Acta Pharm. Sci. Vol 62:(2), 2024
Research article
DOI: 10.23893/1307-2080.APS6230

Study of different factors affecting spreadability and release of Ibuprofen from carbopol gels using screening design methodology

Lama AL HAUSHEY*

Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Tishreen University, Lattakia, Syria

ABSTRACT

The objective of this study was to prepare carbopol gels and to evaluate the effect of various solvents on gel spreadability and release properties of Ibuprofen (a hydrophobic compound) using screening design methodology. Five solvents of different polarities were chosen)alcohol, glycerin, PEG_{400}, acetone, PG(. The statistical analysis of the results allowed determining the most influent solvents. Considering the whole results, it appeared that carbopol reduced spreadability while alcohol, glycerin, PEG_{400} and PG increased spreadability. The total released amounts of Ibuprofen were altered by both gel viscosity and Ibuprofen solubility, hence, when Ibuprofen, alcohol and acetone quantities were increased, the quantity of released Ibuprofen per cm^2 inhanced. On the other hand, Carbopol, glycerin, PEG_{400} and PG decreased Ibuprofen release. An optimized experiment was carried out to verify the mathematical model and in order to maximize Ibuprofen release. Gel spreadability was good and enhanced Ibuprofen release was observed for the objective of relieving pain effectively.

Keywords: carbopol, Ibuprofen, spreadability, *in vitro* release, screening design methodology

*Corresponding author: Lama AL HAUSHEY
E-mail: lamaalhaushey239@gmail.com
ORCID: 0009-0003-8751-5049
(Received 14 Sep 2023, Accepted 24 Oct 2023)

INTRODUCTION

Nowadays, there is a great interest in the field of transdermal drug delivery and vast drugs are evaluated for percutaneous absorption. The skin has been used to deliver drugs to the epidermis, dermis, deeper tissues and to systemic circulation[1].

Among the dermal delivery systems, gels have many advantages; they are easy for administration, nongreasy and can increase patient compliance. They have high residence time on the skin and good drug release parameters[2,3]. Gels are semi-solid systems in which the movements of the dispersion medium are restricted by an interlacing network of macromolecules of the dispersed phase[4]. Various studies of drug release have revealed that drugs in gel vehicle are better absorbed than creams or ointments[5].

Many researchers reported that drug release depends on the vehicle and on the drug physicochemical properties[6-9]. The solubility of the drug is among the critical factors that affect drug release in the vehicle and in receptor medium[1]. In addition, it is necessary not only to develop an effective topical dosage form with good stability but it is important to define the diffusion parameters in the gel base[10].

Among the vast number of gelling agents, carbomers are still interesting molecules for the research[11,12]. Carbomers or carbopols are polymers of acrylic acid that form a gel structure in alkaline solutions due to repulsion of the carboxyl groups charged negatively[13]. Carbopols are ideal for both hydro- and hydroalcolic gels[14,15]. Ibuprofen was the most popular and commonly used NSAID for its relief of pain and inflammatory action[16] associated with injure, rheumatoid arthritis and musculoskeletal problems[17,18]. Topical administration of NSAIDs (including Ibuprofen) has been designed as an alternative to the oral route[19]. Ibuprofen has poor aqueous solubility (log P=3.68)[20] resulting in difficulties in designing dosage forms. Dermal administration of Ibuprofen is useful for minimizing gastrointestinal side-effects[21,22] and hepatic metabolism[23]. Topical delivery systems of Ibuprofen are believed to improve patient compliance[9,24] and bioavailability[25,26]. Cosolvents are added to different formulations to help dissolution of drugs and to prevent their precipitation upon storage[27]. Also, they are added as release and permeation enhancers[28]. Several studies have been attempted to prepare transdermal preparations however a few numbers have focused on the effects of different parameters mathematically and statistically.

The main goal of this study was to develop carbopol gels containing Ibuprofen (a hydrophobic drug) by means of factorial design methodology. Carbopol gels must release Ibuprofen in sufficient amount for rapid pain relief. The screening design methodology was used to investigate the effect of different factors

[carbopol, Ibuprofen, alcohol, glycerin, polyethylene glycol 400 (PEG_{400}), acetone and propylene glycol (PG) concentrations] on gel properties (spreadability and Ibuprofen release). The experiments for the screening study were structured by Plackett and Burman Algorithm[29].

METHODOLOGY

Materials

Ibuprofen was supplied from IOL (India). PEG_{400} was purchased from SRL (India). NaH_2PO_4 and Na_2HPO_4 were obtained from Merck (Germany(. Carbopol 940 and all other solvents and chemicals employed [Glycerin, alcohol, acetone, propylene glycol and triethanolamine) TEA [(were of analytical grade.

Determination of Ibuprofen solubility

An excess amount of Ibuprofen was added to phosphate buffer (pH 7.4), the suspension was stirred at 37° C for 24 hours (Monotherm, variomog, Germany). The mixture was filtered and the difference in weight of filter paper before and after filtration referred to the insoluble fraction of Ibuprofen and the soluble Ibuprofen was calculated and expressed in mg/mL.

Preparation of gel systems

A defined quantity of carbopol (X_1) was dispersed in 15 g of water and left overnight for complete hydration. Ibuprofen at different concentration)X_2(was solubilized in a mixture of various solvents at different concentrations (alcohol X_3, glycerin X_4, PEG_{400} X_5, acetone X_6 and PG X_7). Ibuprofen solution was poured into carbopol dispersion. A determined quantity of triethanolamine (1.5 % of carbopol quantity) in the remaining water quantity was added to the mixture to give rise the viscosity.

Construction of the screening design

A preliminary study showed that the formulation parameters (carbopol, Ibuprofen and cosolvents quantities) had an influence on gel properties (spreadability, amount released). Considering the great number of parameters, a screening design was constructed to determinate the effect and the weight of formulation variables on gels properties in a simple and low cost methodology. According to the preliminary results, the two levels of the studies factors were defined. The experimental domain for each factor is summarized in Table 1.

Table 1. Experimental factors and levels

Factor	Factor signification	Level (-1)	Level (+1)
X_1	Carbopol concentration (%)	0.5	2
X_2	Ibuprofen concentration (%)	0.5	2.5
X_3	Alcohol concentration (%)	4	25
X_4	Glycerin concentration (%)	4	15
X_5	PEG400 concentration (%)	4	15
X_6	Acetone concentration (%)	2	10
X_7	PG concentration (%)	4	8

Eight experiments, structured according to the Plackett and Burman Algorithm were carried out. The calculated model was:

$Y(\text{response}) = b_0 + b_1X_1 + b_2X_2 + \cdots + b_nX_n$.

*b*0: average of the responses for the 8 experiments. $b_1, b_2, \ldots, b_n$: coefficients of the factors $X_1, X_2, \ldots, X_n$ (representing the effect of each factor ordered within $-1, +1)^{30}$.

Table 2 shows the following design obtained of 8 experiments.

Table 2. Experimental design

Experiment	X_1 Carbopol (%)	X_2 Ibuprofen (%)	X_3 Alcohol (%)	X_4 Glycerin (%)	X_5 PEG_{400} (%)	X_6 Acetone (%)	X_7 PG (%)
1	2	2.5	25	4	15	2	4
2	0.5	2.5	25	15	4	10	4
3	0.5	0.5	25	15	15	2	8
4	2	0.5	4	15	15	10	4
5	0.5	2.5	4	4	15	10	8
6	2	0.5	25	4	4	10	8
7	2	2.5	4	15	4	2	8
8	0.5	0.5	4	4	4	2	4

The coefficients (*bi*) were calculated by multiple linear regression and the results were analyzed. The statistical analysis provided several information:

- the regression quality was evaluated by the statistical indicator: the determination coefficient R^2
- the coefficients values *bi* and their S.D. The coefficients were evaluated by using a student test. In this study, the coefficients with significativity lower than 5 %, were assumed to be statistically different from 0. Thus, they have a significant effect on the response.

Gel systems characterization

The prepared gels were evaluated for: visual inspection, pH determination, spreadability and *in vitro* release.

Visual inspection

The bases were inspected for color, appearance, presence of any aggregation or phase separation[23]. A number from 0 to 4 was used to quantify gel consistence visually (Table 1), 0 was attributed to the more fluid preparation and 4 to the more rigid one.

pH determination

One g of each gel was weighed and diluted 40 times with water. The mixture was shaken for 2 hours under magnetic agitation at 100rpm (Monotherm, variomog, Germany). The pH was then determined by pH meter)Sension 3, Model 51910, HACH, USA) in triplicate. The pH of the prepared gel must be suitable for both gel viscosity[31] and dermal application[32].

Spreadability test

Spreadability is a measure of lubricity[33] and reflects the ease of dermal application[27,34]. It depends on viscosity of the formulation and on physical properties of the gelling polymers[34]. Higher spreadability values increase surface area available for drug permeation[35]. Hence, therapeutic efficacy may be enhanced[24].

This test was run according to previous study[36] with little modifications. Briefly, 1 g of each gel (after 24 hours of preparation) was placed between two horizontal plates (20 cm × 20 cm) and the weight of the upper plate was standardized at 1 kg. The experiments were performed at room temperature. The mean spreading diameter «d» (in vertical and horizontal axes) was determined after one minute and the areas of circles «S» ($S=d^2\pi/4$) were noted as spreadability values.

In vitro release study

According to previous study[28], a cylindrical glass tube (with effective diffusional surface area of 3.8 cm^2) opened at the two ends was used in this study. A determined amount of each formulae (0.5 g) was spread uniformly on the surface of cellulose nitrate membrane (Sartorious Stedim Biotech Gmbh, 0.22 μ, Germany). The filter paper was secured in place with a rubber and the filter acted as a membrane for drug release. The system was fixed in such way that the lower end of the tube containing samples just touched (1 mm depth) the surface of receptor medium i.e. 50 mL of phosphate buffer (pH 7.4) at 32±1° C. The receptor medium was stirred with a magnet bar at 100 rpm (Monotherm, variomog, Germany) during 4 hours. Sink conditions were maintained in the experiments (e.g. the concentration of Ibuprofen at the end of the experiments was less than 10 % of its solubility)[37]. Samples of 3 mL were pipetted from the receptor medium after 10, 20, 35, 50, 60, 90, 120, 150, 180, 210 and 240 minutes and replaced with an equal volume of freshly prepared phosphate buffer. The samples were then analyzed spectrophotometrically at 272 nm (Jasco V-530 UV/Vis Spectrophotometer, Japan(. The concentration of Ibuprofen was estimated from the regression equation of the calibration curve (Y= 1.359X+0.004, R^2=0.999) against a suitable blanch.

Determination of diffusion coefficients of Ibuprofen in the gel formulations

Diffusion coefficients were calculated using data obtained from drug diffusion study and Higuchi equation[38]:

$$Q= 2C_0(Dt/\pi)^{0.5}$$

Q is the amount of drug released into the receptor phase per unit area (mg/cm^2), C_0 is the initial drug concentration in the vehicle (mg/ml), D is the diffusion coefficient of the drug (cm^2/min), t is the time after application (min).

Release data were plotted against and the slopes of obtained straight lines were used to calculate $D_{(s)}$. D was used to give an idea about Ibuprofen mobility in gel bases.

RESULTS and DISCUSSION

Gels containing Ibuprofen were prepared using five different cosolvents. The calculated solubility of Ibuprofen was 1.47 mg/mL.

The prepared gels were very different in consistence (Table 1). Carbopol at level -1 (e.g. 0.5%) couldn't form gel structure sufficiently when the quantity of solvents increased, and the score of visual consistence decreased significantly.

All pH values were in suitable range for dermal application without irritation[23,39,40]. The results of the eight experiments carried out are summarized in Table 3.

Table 3. Experiment results

Experiment	Appearance	pH measurements	Spreadability (mm^2) Y_1	Amount released (mg/cm^2) Y_2
1	4	6.12	379.94	1.278129
2	1	6.08	1287.596	1.88839
3	0	6.8	1589.625	0.425455
4	3	6.99	358.6591	0.467837
5	1	6.07	1263.862	1.573604
6	3	7.1	333.9316	0.498763
7	4	6.22	362.8663	1.061023
8	2	6.86	900.7998	0.557522

Influence of the investigated parameters on spreadability (response Y_1)

Increasing gel viscosity decreased their spreadability[33,34]. Therefore, the changes in spreadability in this study will be related to viscosity.

The surface of spreading circles ranged from 334 to 1590 mm^2 depending on variation of different factors (Table 3 and Figure 1). The statistical analysis (Table 4) showed the significant effects of the whole studied parameters.

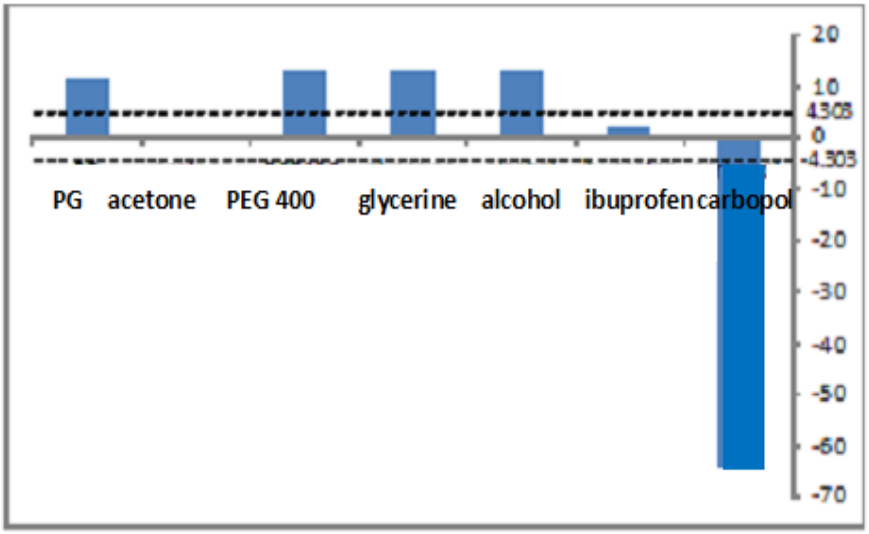

Figure 1: Effects of different factors on the response Y1 (spreadability), the dash line represents the maximal limit over which the factor is statically significant

Table 4. Statistical analysis of Y1 results (spreadability)

Name	Coefficient value	S.D	t exp. Student	Significativity (%)
b_0	809.66	6.98	115.9971	*
b_1	-450.811	6.98	-64.5861	*
b_2	13.90615	6.98	1.992285	-
b_3	88.11318	6.98	12.62367	*
b_4	90.02662	6.98	12.8978	*
b_5	88.36156	6.98	12.65925	*
b_6	1.352285	6.98	0.193737	-
b_7	77.91125	6.98	11.16207	*
R^2	1	FD = 2		

R^2: determination coefficient; FD: freedom degrees which are estimated after repeating experiment 4 three times; the asterisk in the significativity column shows the most influent factors.

The gels spread easily when carbopol quantity was decreased because the gelling agent increased the viscosity of different formulations[41,42]. Increasing polymer concentration increases cohesiveness within the system and the spreading of a delivery vehicle is inversely proportional to its cohesiveness because strong cohesive forces reduce the spreadability[33].

Alcohol decreased viscosity of carbomer gels and a larger carbomer amount might be required to overcome the loss of viscosity[43]. The various other solvents containing OH in their structure (glycerin, PEG_{400} and PG) were known to increase viscosity of carbomer systems[44] however in this investigation, viscosity decreased with these solvents. This might be attributed to the fact that increasing any of these solvents resulted in a new hydrophilic cosolvent system that attracted water from carbomer chains hence the viscosity decreased. The small quantity of carbomer couldn't enter in competition against cosolvent mixture that attracted water. Therefore, the presence of carbopol in small amounts (experiments 2, 3 and 5) couldn't restrict the solvent quantity. In order to reform this gel structure, the quantity of solvents must be decreased (experiment 8) or an increase in carbopol concentration might be required to overcome the loss of viscosity. For example, the formula 5 containing 41 mL of different solvents was fluid while formula 6 containing 51 mL of solvents was gelled considering carbopol concentration (e.g. 2 %). The new additional amount of carbomer (for formula 6) would be hydrated by water and other cosolvents, hence the viscosity would increase in the system in which there was no more free cosolvent.

Ibuprofen and acetone appeared to have no effect on spreadability at studied levels.

Influence of the investigated parameters on the Cumulated released amount of Ibuprofen (response Y_2)

Figure 2 and Table 5 showed the significant factors on the cumulated released amount of Ibuprofen (response Y_2). Differences in released amounts per cm^2 (Figure 3) are mainly due to the differences in both solubility of the active ingredient in the vehicle and viscosity of gel matrix[45,46,47]. The viscosity of the gel base may play an important role in modifying drug release into the receptor medium[10,48,49]. Therefore, the released amounts of Ibuprofen will be discussed in terms of viscosity and solubility.

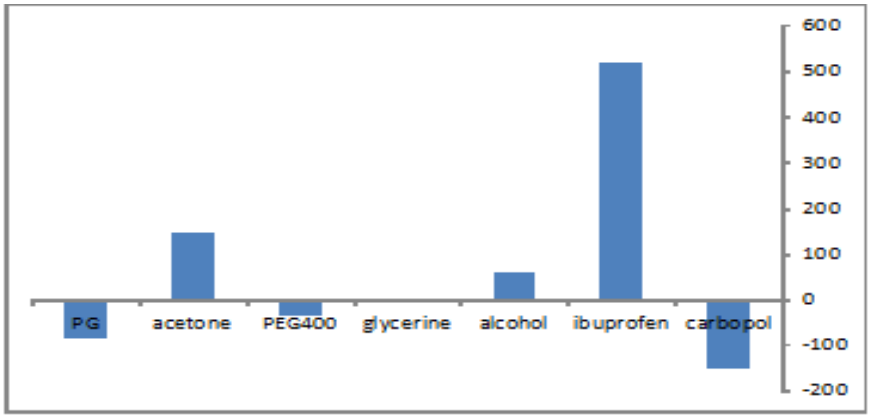

Figure 2: Effects of different factors on the response Y_2 (amount released)

Figure 2. Effects of different factors on the response Y_2 (released amount)

Table 5. Statistical analysis of Y2 results (cumulated released amount /cm^2)

Name	Coefficient value	S.D	t exp. Student	Significativity (%)
b_0	0.96884	0.00093	1041.764	*
b_1	-0.1424	0.00093	-153.121	*
b_2	0.481446	0.00093	517.684	*
b_3	0.053844	0.00093	57.8968	*
b_4	-0.00816	0.00093	-8.77862	*
b_5	-0.03258	0.00093	-35.0367	*
b_6	0.138308	0.00093	148.7183	*
b_7	-0.07913	0.00093	-85.0852	*
R^2	1	FD = 2		

R^2: determination coefficient; FD: freedom degrees which are estimated after repeating experiment 4 three times; the asterisk in the significativity column shows the most influent factors

The factors enhancing the release of Ibuprofen were concentrations of Ibuprofen, alcohol and acetone while the factors decreasing the released amount were: concentrations of carbopol, glycerin, PEG_{400} and PG.

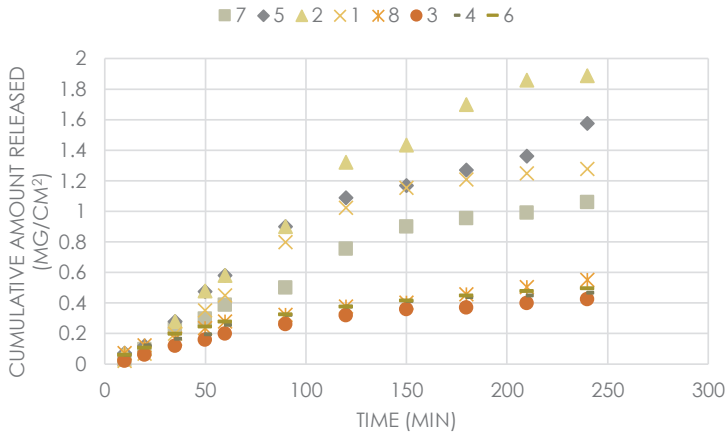

Figure 3. Cumulated released amount of Ibuprofen from different gels

When carbopol concentration was increased in the system, the spreadability was decreased leading to a decrease in released amount[50]. At molecular level, increasing carbopol concentration results in higher viscosity and more tortuous path of migration as a consequence of reduced solvent content[51].

An increase in Ibuprofen concentration led to an increase in released amount per cm² and this was in accordance with other previous studies[28,52]. Increasing drug concentration in the vehicle increases drug release according to Higuchi equation[38].

It was observed that an increase in concentrations of alcohol and acetone was followed by an increase in the total amount of released Ibuprofen. This might be explained partially by the decrease in associated viscosity (expressed by lower diameters of the spreading areas). This agreed with the results of Hasçicek C (2009) who explained the increased released amounts with decrease in viscosity[19]. Additionally, acetone being a solvent of choice for Ibuprofen[53], it increased the amount liberated of Ibuprofen and this might be due to the increase of the solubilized form of Ibuprofen without increasing its affinity to the system. It was reported that the solubility was enhanced in presence of certain solvent and consequently the release rate increased[28,54].

For glycerin, PEG_{400} and PG, it was noted that there was a lack of correlation between spreadability (related to viscosity) and the released amount and this indicated that the viscosity was not the main factor for release[55,56]. This lack of correlation might be explained by the enhanced Ibuprofen solubility and higher affinity for the vehicles (less thermodynamic activity) thus, it was difficult for Ibuprofen to migrate. These data revealed the important action of glycerin,

PEG_{400} and PG as cosolvents, because flux declined as the affinity of the drug to the vehicle raised[54,57,58].

In this paper, it was observed that neither viscosity nor solubility played alone the main role of release but these two physiochemical properties complete each other in determining the release parameters.

The rank order of the gel formulations based upon their maximum Ibuprofen release is indicated in Table 6. This table illustrates the relationship between released Ibuprofen (per cm^2) and concentrations of both Ibuprofen and carbopol.

Table 6. Effect of Ibuprofen and carbopol concentrations on Ibuprofen release

Experiment	Ibuprofen %	Carbopol %	Cosolvents %	Amount released (mg/cm^2)
2	+	-	58	1.88839
5	+	-	41	1.573604
1	+	+	50	1.278129
7	+	+	33	1.061023
8	-	-	18	0.557522
6	-	+	51	0.498763
4	-	+	48	0.467837
3	-	-	65	0.425455

Data from Table 4 reveal that the concentration of Ibuprofen had the greatest effect on release from carbopol gels (experiments in the order: 2 > 5 > 1 > 7) followed by the carbopol concentration (the experiments 5 and 2 had the greatest released amount wherein the level of carbopol was at -1, the same matter for experiments 8). The calculated diffusion coefficients of Ibuprofen for experiments 2 and 5 ($8.82*10^{-6}$ cm^2/min and $5*10^{-6}cm^2$/min respectively) were greater than those for experiments 1 and 7 ($4.39*10^{-6}$ cm^2/min and $2.58*10^{-6}$ cm^2/min respectively). The nature and concentration of cosolvent played a significative role in Ibuprofen release and might overcome carbopol concentration at level -1 (experiment 3).

In order to test the factorial design used in this study, an additional experiment was prepared in order to increase the released amount of Ibuprofen for accelerating pain relief and inflammation[16]. The coded factor level for this experiment had to be in Table 7:

- +1 for Ibuprofen for increasing released amount, also, level +1 for acetone for its role in solubilizing Ibuprofen.
- Intermediate values {≈} for carbopol, alcohol, Glycerin, PEG_{400}, PG concentrations (for good consistency and good release parameters).

Table 7. Conditions for experiment 9

Factor	Factor signification and value
X_1	Carbopol concentration (%): 1
X_2	Ibuprofen concentration (%): 2.5
X_3	Alcohol concentration (%): 14.5
X_4	Glycerin concentration (%): 9.5
X_5	PEG_{400} concentration (%): 9.5
X_6	Acetone concentration (%): 10
X_7	PG concentration (%): 6

The prepared gel was homogenous and of good consistence. The percentage of released Ibuprofen from this optimal gel reached at ~53 % of initial amount at 4 hours of the study and theoretically it may preserve releasing Ibuprofen for further time and in suitable amounts for improving therapeutic efficacy. The released amount from this new gel (1.742 mg/cm², $D=3.23*10^{-6}$ cm²/min) was important in comparison with formulas 1 and 7 containing the maximal initial carbopol concentration, thus, good therapeutic efficacy can be expected. The formulas 2 and 5 were neglected in the comparison because they were very fluid.

STATEMENT OF ETHICS

Not applicable for this study.

CONFLICT OF INTEREST STATEMENT

The author has no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

The author confirms sole responsibility.

FUNDING SOURCES

This research did not receive any funding.

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