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Positively charged polymeric nanoparticles: application in improving therapeutic efficacy of meloxicam after oral administration

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The potential of positively charged polymeric nanoparticles in improving therapeutic efficacy of meloxicam (MLX), a poorly water-soluble anti-inflammatory agent was evaluated. MLX loaded positively charged nanoparticles were prepared by using poly-ε-caprolactone (PCL) as a biodegradable polymer and didodecyldimethylammonium bromide (DDAB) as a cationic surfactant. The MLX nanoparticles were characterized for particle size and encapsulation efficiency. MLX loaded PCL nanoparticles and MLX suspension were evaluated for their *in vivo* anti-inflammatory activity and ulcerogenic potential. MLX loaded PCL nanoparticles had particle sizes of $\sim$300 nm and the encapsulation efficiency of MLX was $\sim$90%. The polymeric nanoparticles significantly improved the anti-inflammatory activity of MLX ($P < 0.01$) as compared to that of MLX suspension. The higher anti-inflammatory effect was maintained for a longer duration (6 h). The polymeric nanoparticles also resulted in less ulcerogenicity as compared to that of MLX suspension.

1. Introduction

Meloxicam (MLX) is a poorly water-soluble nonsteroidal anti-inflammatory, analgesic and anti-pyretic agent used in the treatment of rheumatoid arthritis, osteoarthritis and other joint diseases (Ahmed et al. 2005; Gates et al. 2005). Besides its main therapeutic application as an anti-inflammatory and strong analgesic agent, it is also emerging as a promising drug for the treatment of Alzheimer's disease and cancer (Di Girolamo et al. 2003; Naruse et al. 2007). However, the clinical utility of MLX is severely limited due to its poor water solubility. MLX is practically water-insoluble at physiological pH and has a zwitterionic property with two pKa values (pKa$_1$ = 1.09; pKa$_2$ = 4.8). The poor water solubility of MLX is responsible for its poor dissolution in gastrointestinal fluids which ultimately delays the absorption of MLX. The maximum peak plasma concentration of MLX is reached 3–7 h following the administration of an oral suspension, and after 5–9 h for tablets (Hanft et al. 2001).

It is important that drugs such as anti-inflammatory agents should have rapid onset of action in order to give quick relief from the excruciating pain. Hence, it is important to improve the solubility of MLX to achieve rapid onset of action, improved oral absorption and greater therapeutic efficacy. A zwitterionic drug like MLX possesses a large intramolecular multipole moment due to its multiplicity of oppositely charged groups. Consequently, most of these drugs show low solubility in polar and nonpolar media (Hatanaka et al. 2000). Hence, a conventional cosolvent approach has very limited scope in improving solubility and efficacy of MLX.

Salt formation is one of the easiest approaches to improve water solubility and bioavailability of hydrophobic drug. Recently, Han and Choi (2007) have demonstrated the potential of various ethanolamine salts of MLX in improving its solubility and

onset of action. However, these salts have to be treated as new drugs and need to undergo extensive trials before reaching the clinic. Researchers have also explored approaches such as solid dispersions (Mishra and Vijaya Kumar 2006; Vijaya Kumar and Mishra 2006) and cyclodextrin complexation (Baboota and Agarwal 2003; Naidu et al. 2004) to improve solubility (or dissolution rate) and/or therapeutic efficacy of MLX. Till date, the potential of polymeric nanoparticles in improving therapeutic efficacy of MLX has not been explored.

Polymeric nanoparticles have shown a great potential in improving oral bioavailability of various hydrophobic drugs such as cyclosporine A (Varela et al. 2001; El-Shabouri 2002) ellagic acid (Sonaje et al. 2007) and curcumin (Sheikh et al. 2009). The nanoparticles by virtue of their size and surface properties are quickly taken up intact by M cells in Payer's patches of the gut associate lymphoid tissue followed by its systemic circulation. These polymeric nanocarriers are capable of preventing the gastro-intestinal degradation and first pass metabolism of encapsulated drugs (Bhardwaj et al. 2005). Additionally, polymeric nanoparticles increase residence time of the drug in the body (Italia et al. 2007) and can lead to a dramatic reduction in dosing frequency.

In view of this information, it can be assumed that polymeric nanoparticles may lead to quick onset of action for MLX and may also maintain the anti-inflammatory effect for a time period. More particularly, we focused on fabrication of cationic i.e. positively charged polymeric nanoparticles of MLX as it has been shown that positive charge on the nanocarriers can lead to a significant increase in the oral bioavailability as compared to that of negatively charged nanocarriers (El-Shabouri 2002). It is anticipated that positively charged delivery systems that could strongly interact with epithelial cells in the gastrointestinal tract will result in better permeability and overall bioavailability of

Table 1: Effect of various cationic surfactants on the particle size and polydispersity index of polycaprolactone (PCL) nanoparticles (n = 3)

Cationic surfactant	Mean particle size (nm)	Polydispersity index
Cetyltrimethylammonium bromide (CTAB)	234.3 ± 2.43	0.116 ± 0.040
Cetylpyridinium chloride (CPC)	244.7 ± 1.56	0.281 ± 0.195
Dimethyldidodecylammonium bromide (DDAB)	132.2 ± 3.09	0.168 ± 0.002

Concentration of all the cationic surfactants was 1% w/v in the final dispersion and that of PCL was 2.5 mg/ml
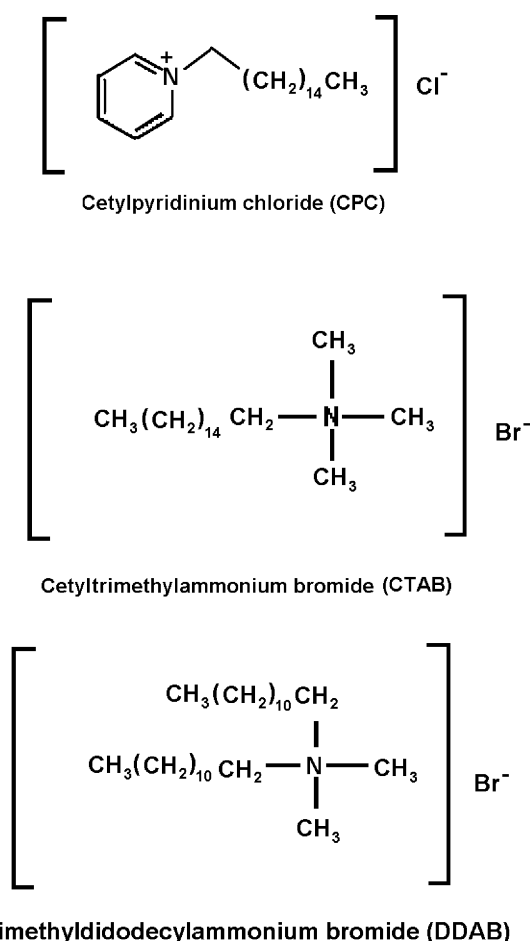

Fig. 1: Structure of cationic surfactants

the drugs. The advantage of positive charge in improving oral bioavailability has been well established for various nanocarriers such as submicronic emulsions, self-emulsifying systems and nanoparticles (Gershanik and Benita 1996; Gershanik et al. 2000; El-Shabouri 2002).

In the present investigation, we prepared positively charged polymeric nanoparticles of MLX. We employed a biodegradable polymer poly-ε-caprolactone (PCL) for the fabrication of the nanoparticles. The polymeric nanoparticles were evaluated for their ability to improve anti-inflammatory activity of MLX in comparison to MLX suspension.

2. Investigations, results and discussion

Biodegradable polymeric nanoparticles, such as poly(ε-caprolactone) (PCL) are useful drug delivery carriers. Biocompatibility and degradation methods of PCL have been widely studied and it was found that PCL is completely safe for human use. PCL is approved by the U.S. Food and Drug Administration for medical applications. Additionally,

the alkyl structure of PCL efficiently encapsulates hydrophobic compounds whereas slow degradation of this polymer offers sustained release of the drug (Vlerken et al. 2007). The application of PCL nanoparticles in improving oral bioavailability of cyclosporine and ellagic acid has already been reported in the literature (Varela et al. 2001; Sonaje et al. 2007).

2.1. Preparation of blank PCL nanoparticles

We evaluated potential of three cationic surfactants viz. CPC, CTAB and DDAB (Fig. 1) blank PCL nanoparticles. These cationic surfactants differ in their chemical structure and/or alkyl group chain length. CPC and CTAB are single (alkyl) chain cationic surfactants whereas DDAB is a double chain cationic surfactant. There are no reports which compare the ability of these surfactants to yield polymeric nanoparticles. Table 1 shows the particle sizes and polydispersity indices obtained with these cationic surfactants. It is evident from Table 1 that DDAB, double chain cationic surfactant yielded PCL nanoparticles with the lowest particle size. Between CPC and CTAB which have the same alkyl side chain, CTAB yielded smaller nanoparticles than CPC. This also indicates that apart from the alkyl side chain, the structure of the cationic surfactant has some influence on the particle size of PCL nanoparticles. DDAB was selected as a nanoparticle stabilizer for further studies as it could yield nanoparticles with the lowest size.

2.2. Effect of reduction in DDAB concentration on the particle size of PCL nanoparticles

It is also important to restrict use of cationic surfactants in the preparation because high surfactant content may induce some changes in gastrointestinal permeability and may cause irritation. Hence, we decided to study the effect of reduction in DDAB concentration on the particle size of PCL nanoparticles. We studied various concentrations of DDAB viz. 0.1%, 0.25% and 0.5% w/v. The results are shown in Table 2. DDAB is a very effective nanoparticle stabilizer and can yield nanoparticles at a concentration as low as 0.1% w/v. It is also evident that there was no significant difference ($P > 0.05$) in particle size of PCL nanoparticles when DDAB concentration was reduced from 1% wv^{-1} to 0.5% w/v. Hence, we decided to use 0.5% w/v DDAB as a stabilizer for further studies.

Table 2: Effect of various concentrations of DDAB on the particle size and polydispersity index of PCL nanoparticles (n = 3)

DDAB concentration (%w/v)	Mean particle size (nm)	Polydispersity index
0.1	188.5 ± 1.20	0.089 ± 0.003
0.25	139.6 ± 5.47	0.215 ± 0.891
0.5	130.3 ± 3.52	0.131 ± 0.0820
1	132.2 ± 3.09	0.168 ± 0.002

Table 3: Effect of cryoprotectant type and concentration on MLX loaded PCL nanoparticles

Cryoprotectant	Mean particle size (nm)	Polydispersity index
Dextrose (5% w/v)	247.7 ± 30.36	0.670 ± 0.274
Dextrose (10% w/v)	279.9 ± 65.82	0.868 ± 0.229
Trehalose (5% w/v)	324.4 ± 78.89	0.792 ± 0.470
Trehalose (10% w/v)	301.2 ± 22.39	0.647 ± 0.066

Particle size of MLX nanoparticles before freeze drying was 299.8 ± 5.11

It was important to confirm the positive charge on the PCL nanoparticles stabilized by DDAB. The zeta potential measurements indicated that PCL nanoparticles stabilized by DDAB have a zeta potential value of 34.2 ± 0.3 mV (n = 3).

2.3. MLX loaded PCL nanoparticles

MLX loaded nanoparticles were characterized for particle size and entrapment efficiency. The particle size of MLX loaded PCL nanoparticles was 299.8 ± 5.11 (n = 3) and their polydispersity index was 0.61 ± 0.071 (n = 3). It was observed that the encapsulation efficiency of the MLX in nanoparticles was $88.9 \pm 2.1\%$ (n = 3). It is evident that loading of MLX in nanoparticles led to an increase in the nanoparticles size from ∼135 nm to ∼300 nm. This clearly indicates the influence of the drug characteristics on the particle size of the nanoparticles. The encapsulation efficiency of the MLX in nanoparticles was very good. Literature indicates that dextrose and trehalose are better cryprotectants for PCL nanoparticles than other cryoprotectants such as lactose, sucrose, fructose and mannitol (Abdelwahed et al. 2006). Hence, we employed only two cryoprotectants for freeze drying of MLX loaded PCL nanoparticles. It is well known that the concentration of cryoprotectant can also have an impact on the particle size and redispersibility of nanoparticles. Hence, we employed two concentrations of cryoprotectants 5% and 10% w/v. All the freeze dried formulations exhibited good redispersibility. Particle sizes and polydispersity indices are shown in Table 3. Nanoparticles freeze dried with dextrose and trehalose (at both the concentrations employed in the investigation) did not have a significantly higher mean particle size after reconstitution.

2.4. Anti-inflammatory activity of MLX loaded nanoparticles

The anti-inflammatory activity of the MLX loaded nanoparticles was compared with that of MLX suspension. The results of anti-inflammatory study are shown in Fig. 2. MLX loaded nanoparticles showed a 2.2-fold higher anti-inflammatory activity ($P < 0.001$) than MLX suspension at all the time points and a quick onset of action (2 h) as compared to that of MLX suspension (3 h). It is also noteworthy that the MLX loaded nanoparticles could maintain significantly high anti-inflammatory effect for a longer duration. This is very beneficial for anti-inflammatory drugs and will help in reducing dosage frequency. This clearly demonstrates the advantage of polymeric nanoparticles in improving oral delivery of MLX.

This study clearly indicated that loading of MLX in nanoparticles could successfully increase its oral bioavailability which in turn led to greater therapeutic efficacy. The greater oral bioavailability mainly results from greater surface area offered by nanoparticles which increases the drug absorption. Also, it has been demonstrated that positively charged nanocarriers can traverse across the gastrointestinal mucus (one of the barriers for in the process of absorption of drugs) better than anionic nanoparticles of the same size (Dawson et al. 2004). Bala et al. (2006) have also demonstrated that positively charged nanopar-
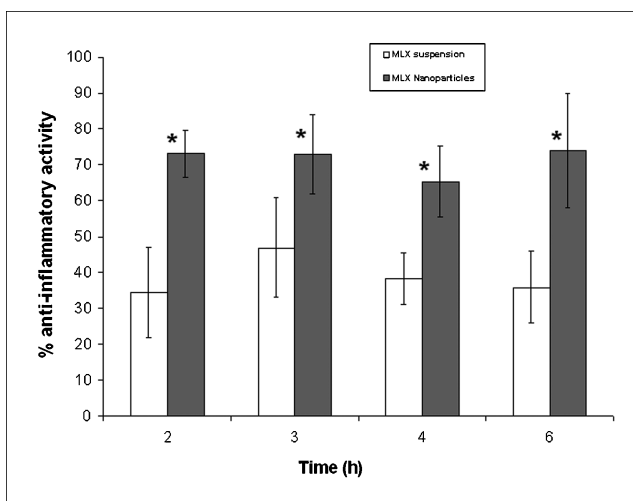

Fig. 2: Anti-inflammatory activity of MLX loaded PCL nanoparticles and MLX suspension in rats (n = 6); * ($P < 0.01$) as compared to that of MLX suspension

ticles exhibit greater intestinal permeability than pure drug and anionic nanoparticles. All these attributes of positively charged nanoparticles would also help in improving bioavailability of MLX on oral delivery. Furthermore, the nanoparticles could also result in sustained release of MLX which in turn yielded anti-inflammatory effect for a longer duration. The sustained release potential of nanoparticles in plasma has been demonstrated for the cyclosporin A by Italia et al. (2007).

2.5. Ulcerogenicity study

The major reason for gastrointestinal ulcers is NSAID induced inhibition of PGI_1 and PGE_2 which have protective action on gastric mucosa. In addition, it has been reported that NSAIDs such as diclofenac, piroxicam and MLX remain as crystals in gastric acid due to their poor solubility (Nagarsenker et al. 2000; Mishra and Vijaya Kumar 2006; Vijaya Kumar and Mishra 2006). These crystalline drugs remain in contact with the stomach wall for a longer time, thus producing a highly dangerous local concentration. This leads to local irritation of the stomach wall followed by ulceration. The results obtained with MLX suspensions are in accordance with this statement. Fig. 3(a) to (c) show representative pictures of stomach ulceration obtained with various treatment groups. It is evident that the control group (no treatment) showed no ulceration. MLX suspension showed a significantly higher ulcerogenic potential than that of control (Fig. 3a and b). The ulceration index observed with MLX suspension was 1.125 (Fig. 3b). The ulceration observed with MLX suspension is a combined result of MLX mediated inhibition of PGI_1 and PGE_2 and crystalline form of MLX. It is evident from encapsulation efficiency studies that almost 90% of MLX is molecularly dispersed in the PCL matrix. This is expected to reduce (or abolish) the contact of MLX with the gastric mucosa resulting in a lower ulceration index. Thus, we believe that loading of MLX in nanoparticles would reduce ulceration associated with crystalline MLX. Interestingly, MLX loaded PCL nanoparticles showed a considerably lower ulceration index (0.75) than MLX suspension (Fig. 3c) and these results are in accordance with our aforementioned hypothesis.

3. Experimental

3.1. Materials

Meloxicam (Sun Pharmaceuticals Ltd., Mumbai, India) and Soluphor P (BASF India Ltd., Mumbai, India) were received as gift samples. Polycaprolactone (PCL, Avg. Mol. Wt. 10000), didodecyldimethylammo-

(A)

(B)

(C)

Fig. 3: (a) A representative picture of stomach ulceration observed with no treatment (control) (b): A representative picture of stomach ulceration observed with MLX suspension (c): A representative picture of stomach ulceration observed with MLX loaded PCL nanoparticles

nium bromide (DDAB), Type II carageenan and cetyltrimethylammonium bromide (CTAB) were purchased from Fluka Chemicals (NJ, USA). Cetylpyridinium chloride (CPC) and acetone (AR grade) were purchased from Qualichem Ltd., (Mumbai, India). Double distilled water was used for all the experiments. All the other chemicals and reagents were of highest commercially available grade.

3.2. Preparation of blank PCL nanoparticles

Blank PCL nanoparticles were prepared by a simple nanoprecipitation method with slight modifications. Briefly, 25 mg of PCL was dissolved in a

mixture of acetone (4.5 ml) and Soluphor P (0.5 ml). This organic phase was added under magnetic stirring at 1200 rpm to 10 ml of water containing 1% w/v of the cationic surfactant (rate of addition of organic phase: 10 ml/min). The organic solvent was removed from nanoparticles dispersion by a rotary evaporator. The experiments were carried out in triplicate.

3.3. Particle size determination

The average particle size and polydispersity index of the polymeric nanoparticles obtained by various experiments were determined in triplicate by the photon correlation spectroscopy (PCS; Beckman Coulter N4 plus, Wipro, India). Measurements were carried at an angle of 90° at 25 °C. Dispersions were diluted with double distilled water to ensure that the light scattering intensity was within the instrument's sensitivity range. Double distilled water was filtered through 0.45 μm membrane filters (Pall Life sciences, Mumbai) prior to particle size determination.

3.4. Effect of reduction in DDAB concentration on the particle size of PCL nanoparticles

The PCL nanoparticles were prepared by the method described earlier. The concentration of DDAB in the aqueous phase was varied from 0.5% w/v, 0.25% w/v and 0.1% w/v. The particle size and polydispersity index of resulting PCL nanoparticles were determined in triplicate as described earlier.

3.5. Zeta potential of Blank PCL nanoparticles

In order to confirm the positive charge on the nanoparticles, the zeta potential of blank PCL nanoparticles containing 0.5% w/v DDAB was measured using Malvern Zetasizer (NY, USA).

3.6. Preparation of MLX loaded PCL nanoparticles

The MLX loaded PCL nanoparticles were prepared by the method described earlier. Briefly, 25 mg PCL and 15 mg MLX were dissolved in a mixture of acetone (4.5 ml) and Soluphor P (0.5 ml). This organic phase was added (under stirring) at the rate of 10 ml/min to 10 ml of 0.5% w/v DDAB solution. The organic solvent was removed from nanoparticles dispersion by a rotary evaporator. The experiment was carried out in triplicate.

3.7. Characterization of MLX loaded PCL nanoparticles

3.7.1. Particle size determination

The average particle size and polydispersity index of the MLX loaded PCL nanoparticles was determined in triplicate as described earlier.

3.7.2. Entrapment efficiency (EE) of MLX in nanoparticles

The entrapment efficiency (EE), which corresponds to the percentage of MLX encapsulated within and adsorbed onto the nanoparticles, was determined by measuring the concentration of free MLX in the dispersion medium. Nanopartitcle dispersion (1 ml) was centrifuged at 14000 rpm (Eppendorf Mini-centrifuge) for 20 min to separate nanoparticles. The supernatant was analyzed for unencapsulated MLX at 362 nm by using validated UV-spectrophotometric method after suitable dilution.
The entrapment efficiency was calculated by the following equation:

$$\%EE = \left[\frac{M_{\text{initial drug}} - M_{\text{free drug}}}{M_{\text{initial drug}}} \right] \times 100 \qquad (1)$$

where "$M_{\text{initial drug}}$" is the mass of initial drug used for the assay and the "$M_{\text{free drug}}$" is the mass of free drug detected in the supernatant after centrifugation of the aqueous dispersion.

3.8. Freeze drying of MLX loaded PCL nanoparticles

Freeze drying was carried out to impart greater shelf-life to the MLX loaded PCL nanoparticles. MLX loaded PCL nanoparticles were freeze dried using an automated system (AdVantage, VirTis, USA) that was previously optimized for MLX. In brief, the conditions were as follows: condenser temperature –60 °C and pressure applied during each step was 200 torr. Briefly, 5 ml of the nanoparticle suspension was filled in 10 ml glass vials. Dextrose or trehalose were added to this suspension as a cryoprotectant to preserve the particle properties during freezing step. Two concentrations of cryoprotectant viz. 5% w/v, and 10% w/v were employed for the freeze drying in order to arrive at suitable concentration. After freeze drying, the redispersibility and particle size of the nanoparticles was evaluated.

3.9. Evaluation of anti-inflammatory activity

The anti-inflammatory activity of orally administered MLX suspension and MLX loaded nanoparticles was determined in Sprague-Dawley rats (200–250 g) using carrageenan-induced paw edema model. Animal care and handling throughout the experimental procedure were performed in accordance to the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines. The experimental protocol was approved by the Animal Ethical Committee of Bombay College of Pharmacy. The overnight fasted animals were divided into three groups (6 rats per group) as follows
Group 1: Control (No treatment)
Group 2: Oral administration of MLX suspension equivalent to 4 mg/kg MLX
Group 3: Oral administration of MLX nanoparticles equivalent to 4 mg/kg MLX
After 30 min of drug administration, rats of all three groups were challenged by a subcutaneous injection of 0.1 ml of a 1% w/v carrageenan solution, into the plantar site of the left hind paw. The paw volumes were measured using Ugo basile 7140 Plethysmometer, just before and after 2, 3, 4 and 6 h of carrageenan administration. The percent inhibition of edema at any time for each rat was calculated as

$$\% \text{ inhibition} = 100 \text{ x } [1 - (A - x)/(B - y)] \quad (2)$$

where A is paw volume after administration of carrageenan at time t, and x is paw volume before administration of carrageenan. B is the mean paw volume of control rats after administration of carrageenan at time t and y is mean paw volume of control rats before administration of carrageenan.
The percent edema inhibition observed with the MLX suspension and MLX nanoparticles was compared using the 2 tailed paired 't' test (GraphPad InStat Demo Version). Differences were considered statistically significant at $P < 0.05$.

3.10. Ulcerogenic study

The ulcerogenic potential of MLX suspension and MLX nanoparticles was evaluated by the ulcer model reported earlier (Nagarsenker et al. 2000). Male Sprague-Dawley rats (200–250 g) were used for the study and were divided randomly into three groups (3 rats per group) as follows
Group 1: Control (No treatment)
Group 2: Oral administration of MLX suspension equivalent to 7.5 mg/kg MLX
Group 3: Oral administration of MLX nanoparticles equivalent to 7.5 mg/kg MLX
The second and the third group were administered MLX and MLX nanoparticles respectively for five consecutive days at a dose of 7.5 mg/kg. The control group received water for the five days of study. On the sixth day, the rats were starved but water was provided ad libidum. On the seventh day, rats were sacrificed and the abdomen was opened. The stomach was removed, incised along the greater curvature and gently washed with water. Hemorrhagic lesions, produced in the glandular portion were observed under a dissection microscope (X20 magnification) and evaluated by the following score:
0.0 Normal (no injury, bleeding and latent injury).
0.5 Latent injury or widespread bleeding.
1.0 Slight injury (2 to 3 dotted lines).
2.0 Severe injury (continuous lined injury or 5–6 dotted injuries).
3.0 Very severe injury (several continuous lined injuries).
4.0 Widespread lined injury or widened injury.

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