IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
July 2020 Vol.:18, Issue:4

Applications of Mixed Hydrotropy in Formulation of Various Dosage Form

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
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Submission: 20 June 2020
Accepted: 27 June 2020
Published: 30 July 2020

Keywords: solubility, solubility enhancement, hydrotropy, mixed hydrotropy

ABSTRACT

The effectiveness of the formulation depends on the efficiency of active pharmaceutical ingredients to reach the site of action. The therapeutic effectiveness of the drug depends on two factors bioavailability and solubility of the drug. More than 40 percent of new drug candidates fail due to non-optimal biopharmaceutical properties. 'Hydrotropy' is the technique to enhance the solubility and dissolution profile of drugs which enhances oral bioavailability. Advantages of this technique are ease of availability, green chemistry approach, and lack of fire hazards.

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INTRODUCTION

Most of the drug molecules are lipophilic and possess low aqueous solubility. In 1916, the term 'Hydrotropy' was coined by scientist Carl A. Neuberg to describe anionic organic salts[1]. He indicated that substances having the ability to make 'water-soluble' would be labeled as "hydrotropic substances."Itis one of the method in which aqueous solubility of poorly water-soluble drugs is improved by co-dissolving with other extremely water-soluble inert compounds. These agents are termed as hydrotropic agents or Hydrotropes. Sodium benzoate, Nicotinamide, sodium citrate, sodium acetate, and urea are few hydrotropic agents which are used to increase the solubility of a poorly water-soluble drug in an aqueous medium. Hydrotropic mixtures may also be used to improve the solubility of poorly water-soluble compounds by the synergistic or additive effect of combined hydrotropic solubilizers. [1, 2, 6, 8]

SOLUBILITY

Solubility refers to the ability of the solvent to dissolve a given substance, this is determined at equilibrium in terms of the average volume of solute dissolved in a solvent; the resulting solution is called a saturated solution.

The pharmacopeia mentions solubility in terms of several milliliters of solvent required to dissolve 1 g of solute. It is mentioned as a range if exact solubilities are not identified. Table 1 lists some descriptive words. [2]

Table No. 1: Expression for Approximate Solubility

Descriptive terms	Relative amounts of solvents to dissolve 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1-10
Soluble	From 10-30
Sparingly soluble	From 30-100
Slightly soluble	From100-1000
Very slightly soluble	From 1000-10,000
Insoluble or practically insoluble	More than 10,000

DRUG SOLUBILITY CAN BE ENHANCED BY FOLLOWING METHODS:

[2, 4, 5, 6, 13]

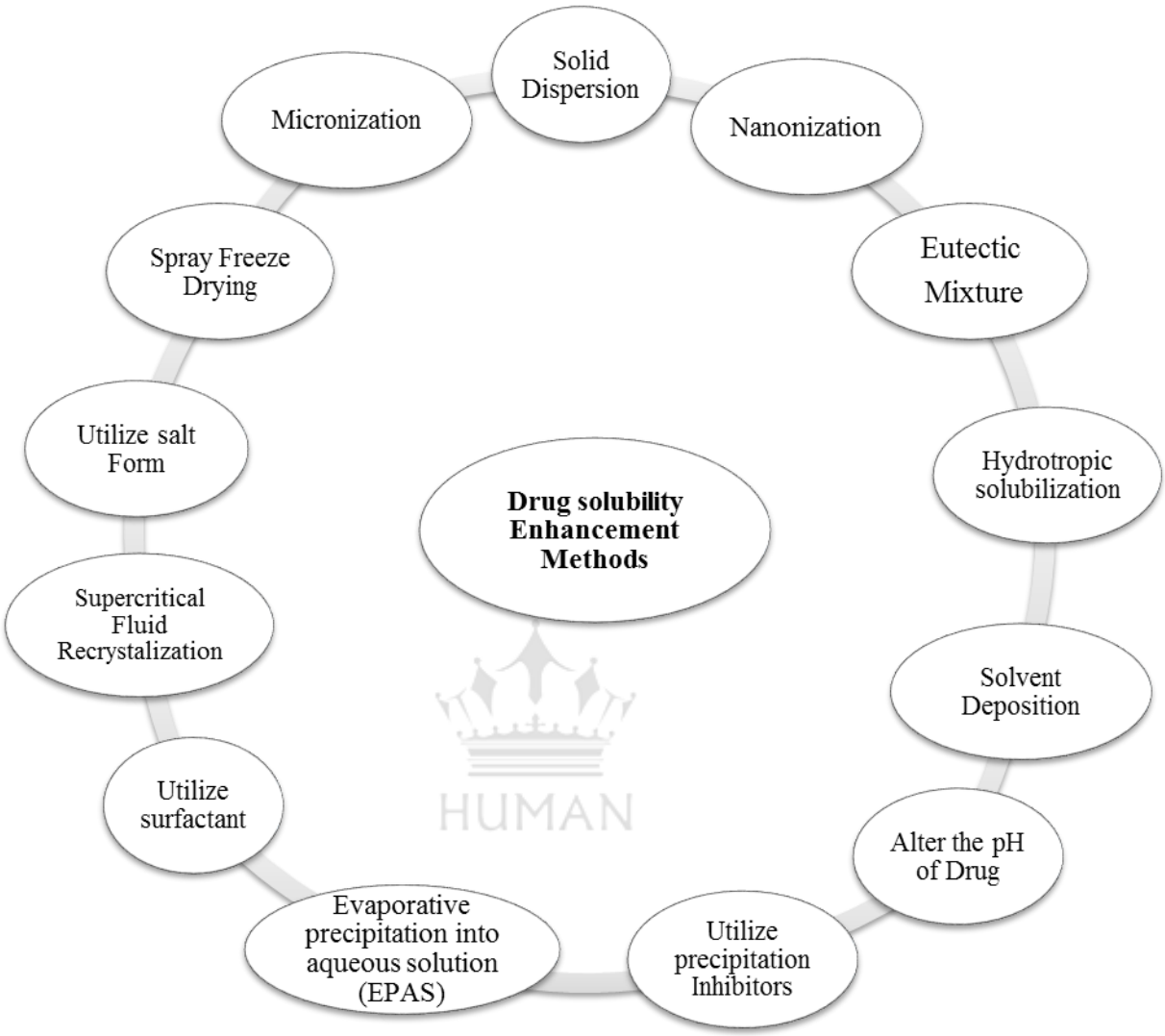

Figure No. 1: Drug solubility enhancement methods

HYDROTROPY:

Hydrotropes are capable of increasing solubility of a sparsely soluble organic molecule in water. It is a process that helps to improve the aqueous solubility of poorly soluble solutes by adding a second solution (hydrotrope). A hydrotropic molecule interacts with a less water-soluble molecule through weak van der Waals interactions such as π–π or attractive interaction between dipole and dipole. The presence of a large quantity of one solvent improves the solubility of another.[1, 2, 6, 7, 8]

STRUCTURE OF HYDROTROPE:

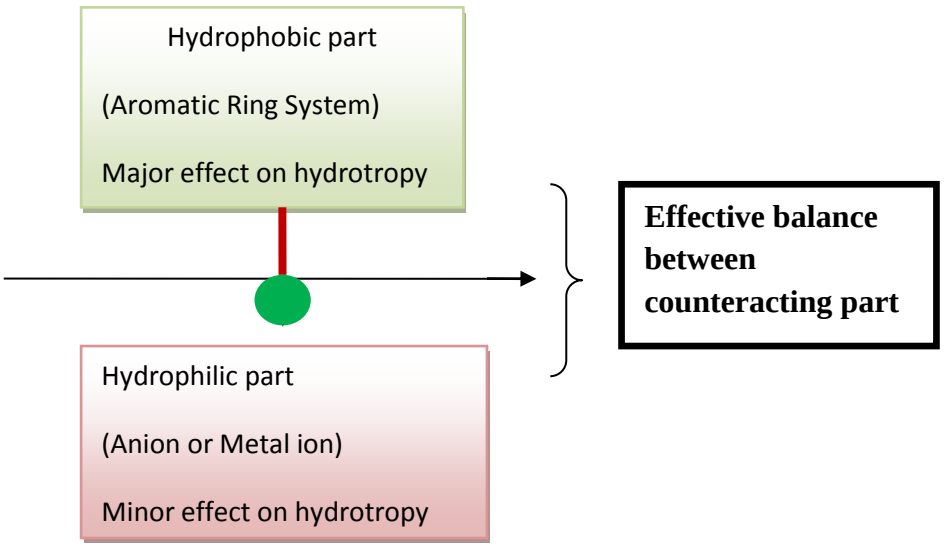

Figure No. 2: Structure of Hydrotope

Hydrotropes contain both hydrophobic and hydrophilic fractions. Hydrophobic-hydrophilic portion of the hydrotrope balance decides the efficiency of hydrotrope solubilization. The bigger the hydrophobic portion of an additive, the better the hydrotropic efficiency; the less important is the presence of the charge on the hydrophilic component. Hydrotropic agents may be liquid or solids, they may be anionic, cationic, or neutral, or anionic or inorganic, hydrotropic compounds are freely soluble in water, they enhance the aqueous solubility of organic substances by creating aggregations of stack forms.[8]

MECHANISM OF HYDROTROPY SOLUBILIZATION:

The mechanism of Hydrotropy is not very clear yet. Some researchers have hypothesized that hydrotropy is simply another form of solubilization. Hydrotropic solutions do not show colloidal properties. The conventional hydrotropic salts of Neuberg generally consist of two parts, an aromatic hydrophobic ring or ring system, an anionic group. The prerequisite for a hydrotropic substance is the anionic group responsible for bringing high solubility in the aqueous environment. The form of anion or metal ion has a slight influence.

The salts or additives that improve solubility in a solvent are referred to as "salt in" and those salts that are decreased solubility, referred to as "salt out." Hydrotropism refers to the salting of highly soluble non-electrolytes of water. In the hydrophobic portion flip side planarity also

plays a crucial role in the mechanism of hydrotropical solubilization. It is also related to complexation which involves the interaction of hydrotropic agents such as urea, Nicotinamide, sodium alginate, sodium benzoate, etc. with lipophilic drugs.

Hydrotropic molecular self-association and the combination of hydrotropic molecules with the solute enhance water solubility.

The following mechanisms are suggested to explain the mechanisms of hydrotropy.

1. Self-aggregation potential

2. Structure-breaker and structure –maker

3. Ability to form micelles like structure[1, 2, 4, 5, 8, 12]

HYDROTROPIC MECHANISM OF SEPARATION: [8]

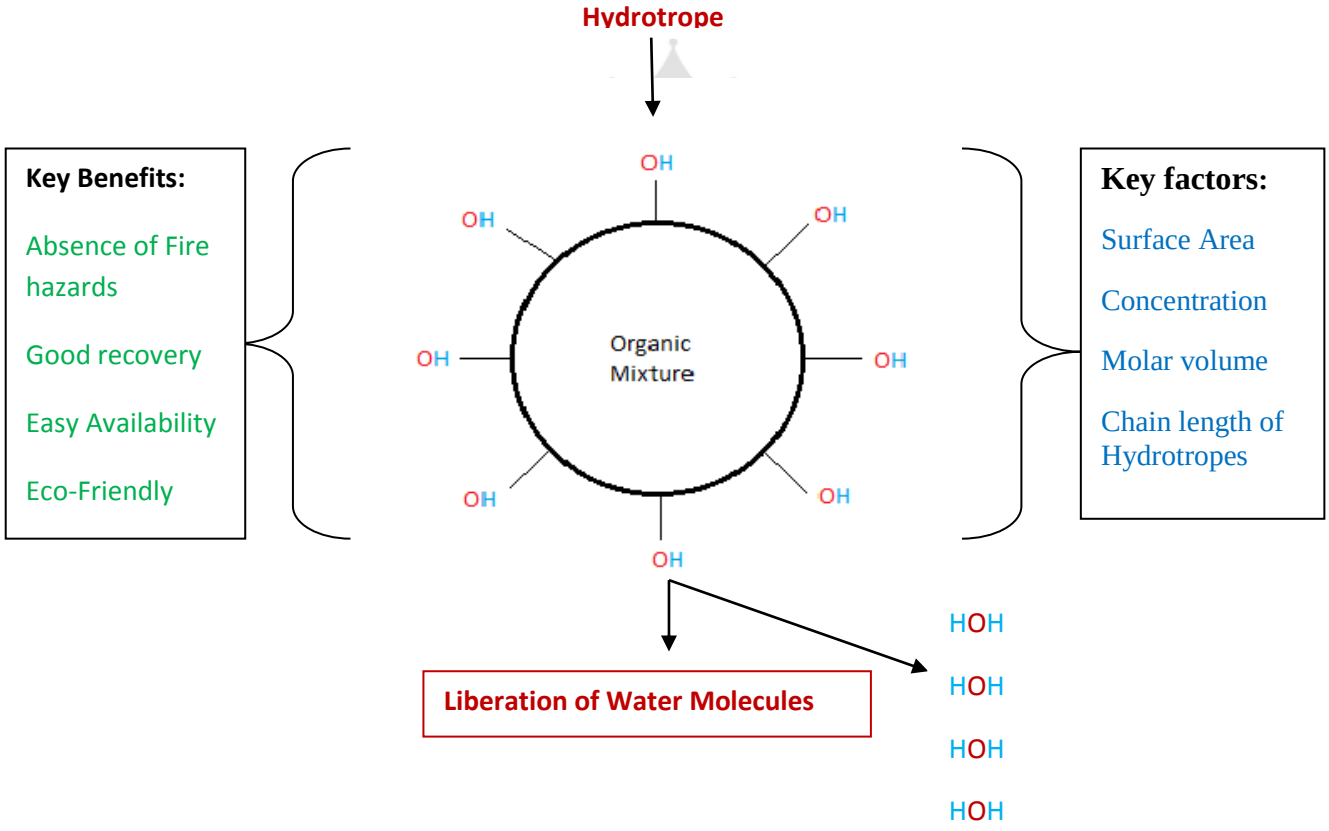

Figure No. 3: Hydrotropic Mechanism of Separation

CHARACTERISTIC FEATURES OF HYDROTROPES:

1. The hydrotropesystem is absolutely water-soluble and virtually insoluble.

2. Hydrotropes are active at the surface and accumulate in aqueous solution due to its amphiphilic nature.

3. Hydrotrope solution is not exothermic.

4. Hydrotropes are cheap, on poisonous and non-reactive.

5. The solvent character of hydrotrope is highly selective, it is insensitive to the effects of temperature, and it is independent of pH.

ADVANTAGES OF HYDROTROPIC SOLUBILIZATION:

Hydrotropyinvolves simply mixing the drug in water with the hydrotrope. The solvent character is independent of pH, has high selectivity, and does not require emulsification; hence it is superior to miscibility, micellar solubilization, co-solvency, and salting in methods of solubilization. Solubilization doesn't require chemical modification of hydrophobic products, the use of organic solvents, or emulsion system preparation.[2, 4, 6, 12]

MIXED HYDROTROPIC SOLUBILIZATION:

In this technique, instead of using a single hydrotropic agent in high concentration, the combination of hydrotropic agents is used in lower concentrations, to increase the aqueous solubility of the poorly water-soluble drug.[1, 2, 4, 6]

ADVANTAGES OF MIXED HYDROTROPIC SOLUBILIZATION:

1. The high total concentration of hydrotropic agents required to achieve a small increase in solubility can be minimized by using a combination of hydrotropic agents at a lower concentration. The reduction of the concentration of individual hydrotropic agents to reduce side effect scan reduces their toxicity.

2. It is a modern, quick, cost-effective, safe, reliable, and environmentally friendly method for the analysis of poorly water-soluble drugs (Titrimetric, Spectrophotometric, and Chromatographic).

3. It replaces the use of organic solvents and thus avoids problems associated with organic solvents such as residual toxicity, volatility error, contamination, and expense.

4. Mixedhydrotropy technology can be applied for designing a variety of dosage forms of poorly water-soluble drugs.

5. Application of hydrotropic solubilization (by controlled precipitation) in nanotechnology.

6. Usage of hydrotropical solubilization to extract active constituents from crude products.[1, 2, 6, 8, 11, 12,]

APPLICATIONS:

❖ Preparation of dry syrups with poorly water-soluble medicines (for reconstitution).

❖ UV-Visible Spectrophotometric analysis quantitative estimates of poorly water-soluble drugs that restrict the use of organic solvents.

❖ Quantitative estimations of poorly water-soluble drugs by titrimetric analysis. Such as Ibuprofen, Flurbiprofen.

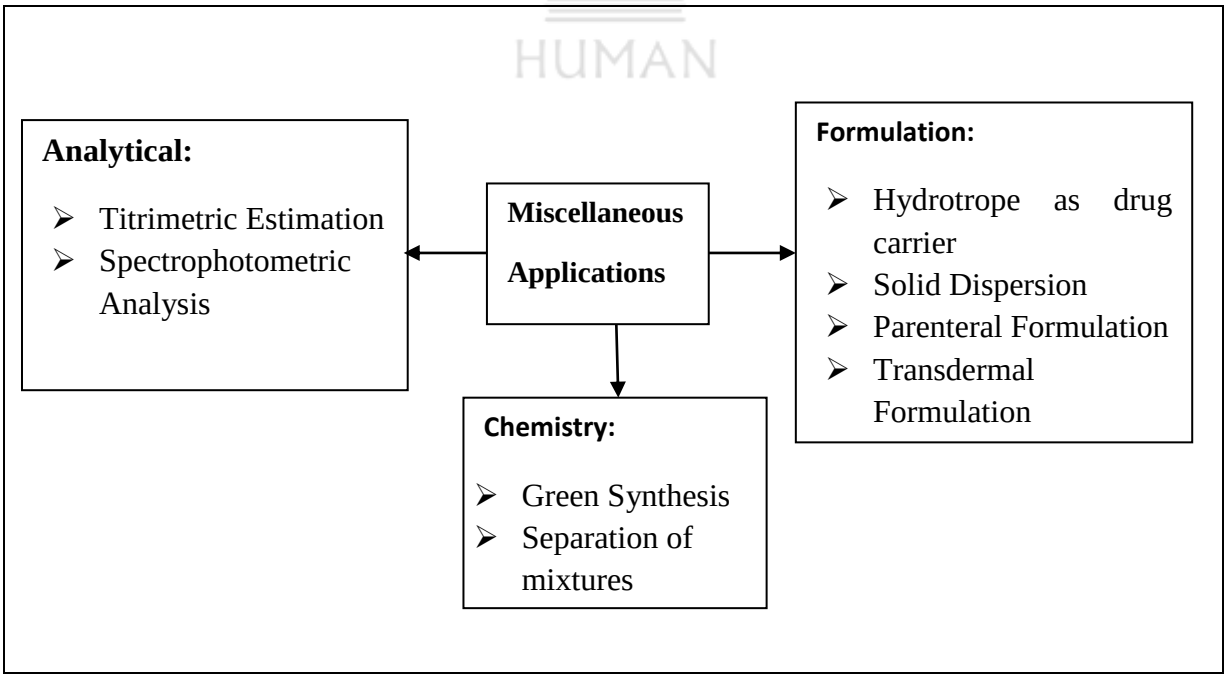

Figure No. 4: Applications of Hydrotrophy

VARIOUS FORMULATIONS FOR WHICH HYDROTROPIC AGENTS ARE USED:

1. TABLET:

Jyotsana R. Madan et al have enhanced solubility of the Luracidone applying concept of mixed hydrotropy. LRD solubility was measured individually by using distilled water as a solvent in Urea, Nicotinamide, sodium citrate, and sodium benzoate at concentrations of 10%, 20%, 30% and 40% W /v solutions. In a 40% sodium benzoate solution, the maximum solubility was obtained. In Mixed hydrotropy best solubility of Nicotinamide + sodium benzoate + sodium citrate was obtained in 15:20:5 ratios. This mixture was used in solid dispersion preparation. Compressed to form fast-dissolving tablets.[14]

Similarly, Bosentanmonohydrate [15], Zaleplon [16], Gliclazide [17], Lansoprazole [18], Lamotrigine [19], Efravirenze [20], Azilsartan Medoxomil[21] are examples of low aqueous solubility and Hydrotropy principle was used to prepare tablet formulations of these drugs.

2. FILM:

Carpenter G. et al have formulated and evaluated Furosemide film by mixed hydrotropy concept. Solubility tests were conducted to select water-soluble additives for the fast-dissolving drug layer formulation Specific aqueous blends were formulated using solubilizers from Sodium benzoate, Sodium acetate, Sodium citrate, Urea, niacinamide, Glycerin, Propylene glycol, Polyethylene glycol 200, Polyethylene glycol 400, Polyethylene glycol 600, and PVP K 30. High Furosemide solubility was observed in mixture (10 per cent sodium caprylate +2.5%sodium benzoate+ 2.5% niacinamide) and in blend (10% sodium caprylate +2.5%sodium benzoate +2.5% sodium citrate + 2.5% niacinamide)[22].

Similarly, the principle of mixed hydrotropy was applied to formulate film of Piroxicam[23], Metronidazole[24], and poorly water-soluble drugs.

3. INJECTION:

Maheshwari R.K. et al studied the effect of hydrotropy in Aceclofenac injection. The effect on Aceclofenac solubility of Hydrotropes such as urea and sodium citrate and mixtures (urea + sodium citrate) has been studied. The enhancement in Aceclofenac solubility was more than 5 and 25 folds in 30% sodium citrate and urea solution, respectively. The enhancement of Aceclofenac solubility in a mixed hydrotropic solution containing 20% urea and 10%

sodium citrate solution was more than 250 folds (compared to its distilled water solubility). This proved a synergistic improvement in the solubility due to mixed hydrotropy of a poorly water-soluble compound. Aqueous injection of Aceclofenac was developed using the mixed hydrotropic solubilization process, and the issue of insufficient Aceclofenac stability in aqueous solution was solved by using the lyophilization method. [25]

Similarly, Furosemide[26] Injection formulated by using a mixed hydrotropy concept.

4. SYRUP:

Maheshwari Y. et al used mixed solvency to improve the solubility of poorly water-soluble naproxen and Furosemide. Blends (with a total strength of 40 % w/v) containing various solubilizers among the widely used Hydrotropes (urea, sodium benzoate, and sodium citrate), co-solvents (glycerin, ethanol, propylene glycol, PEG 600 and PEG 400), and water-soluble solids (PEG 4000 and PEG 6000) were individually formulated to test the effect of Naproxen and Furosemide on solubility. Most of the blends were found to make both drugs more soluble. This method has combined various water-soluble excipients in safe concentrations to create a suitable aqueous solubility of poorly water-soluble drugs to improve various formulations of weak water-soluble drugs.[27]

Similarly, Tinidazole Syrup[28]was formulated by a mixed hydrotropy approach.

5. SUSPENSION:

Shete A.S. et al have enhanced the solubility of Griseofulvin using the technique of hydrotropy and it is formulated as an oral liquid dosage form (suspension) with enhanced bioavailability.

0.5M, 1M, 2M of the Hydrotropes (trisodium citrate, urea, sodium acetate, sodium benzoate, and sodium salicylates) were used to study the saturation solubility. Solubility was found to be greater with sodium benzoate. Suspensions were prepared by using sodium benzoate solution, Griseofulvin, xanthan gum, acacia, and sodium alginate as an aqueous phase, dispersed phase, and suspending agents respectively.

All formulations of sodium benzoate suspension were uniformly distributed, density in the range of 1.020 to 1.050 gm/ml, the particle size of the dispersed phase was 10µm to 20µm, and

suspensions were easily pourable from the bottle and sedimentation volume in the rage of 0.5-1. More than 70% of drug release was obtained at the end of the 45 minutes. [29]

CONCLUSION:

Aqueous solubility of drugs is the most important parameter for oral bioavailability and hence for designing various dosage forms. Mixed Hydrotropy is the most promising approach to enhance the solubility of poorly water-soluble drugs.

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