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## Formulation and Evaluation of Naproxen Emulgels Topical Drug Delivery Systems

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### ABSTRACT

The objective of current research is to formulate and evaluate Naproxen emulgel for tropical drug delivery. Naproxen Emulgels (F1-F10) were formulated by using Carbopol 940 with 0.5% w/w and HPMC K100 with 2.5% w/w. Arachis oil containing Span 20 acts as oil phase and water containing Tween 20 constitutes aqueous phase. All the formulations tested for physical appearance, homogeneity and consistency. All the emulgels were found to be opaque, homogenous, with good consistency and no phase separation. The drug content of all formulations recorded within  $98.57 \pm 0.25$  to  $99.60 \pm 0.22\%$  indicating content uniformity. *In vitro* release studies indicate higher release rate for F4 and F9 in 5 hrs of  $99.68 \pm 0.54\%$  and  $92.65 \pm 0.61\%$  respectively. The percentage *ex-vivo* drug release of F4 at 6 hrs was  $98.98 \pm 0.41\%$  which is higher than market formulation ( $66.94 \pm 0.51\%$ ). The release kinetics data indicate that the drug released by Fickian diffusion predominated with all formulations. Based on permeability ( $2.49 \times 10^{-3} \text{cm}^2/\text{h}$ ) and enhancement ratio (2.22) F4 is considered as optimized formulation. The formulation F4 shows higher enhancement ratio than that of F9 and marketed gel, hence considered optimized formulation. Drug excipient compatibility studies by FTIR and DSC indicate no significant interaction. No significant changes observed in physicochemical properties of optimized formulation (F4) on exposure to accelerated conditions of temperature and humidity. Hence the developed Naproxen emulgel formulation was found to be stable with no skin irritations, increased absorption and drug release.

**Keywords:** Tropical drug delivery system, naproxen, emulgel, NSAID, arachis oil, permeability.

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## INTRODUCTION

Tropical drug delivery systems involve application of drug formulation on skin to treat injuries and disorders directly. This system is applied when the other routes of administration such as oral, rectal or parental fail to deliver the drug effectively <sup>1,2</sup>. These system have the advantage if by passing first pass metabolism, avoid intravenous therapy, avoid GI incompatibility, and increase loading capacity and absorption of the drug. Tropical delivery systems can be used for localized drug delivery to different parts of the body including skin, rectum, vagina and ophama <sup>3,4</sup>. Skin is the most accessible part of human body that allows maximum penetration of drug through sweat ducts, stratum and sebaceous glands. Emulsion gels are of growing importance as tropical drug delivery systems through skin. These are combination of gel and emulsion that include both water-in-oil and oil-in-water type emulsion for drug delivery <sup>5,6</sup>. These have high penetration, they are thixotropic, easily spreadable, water soluble, have longer shelf life and are bio friendly. The drugs are entrapped in emulsion and are slowly passed on to the skin through external phase. The drugs are entrapped by formation of cross linked network with emulsions. This mucoadhesive property of emulgel will prolong the contact time between drug and skin. Emulgels serve as best drug delivery systems for class II drugs that are poorly soluble and highly permeable. These are best vehicles for hydrophilic drugs that are captured in oil phase of emulsion and released onto skin. Recently these emulgels are used for treating infections due to virus, bacteria and fungi <sup>7,8,9</sup>. Naproxen is a nonsteroidal anti-inflammatory drug that relieves inflammation and joint stiffness. It has both analgesic and antipyretic activities. It blocks the enzymes that produce prostaglandins which play major role in causing inflammation. Prostaglandins are produced at injured sites hence causing swelling and pain. In the current research Naproxen is formulated into emulgel for enhances transdermal application.

## MATERIALS AND METHOD

### Materials

Naproxen was procured from Hetero drugs, Hyderabad. Carbopol 940 (Loba Chemie Pvt. Ltd., Mumbai, India), HPMC (Qualigens Fine Chemicals, Mumbai, India), Arachis oil (S.D Fine chemicals, Mumbai, India) Propylene glycol (Prime laboratories, Hyderabad), Tween 20, span 20 (S.D Fine chemicals, Mumbai, India), sodium hydroxide (S.D Fine chemicals, Mumbai, India), potassium dihydrogen orthophosphate (S.D Fine chemicals, Mumbai, India) were procured and used without further purification.

### Instrumentation

Viscosity of the gels was determined using a Brookfield viscometer at 100rpm using spindle no. 7 at 25°C. The pH determined using digital pH meter (Digital potentiometer 101). Spectrophotometric analysis of the formulation checked by UV-VISIBLE spectrophotometer (Elico SL150). *Ex vivo* studies carried out by Franz diffusion cell. FTIR analysis was done by Perkin Elmer, USA and DSC by Perkin Elmer, USA.

### Preformulation studies

#### Melting Point determination

The melting point determined by Capillary method<sup>10</sup>

#### Determination of partition coefficient

The partition coefficient studied between n-octanol and phosphate buffer<sup>10</sup>

The partition coefficient of drug (K<sub>o/w</sub>) was calculated using following expression.

#### Concentration in Octanol

$$K_{o/w} = \frac{\text{Concentration in Octanol}}{\text{Concentration in buffer}}$$

#### Concentration in buffer

#### Solubility analysis

Naproxen solubility in pH 7.4 phosphate buffer and pH 7.4 phosphate buffer (containing 0.5% v/v of Tween20) at 37°C was determined by preparing saturated naproxen solution and assayed by ultra violet visible spectrophotometer at 273nm<sup>11</sup>

#### Formulation of Naproxen emulgel

Carbopol 940 dispersed in water to generate carbopol based gel while HPMC id dispersed in water for corresponding gel<sup>12</sup>. The contents stirred constantly by adjusting the pH to 6.5 using Triethanolamine. Combination of span 20 and arachis oil (oil phase) and tween 20 in water (aqueous phase) along with Methyl and propyl parabens and propylene glycol are prepared. The drug dissolved in the oil phase containing oil and surfactant. Both phases heated separately to 60–70°C, and mixed together with stirring. Contents cooled and mixed with gel at 1:1 ratio with stirring (Table 1).

**Table 1: Composition of Naproxen emulgel Formulations**

Ingredients (%w/w)	Formulation Code									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Naproxen	10	10	10	10	10	10	10	10	10	10
Carbopol-940	0.5	0.5	0.5	0.5	0.5	-	-	-	-	-
HPMC	-	-	-	-	-	2.5	2.5	2.5	2.5	2.5
Arachis oil	7.5	10	12.5	10	10	7.5	10	12.5	10	10
Tween 20	1.6	1.6	1.6	1.2	0.8	1.6	1.6	1.6	1.2	0.8

Span 20	2.4	2.4	2.4	1.8	1.2	2.4	2.4	2.4	1.8	1.2
Propylene glycol	6	6	6	7	8	6	6	6	7	8
Methyl paraben	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Propyl paraben	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01
Purified water up to	100	100	100	100	100	100	100	100	100	100

## Evaluation of Naproxen Emulgels

### Physical examination

The prepared Naproxen emulgel formulations are visually observed for colour, phase separation and consistency<sup>13</sup>

### Determination of pH

2.5 g of gel was accurately weighed and dispersed in 25 mL of distilled water<sup>14</sup>. The pH of dispersion was measured with digital pH meter (Digital potentiometer 101).

### Homogeneity

All developed gels were tested for homogeneity by visual inspection.

### Drug content estimation

The naproxen emulgel (100 mg) dissolved in 50 mL phosphate buffer pH 7.4, mixed for 2 h on mechanical shaker. This solution filtered and drug content estimated spectrophotometrically at wavelength 273 nm<sup>15</sup>.

### Measurement of viscosity

Viscosity of the gels was determined using a Brookfield digital viscometer<sup>16</sup>.

### Determination of spreadability

The spreadability is determined by sandwiching the formulations between two glass slides. The lower slide was fixed on the board of the apparatus and the upper slide was tied to a string to which 80 gm load could be applied with the help of a simple pulley. The time taken for the upper slide to travel the distance of 6 cm and separate away from lower slide under the direction of the weight was noted<sup>17</sup>.

### Skin irritability test

The skin irritability test conducted on properly washed rat skin, by applying 1g gel formulation on 2 square inch area of skin and covered with cotton. After 24 h observe for any undesirable skin changes like irritation or redness of the skin and report if observed<sup>18</sup>.

### In vitro drug diffusion studies

The *in vitro* drug release studies conducted by modified Franz diffusion (FD) cell. The formulation applied on dialysis membrane and placed between the two compartments of the FD cell with Phosphate buffer pH 7.4 as dissolution media. The contents stirred continuously at 37°C. Samples

drawn at regular intervals and analysed spectrophotometrically at 273 nm<sup>19</sup>.

### **Ex vivo drug release study**

The ex vivo studies conducted on using Wistar male rat skin using modified Franz diffusion cell. The skin placed between the two compartments of FD cell with Phosphate buffer pH 7.4 as dissolution media. The contents stirred continuously at 37°C. Samples drawn at regular intervals and analysed spectrophotometrically at 273 nm<sup>20</sup>.

### **Compatibility between Drug and Excipients by FTIR**

FTIR spectra's analysed to check compatibility of drug with excipients. Infrared spectrum of Naproxen was determined on Fourier Transform Infrared spectrophotometer (8400 S Shimadzu) using KBr dispersion method in the wavelength region between 4000 and 400 cm<sup>-1</sup>.

### **Stability Studies**

The stability studies conducted for three months at accelerated conditions of temperature (40°C) and humidity conditions (75± 5%RH).

## **RESULTS AND DISCUSSION**

### **Preformulation studies**

#### **Melting point and partition coefficient:**

Melting point of Naproxen was determined by capillary method and found to be 152°C which correlates with that of standard melting point range of Naproxen. The partition coefficient of Naproxen in n-octanol/water system was found to be 3.28±0.01 and is within the range of 1-4 an ideal property of the drug to be formulated as transdermal system.

#### **Solubility studies**

Solubility of Naproxen was found to high in Tween 20, Arachis oil, and propylene glycol and were selected to dissolve the drug. (Table 2)

**Table 2: Evaluation parameters of Naproxen emulgels**

<b>Formulation code</b>	<b>Colour</b>	<b>Homogeneity</b>	<b>Consistency</b>	<b>Phase separation</b>	<b>Skin compatibility</b>
F1	White	Homogenous	+	None	Compatible
F2	White	Homogenous	+	None	Compatible
F3	White	Homogenous	+	None	Compatible
F4	White	Homogenous	+	None	Compatible
F5	White	Homogenous	+	None	Compatible
F6	White	Homogenous	+	None	Compatible
F7	White	Homogenous	+	None	Compatible
F8	White	Homogenous	+	None	Compatible
F9	White	Homogenous	+	None	Compatible
F10	White	Homogenous	+	None	Compatible

### Formulation and evaluation of Naproxen emulgel

Naproxen emulgels were formulated by using carbopol 940 and HPMC K100 in concentrations of 0.5 and 2.5 %w/w respectively to provide the adequate consistency and elegance also it is free from the toxicological effects on skin. All ten formulations evaluated for clarity, homogeneity, pH, viscosity, spreadability, skin irritation test, drug content, *in vitro* and *ex vivo* dissolution studies. The physical appearance of all formulations (F1-F10) was found to be white viscous and creamy with homogenous appearance no phase separation. The pH values of all formulation lies within  $6.81\pm 0.12$  to  $6.95\pm 0.02$  which is ideal to avoid skin irritation.

Homogeneity of all the formulated gels was determined by visual inspection and all the selected formulations were found to be homogenous without any aggregates or lumps.

The skin compatibility studies indicate that all the formulations are compatible (Table 3). The % drug content values were determined and tabulated in the Table 4. All the values were within 98.5-100.5%. Viscosity of all formulations (F1-F10) were found to be comparable with the viscosity of marketed formulation. The observed viscosity values were between  $2926.6\pm 0.05$  to  $3056.7\pm 0.09$  cps (Table 4).

**Table 3: Evaluation parameters of Naproxen emulgels**

Formulation code	Drug Content (%)	Viscosity (cps)	Spreadability (g.cm/sec)	pH
F1	98.56±0.22	3018.5±0.07	27.31±0.09	6.89±0.11
F2	98.61±0.36	2946.3±0.02	27.51±0.10	6.95±0.02
F3	98.83±0.24	3041.4±0.04	26.52±0.03	6.93±0.06
F4	99.35±0.19	2910.1±0.06	28.53±0.34	6.87±0.09
F5	99.02±0.26	2931.9±0.04	27.68±0.32	6.81±0.12
F6	98.17±0.25	3056.7±0.09	26.45±0.21	6.90±0.03
F7	98.13±0.34	3021.5±0.08	27.41±0.09	6.88±0.06
F8	98.66±0.28	3032.8±0.10	26.72±0.14	6.83±0.02
F9	99.60±0.22	2926.6±0.05	27.91±0.16	6.89±0.11
F10	98.73±0.31	2996.3±0.07	27.25±0.34	6.92±0.10

**Table 4: Permeability parameter of Naproxen emulgels (F4 & F9) and marketed products**

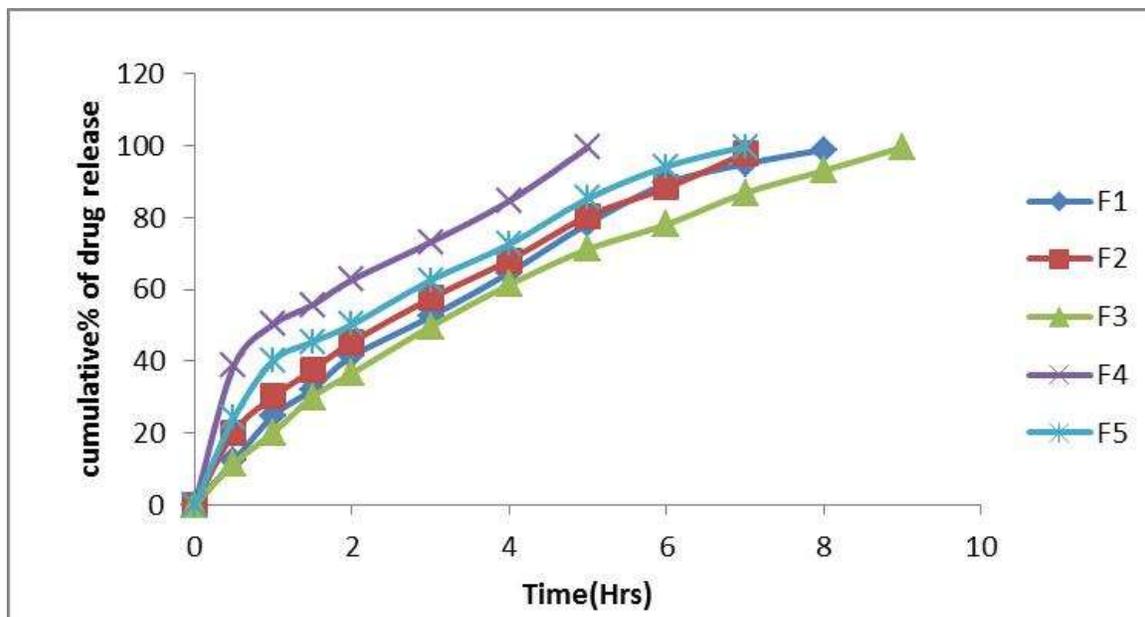
Formulation code	Drug flux at Steady state (J <sub>ss</sub> ) (mg/cm <sup>2</sup> /h)	r <sup>2</sup>	Permeability Coefficient (10 <sup>-3</sup> cm <sup>2</sup> /h)	Enhancement Ratio (E <sub>r</sub> )
F4	1.249	0.922	2.49	2.22
F9	0.757	0.957	1.51	1.34
Marketed	0.561	0.956	1.12	1

Spreadability of the formulated gels varies from  $26.45\pm 0.21$  to  $28.53\pm 0.34$  g.cm/sec. The selected gels were found to be easily spreadable and thus shows good patient compliance and good absorption from skin. The selected gel formulations were found to show no redness of skin and no

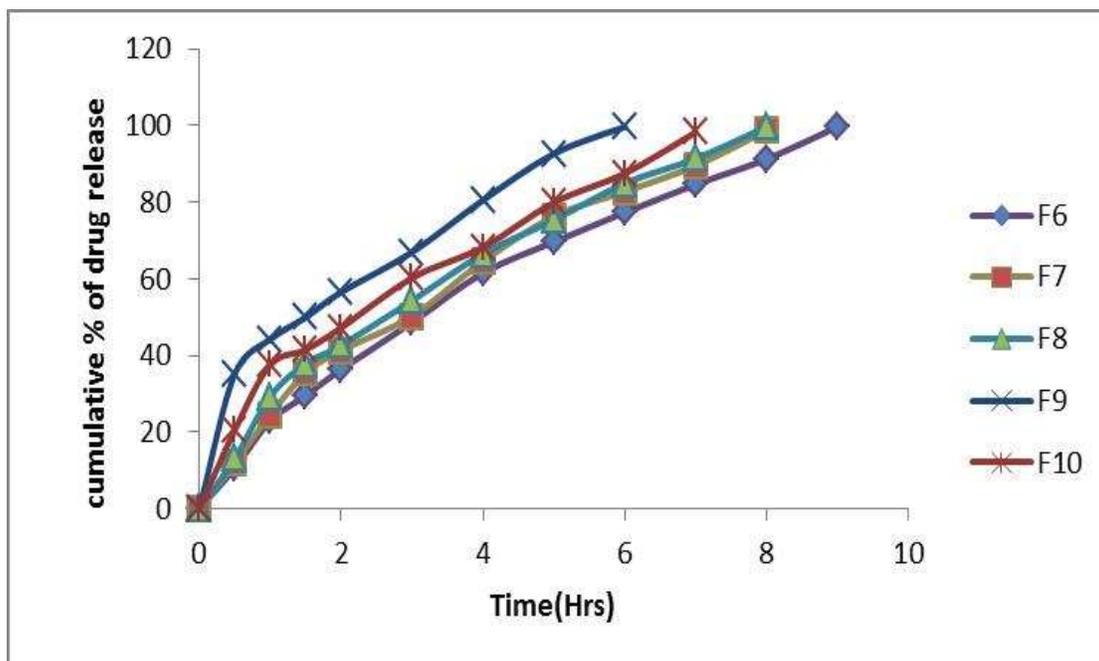
skin irritation.

### ***In vitro* drug release studies**

*In vitro* drug release study carried out by dialysis sac method and the highest release was observed for formulations F4 and F9 at rate of  $99.68 \pm 0.54$  and  $99.63 \pm 0.58\%$  after 6 hrs (Figure 1 and 2).



**Figure 1: *In vitro* drug release of Naproxen emulgels (F1 – F5)**

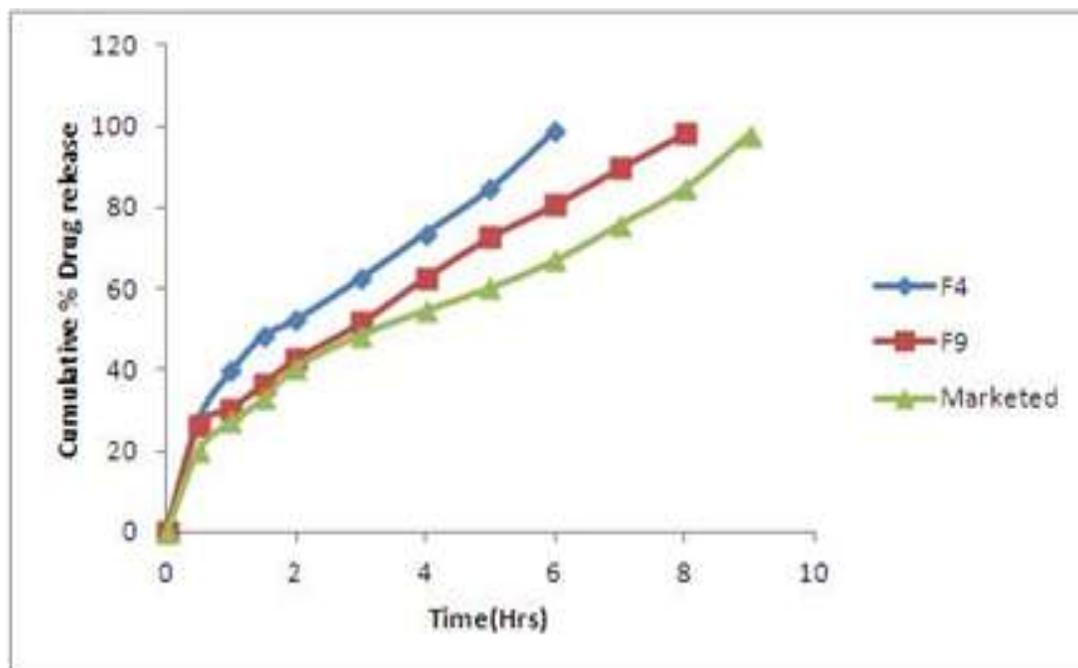


**Figure 2: *In vitro* drug release of Naproxen emulgels (F6 – F10)**

### ***Ex vivo* drug release studies**

The gel formulations having maximum Drug release were selected (F4 & F9) and treated for further release study using rat abdominal skin as diffusion barrier and compared the release profile

of drug from F4 and F9 with that of marketed gel. The ex vivo drug release of F4 is  $98.98 \pm 0.41\%$  within 6hrs and that of F9 is  $98.16 \pm 0.34\%$  within 8 hrs. These were higher than that of marketed product whose drug release is  $98.01 \pm 0.43\%$  in 9 hrs (Figure 3).



**Figure 3: Ex vivo drug release of Naproxen from F4, F9 and Marketed gel**

#### Permeability parameters of Naproxen emulgel

The permeability coefficient of F4 is  $2.49 \times 10^{-3} \text{cm}^2/\text{h}$  is higher than the marketed formulation ( $1.12 \times 10^{-3} \text{cm}^2/\text{h}$ ). The enhancement ratio of optimized formulations were higher than that of marketed gel. The formulation F4 has enhancement ratio of 2.22 and considered as optimized formulation (Table 4).  $T_{50}$  and  $T_{90}$  were calculated for optimized and marketed formulations (Table 6).

**Table 5 Accelerated stability studies of formulation F4**

Physical Parameter	Temperature: $40^\circ \pm 2^\circ\text{C}$ ;Relative humidity(RH): $75 \pm 5\% \text{RH}$			
	Initial	After 1 month	After 2 month	After 3 month
pH	$6.87 \pm 0.09$	$6.87 \pm 0.07$	$6.86 \pm 0.07$	$6.86 \pm 0.01$
Drug content (%)	$99.35 \pm 0.19$	$99.35 \pm 0.2$	$99.35 \pm 0.1$	$99.34 \pm 0.1$
Viscosity (cps)	$2938.1 \pm 0.06$	$2937.9 \pm 0.05$	$2937.8 \pm 0.03$	$2937.1 \pm 0.06$
Spreadability (g.cm/sec)	$27.39 \pm 0.34$	$27.41 \pm 0.36$	$27.42 \pm 0.29$	$27.42 \pm 0.01$
Phase separation	None	None	None	None
In-vitro drug release (%)	$99.68 \pm 0.54$	$99.68 \pm 0.61$	$99.67 \pm 0.42$	$99.65 \pm 0.58$

#### FTIR studies for drug compatibility

FTIR studies were carried out on drugs and excipient samples (Figure 4 and 5). No new peaks were found and hence the drug and the excipients are compatible. Naproxen shows 3 principle peaks at  $1685 \text{cm}^{-1}$  due to  $\text{-C=O}$  of carboxylic acid,  $2893 \text{cm}^{-1}$  due to  $\text{O-H}$  of carboxylic acid,  $3072$



## CONCLUSION

Naproxen emulgels were formulated and evaluated for topical drug delivery. All the 10 formulated gels were tested for physical appearance, homogeneity, and consistency. All the emulgels were found to be opaque, homogenous, with good consistency and no phase separation was observed. The drug content uniformity is the indicative of uniform dispersion of drug throughout the gels. Higher release rate was found in case F4 and F9. Based on the results F4 and F9 were considered suitable for topical drug application and analyzed further. The % *ex-vivo* cumulative drug release from formulation F4 is found to be higher than marketed formulation. It can be concluded from the study that the formulated Naproxen emulgels can be potentially used for improved topical drug delivery with increased absorption and drug release.

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