to determination of functional groups within a sample since different functional group absorbs different particular frequency of IR radiation. Also, each molecule has a characteristic spectrum often referred to as the fingerprint. A molecule can be identified by comparing its absorption peak to a data bank of spectra. IR spectroscopy is very useful in the

identification and structure analysis of a variety of organic compounds. It can also be used for both qualitative and quantitative analysis of complex mixtures of similar compounds.

Neostigmine methylsulfate when absorbs Water from the atmosphere, during IR Spectroscopic analysis wavenumber peak at about 2900 cm^{-1} and 3020 cm^{-1} gets split into multiple peaks in this region. As Neostigmine methylsulfate is quaternary salt, possibility of weak intermolecular hydrogen bonding exists with that of methylsulfate and counter ion of drug substance, which results in shift of C----H stretch observed at about 2900 cm^{-1} and 3020 cm^{-1}. Hydrogen bonding has a significant influence on the peak shape and intensities, generally causing peak broadening and shifts in absorption to lower frequencies. The C-H stretching vibration occurred in the region of 3300 to 2800 cm^{-1}.

Also, Neostigmine methylsulfate is hygroscopic in nature and will absorb the moisture from atmosphere, if it is exposed accidently. Thus, water molecule reacts with methylsulfate ion to form O----H intramolecular hydrogen bonding. Due to this, IR spectra of Neostigmine methylsulfate shows difference and pattern of IR spectra of standard and sample may vary during analysis. Experiment-1 confirms the same i.e. IR Spectra of Test Sample varies with Spectra of Standard at about 2900 cm^{-1} and 3020 cm^{-1}. In Experiment-2, when the same test sample treated with Chloroform and re-crystallized, the IR Spectra of test sample is found concordant with IR spectra of standard at region about 2900 cm^{-1} and 3020 cm^{-1}.

Mechanism

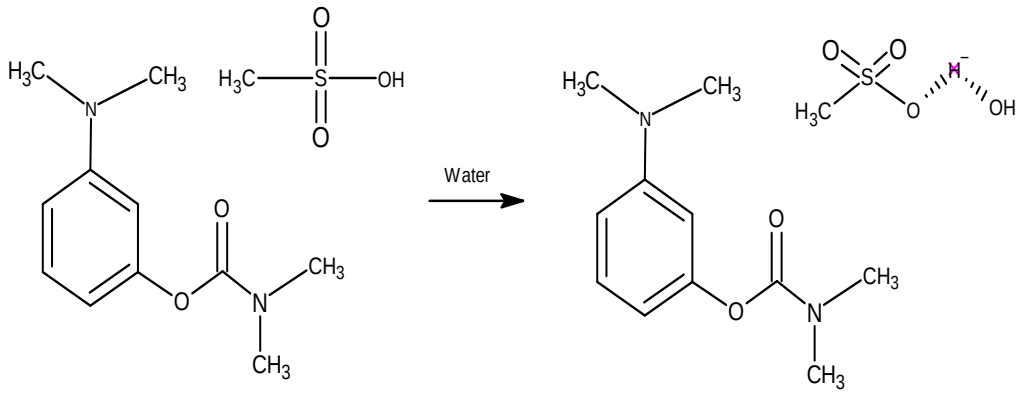

Figure 8: Structural Mechanism of Neostigmine Methylsulfate.

CONCLUSION

The FTIR spectra were recorded for the Neostigmine methylsulfate, from these measurements, identified the nature of interactions. No frequency shift or noise is observed in

the Neostigmine methylsulfate with treatment of chloroform in the range 2900 cm^{-1} and 3020 cm^{-1}. This indicates, water molecule interacts with Neostigmine methylsulfate giving rise to additional band in the range 2900 cm^{-1} and 3020 cm^{-1}, giving rise to noise and chemical shift in the IR pattern.

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