ORIGINAL ARTICLE

Design and Optimization of Cyproheptadine Hydrochloride Fast-dissolving Tablet Using Design of Experiment

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Abstract

Aim: The aim of the current research project was to formulate and optimize a fast-dissolving tablet containing the antihistamine drug cyproheptadine hydrochloride (HCl), which is frequently used to treat allergies and other conditions. **Materials and Methods:** The direct compression method was used to prepare the fast-dissolving tablets of cyproheptadine HCl. Fourier-transform infrared spectroscopy was employed to evaluate the blend's compatibility and ensure the stability of the active ingredient. The effect of two critical formulation variables: The amount of super-disintegrant (X1) and amount of effervescent agent (X2) – on the dependent variables: disintegration time (DT) (Y1), percentage drug release at 5 min (Y2), and percentage drug release at 10 min (Y3) – was examined using a two-factor, two-level Central Composite Design. **Results:** Design-Expert® software by Stat-Ease 360 trial version 13.0 was used to study the effect of formulation variables on dependent variables. Nine formulations were produced and assessed for several physicochemical characteristics as well as *in vitro* drug release. The data were analyzed using Response Surface Methodology and Analysis of variance. In comparison to other formulations, the software suggested an optimized formulation (CP OPT) with 5 mg of super-disintegrant and 49.572 mg of effervescent agent with shorter DT and a faster drug release, with over 85% of the drug being released in <10 min. **Conclusion:** The use of effervescence method with sodium starch glycolate, sodium bicarbonate, and other excipients resulted in fast dissolution of the drug in the tablet formulation. The effervescent technique enhanced in masking the bitter taste of the drug and it offered an effective approach for improving patient compliance and enhancing the therapeutic effects of cyproheptadine HCl through the development of fast-dissolving tablets with desired properties.

Key words: Central composite design, cyproheptadine hydrochloride, effervescent agent, fast-dissolving tablet, super-disintegrant

INTRODUCTION

The upper respiratory tract is affected by allergic rhinitis (AR), a chronic inflammatory condition that shows at least one of the typical symptoms, such as sneezing, itching, nasal congestion, and rhinorrhea. This condition can be classified as episodic rhinitis (intermittent exposure to allergens), seasonal (induced by airborne pollens), perennial (caused by indoor allergens such as mites, home dust, fungal spores, and pet dander), or any combination of these. At present, 10–40% of people have allergic rhinitis. Males experience a somewhat greater incidence. A quarter of the world's population suffers from allergic rhinitis, making it a worldwide health concern due to its rising prevalence.[1,2]

The primary mediator in allergic rhinitis (AR) is histamine, which triggers sneezing, pruritus, and reflexive secretory

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responses by activating H1 receptors on sensory nerve terminals. The most often used first-line drug for moderate allergic reactions is an antihistamine.[3] Cyproheptadine hydrochloride (HCl), having a half-life of 8 h, is one of the drugs that belong to the category of first-generation antihistamines and has a preferential action on H1 receptor and blocks the action of histamine on H1 receptor and thus can be used as an anti-allergic drug in the treatment of allergic reaction. Formulating the fast-dissolving tablet of the model drug would help to achieve the desired aim.

Fast-dissolving tablets help in easy swallowing and thus eliminate the risk of choking, which makes them ideal for older patients with choking anxiety, hand tremors, dysphasia, children with developing neurological and muscular systems, uncooperative patients, people on reduced fluid ingestion plans or who are sick, and patient with motion sickness.[4]

MATERIALS AND METHODS

Materials

Cyproheptadine HCl was generously gifted by Geno Pharmaceuticals Ltd., Goa. Sodium bicarbonate, succinic acid, sodium starch glycolate (SSG), and Avicel 102 were procured from SD Fine Chemicals, Mumbai. All other ingredients used in this study were of pharmaceutical-grade quality.

Experimental design for preparation of cyproheptadine HCl fast-dissolving tablet

Direct compression method was used to prepare the fast-dissolving tablet. The tablet was formulated using sodium bicarbonate and succinic acid as an effervescent agent, SSG as a super-disintegrant, avicel 102 as a diluent, sucralose as sweetener, and cyproheptadine HCl as the main active ingredient. The addition of succinic acid serves dual purpose. It acts as a saliva-stimulating agent, which helps in the tablet's wetting and aids in rapid disintegration and dissolution. Second, succinic acid and sodium bicarbonate together provide effervescence by producing carbon dioxide gas, which enhances the tablet's palatability.

After the experimental trials, the independent and dependent variables were selected for the study. The independent variables selected are stated in Table 1 along with their coded values. The dependent variables, i.e., the responses selected to study the influence of independent variables on formulation were disintegration time (DT) in seconds (Y1), drug release in 5 min (Y2), and drug release in 10 min (Y3). Nine formulations were produced and assessed for various physicochemical characteristics as well as *in vitro* drug release. The composition of the same is given in Table 2.

All the ingredients were sieved through 60 mesh size and weighed accordingly using digital weighing balance and mixed. The weighed powder was then compressed into 120 mg tablet with the help of Karnawati RIMEK Mini Press II with a 7 mm punch by adjusting the weight and thickness. The prepared tablets were then evaluated for their post-compression parameters.

Fourier-transform infrared spectroscopy (FTIR) interpretation

FTIR analysis has been performed utilizing a Shimadzu FTIR spectrophotometer on both pure drugs and drug mixtures containing excipients. Using potassium bromide, the pellets

Table 1: Two factor two level central composite experimental design

Formulation code	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9
Coded factor levels									
Concentration of SSG (mg)	−1	+1	−1	+1	−α	+α	0	0	0
Concentration of $NaHCO_3$ (mg)	−1	−1	+1	+1	0	0	−α	+α	0

SSG: Sodium starch glycolate

Table 2: Composition of cycloheptadine hydrochloride fast-dissolving tablets

Ingredients (mg)	CP 1	CP 2	CP 3	CP 4	CP 5	CP 6	CP 7	CP 8	CP 9
Cyproheptadine HCl	4	4	4	4	4	4	4	4	4
Sodium bicarbonate	20	20	50	50	35	35	13.79	56.21	35
Succinic acid	20	20	20	20	20	20	20	20	20
SSG	5	10	5	10	3.96	11.03	7.5	7.5	7.5
Sucralose	5	5	5	5	5	5	5	5	5
Avicel 102	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight	120	120	120	120	120	120	120	120	120

SSG: Sodium starch glycolate

of pure drug and mixture were made. As a blank, potassium bromide pellets were used. To get the IR spectra, the samples were scanned in the infrared spectrum to check for drug-excipient interactions, and then, spectra were compared.[5,6]

Evaluation of fast-dissolving tablets

Pre-compression parameters

The formulation blend was assessed for various precompression parameters. Precompression parameters include Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio, and Angle of Repose.

Post-compression parameters

i. Diameter, Thickness, Hardness: The tablet's diameter, thickness, and hardness were measured using a digital vernier caliper and monsanto hardness tester, respectively.
ii. Weight Variation: The individual weights of the tablets were measured using a digital weighing balance. Twenty tablets from each batch were used, and the average weight was calculated.
iii. Friability: A Roche Friability tester was used to determine the tablet's friability. The initial weight (Wo) of each tablet was noted. They were then put into the drum and run for 4 min at a speed of 25 rpm and then dedusted. The dedusted tablets were then reweighed (W). The following formula was used to calculate the percentage friability: percentage = ((W - Wo)/Wo) × 100.[7,8]
iv. DT: Tablet DT was recorded at 37°C±2°C using a tablet disintegration tester with distilled water as the medium.
v. Wetting Time (WT): The tablet was soaked for the prescribed amount of time by being placed on a piece of tissue paper that had been folded twice and placed inside a petri dish that had an interior diameter of 6.5 cm and 5 mL of distilled water in it. Next, the number of seconds it took for the tablet to get totally wet was calculated.
vi. Drug Content: The drug content was determined by weighing and powdering 20 tablets. Powder containing the drug equivalent to 4 mg was dissolved in methanol, made up to the mark of 100 mL with 0.1N HCl buffer, filtered, and then absorbance was measured at 285.9 nm.[7,9,10]
vii. *In-vitro* Dissolution Studies: *In vitro* dissolution testing of the tablets was carried out using a USP dissolution apparatus II with 150 mL of 0.1N HCl as the dissolution medium. Samples were then withdrawn at specific time intervals, filtered, diluted, and analyzed using an ultraviolet spectrophotometer at 285.9 nm.
viii. Stability Studies: The stability of the optimized preparation was carried out at room temperature for 1 month. After 1 month, the formulation was again tested for the same parameters, and the data were compared to determine stability status.[7,9,10]

Optimization of fast-dissolving tablets

The main effects, interaction effects, and quadratic effects of the formulation components on the DT and *in vitro* release of cyproheptadine HCl were optimized and evaluated using a Central Composite Design using Design Expert Software.

RESULTS AND DISCUSSION

FTIR analysis

The pure drug and the physical combination of the pure drug and the excipients were the subjects of FTIR analyses. As can be seen from Figures 1 and 2, there were no appreciable differences between the physical mixture's and the pure drug's infrared spectra. There were no noticeable changes or shifts in the peaks, indicating that the drug and the excipients have no significant interaction [Table 3].

Pre-compression evaluation and post-compression evaluation

The prepared powder's bulk density ranged from 0.300 to 0.375 g/cm³, tapped density ranged from 0.348 to 0.434 g/cm³,

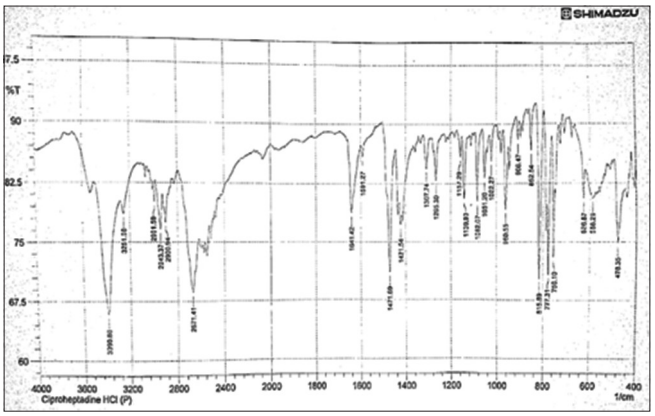

Figure 1: Infrared spectra of pure drug

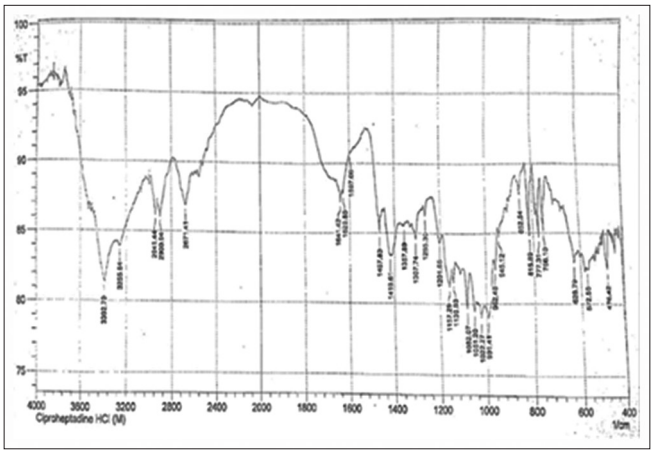

Figure 2: Infrared spectra of the physical mixture

Hauser's ratios in the range of 1.15–1.18, and the Carr's index between 12.50 and 15.11, which showed that the powder had good flow characteristics and compressibility for compression.

The results of the post-compression characteristics are stated in Table 4. The friability percentage for each formulated tablet was within the allowed limit of 1%, indicating good tablet integrity. Weight variation test result was between 119.85 mg and 120.05 mg indicating every tablet falls within the acceptable range. In addition, the disintegration and WT were found to be in a range of 8.21–30.02 s and 22.57–61.8 s, respectively, which complies with the IP limit, suggesting their quick dissolution and potential to improve patient compliance. The drug content uniformity findings which fell within the specified % of the drug content (97–102%) confirmed the constant distribution of drugs throughout the tablet matrix.

In vitro drug dissolution study

In vitro drug dissolution has been significantly influenced by the addition of SSG as a super-disintegrant and sodium bicarbonate as an effervescent agent along with succinic acid in fast-dissolving tablet formulations (CP1 to CP9). In <15 min, more than 90% of the API was released from CP3, which showed the fastest disintegration rate and drug release [Figure 3].

Statistical analysis of the formulation

Design Expert 360 Stat Ease trial edition tool was used to study the effects of two independent variables – SSG (X1) and NaHCO3 (X2) on DT (Y1), drug release in percentage at 5 min (Y2), and drug release in percentage at 10 min (Y3) [Table 5].

When choosing the best model, a number of factors were taken into account, such as lack of fit, statistical significance, high R-squared value, and adequate precision.[11] This study aimed to identify the most effective optimal ratio of effervescent agent to super disintegrant, which can significantly impact the formulation's DT and drug release.

Effect of the formulation variables on the DT

Table 6 presents details of summary of the Analysis of variance and regression analysis. The study yielded a very significant $P < 0.0001$, significantly below the 0.05 threshold, indicating model significance. As the minor differences between the predicted R-squared value (0.9885) and adjusted R-squared value (0.9775), the model demonstrated high predictive ability. Moreover, the model's overall significance was shown by its F-value of 206.91. The increase in concentration of factor A (SSG) and factor B ($NaHCO_3$) was found to decrease the disintegration time and was demonstrated graphically in Figure 4a. Specifically, component A demonstrated a far greater impact than factor B, as seen by its larger coefficient of 11.67 in the polynomial equation.

$$Y1 = +5.914 + 11.67\,A - 0.986\,B + 0.157\,AB - 1.14\,A2 - 0.007\,B2$$

Effect of the formulation variables on the percentage drug release at 5 min

A remarkably significant $P = 0.001$ indicated the model's significance. High predictive performance is shown by the difference of <0.2 between the adjusted R-squared value of 0.8636 and the predicted R-squared of value 0.6827 and with

Table 3: Details of functional peaks of cyproheptadine HCl

Functional group	Cyproheptadine HCl	Physical mixture of drug+excipient
N-CH_3	3390.86, 3251.9	3392.79, 3255.84
Aromatic phenyl stretch	1591.27	1597.06
C=C at C_{10}–C_{11}	1641.42	1641.42

Table 4: Post-compression parameters for the formulation CP1 to CP9

Form. Code	Thickness** (mm)	Hardness* (kg/cm²)	Friability** (%)	Weight ** (mg)	DT* (s)	WT* (s)	% Drug* content
CP 1	2.30±0.02	3.65±0.35	0.18±0.04	119.85±0.003	29.12±2.6	49.77±0.3	102.73±0.64
CP 2	2.41±0.02	3.42±0.24	0.31±0.10	120.05±0.005	16.21±2.3	41.7±0.4	97.75±0.93
CP 3	2.33±0.05	4.02±0.13	0.23±0.02	119.56±0.006	7.34±0.8	22.57±0.3	98.35±0.80
CP 4	2.24±0.02	4.21±0.11	0.16±0.11	120.03±0.003	18.08±1.1	27.81±0.3	101.28±0.88
CP 5	2.33±0.03	3.68±0.17	0.23±0.04	120.0±0.003	11.68±1.4	59.42±0.2	99.91±0.87
CP 6	2.34±0.02	3.65±0.26	0.23±0.10	119.56±0.005	12.57±5.3	60.6±0.5	104.07±0.90
CP 7	2.25±0.02	4.28±0.16	0.26±0.08	120.01±0.006	30.01±0.6	30.56±0.3	99.06±0.85
CP 8	2.20±0.02	4.07±0.19	0.29±0.04	120.04±0.004	16.00±1.1	61.8±0.7	101.48±0.78
CP 9	2.33±0.02	3.42±0.16	0.15±0.02	120.27±0.006	26.52±1.2	50.76±0.5	97.98±0.52

(*n=3, **n=20). Data are represented as mean±SD, DT: Disintegration time, WT: Wetting time

Table 5: Dependent variables for statistical optimization

Form. Code	Disintegration time in seconds (Y1)	Drug release at 5 min (%) (Y2)	Drug release at 10 min (%) (Y3)
CP 1	29.12±2.6	53.2±0.90	63.5±0.74
CP 2	16.21±2.3	65.5±0.49	74.9±0.25
CP 3	7.34±0.8	80.5±0.49	86.5±0.33
CP 4	18.08±1.1	74.1±0.41	81.0±0.25
CP 5	11.68±1.4	67.2±0.25	76.9±0.09
CP 6	12.57±5.3	71.1±0.65	93.2±0.34
CP 7	30.01±0.6	50.7±0.41	63.5±0.43
CP 8	16.00±1.1	67.3±0.16	75.7±0.49
CP 9	26.52±1.2	89.9±0.25	91.1±0.61

Table 6: Model summary statistics for the selected significant models

Parameters	Model F- value	*P*-value	SD	R^2	Adjusted R^2	Predicted R^2	Adequate Precision
Disintegration time	206.23	<0.0001	0.8219	0.9933	0.9884	0.9775	41.5164
Drug release at 5 min	16.19	0.0010	4.74	0.9092	0.8444	0.6520	10.2361
Drug release at 10 min	26.96	0.0002	4.19	0.9288	0.8779	0.6779	11.5103

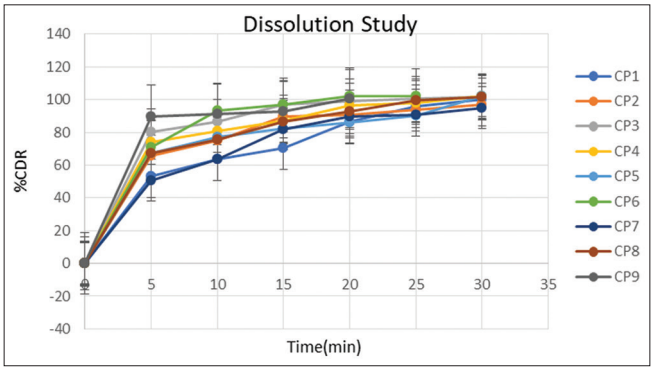

Figure 3: Comparative dissolution profile of CP1-CP9

a F-value of 16.19. At 5 min (Y2), both the super-disintegrant and the effervescent agent showed a significant effect on drug release.

It is evident from Figure 4b that after 5 min, an increase in A and B concentrations leads to increased drug release. Both components appeared to have beneficial effects, suggesting that they had agonistic actions. Component B has a far greater effect than component A, as seen by its larger coefficient (7.44) in the polynomial equation.

$$Y2 = +82.52 + 1.44\,A + 7.44\,B - 4.70\,AB - 5.60\,A2 - 10.68\,B2$$

Effect of the formulation variables on the percentage drug release at 10 min

The model's statistical significance was supported by the study's very significant $P = 0.0002$, which is less than the pre-defined significance level of 0.05. Strong predictive ability was suggested by the relatively small differences between the adjusted R-squared value of 0.9154 and the predicted R-squared value of 0.7137. Furthermore, the model's overall significance was demonstrated by its F-value of 26.96.

Figure 4c demonstrated how factors A (SSG) and B ($NaHCO_3$), at increasing concentrations, increased drug release at 10 min. Both variables had a positive effect on drug release, according to the polynomial equation, factor B's effect was stronger as seen by its bigger coefficient of 5.74.

$$Y3 = +93.10 + 3.64\,A + 5.74\,B - 4.22\,AB - 4.24A2 - 11.87\,B2$$

Numerical optimization

To optimize the cyproheptadine HCl fast-dissolving tablet, the following objectives were taken into consideration: A minimal DT and the maximum drug release at time points of 5 and 10 min. Out of the 12 solutions, the software offered, one solution with an SSG concentration of 5 mg and a sodium bicarbonate concentration of 49.572 mg having a desirability score of 0.832 was selected and tried. This formulation was thought to be the best as it provides the desired drug release at 5 and 10 min with the minimum DT.

The optimized formulation (CP OPT) was evaluated for a wide range of fundamental features, such as hardness, thickness, diameter, DT, WT, friability, and percent drug release at 5 and 10 min. The results of the experimental and predicted values for responses Y1, Y2, and Y3 are displayed in Table 7.

Analysis of Y1, Y2, and Y3 showed that there was no significant difference between the experimental and

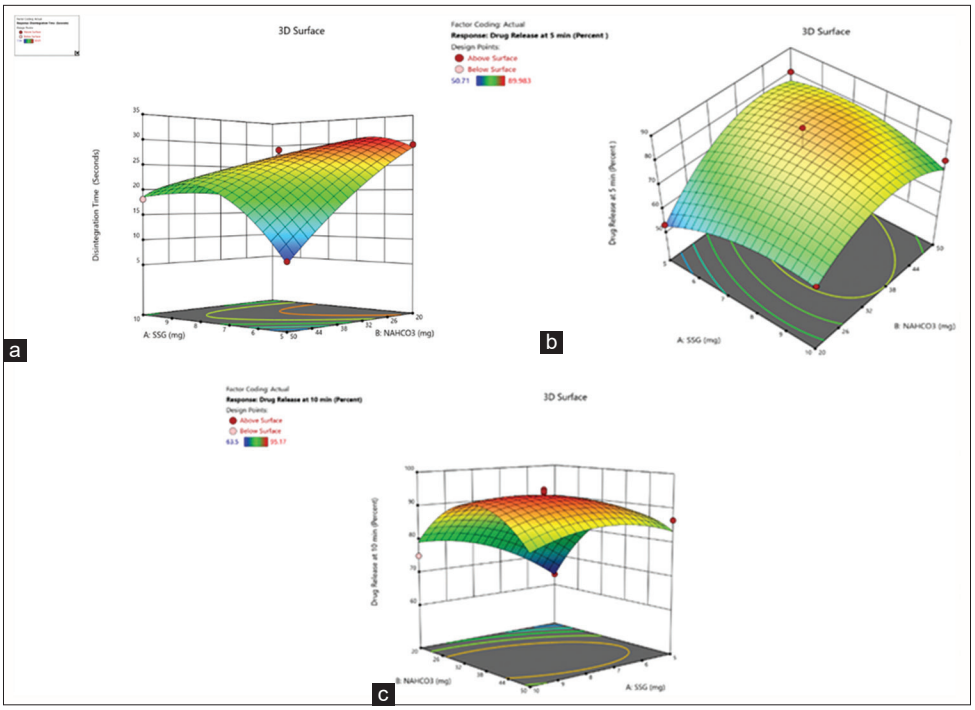

Figure 4: (a-c) 3D response surface plots for dependent variables Y1, Y2, and Y3, respectively

Table 7: Comparison between observed and predicated value for responses Y1, Y2, and Y3

Formulation code	Response variable	Experimental value	Predicted value
CP OPT	DT	8.216	7.340
	Drug release at 5 min	76.47	77.19
	Drug release at 10 min	86.56	83.61

Table 8: Stability study of optimized formulation (CP OPT)

Duration	Hardness (kg/cm²)	Drug content (%)	Wetting time (s)	Disintegration time (s)	Percent drug release at 5 min (%)	Percent drug release at 10 min (%)
1 month	3.78±0.10	98.5±0.5	26.3±0.2	10.04±0.4	73.20±0.97	83.5±0.2

expected outcomes. This similarity indicates a significant capability of the prediction model for predicting these response variables.

Stability study

Using the software-provided optimum batch, a stability study was carried out on cyproheptadine HCl fast-dissolving tablets for a duration of 30 days at room temperature and ambient humidity. The study's objective was to evaluate the tablet's chemical and physical stability. The tablets were closely observed for any alterations in appearance, including color, texture, and odor. To make sure the tablets had their intended qualities, additional analyses were conducted on the hardness, DT, dissolution profile, and other relevant parameters. The findings of the stability investigation are displayed in Table 8.

CONCLUSION

The optimization and formulation of an efficient allergic rhinitis drug with ease of administration were the aims of the study. Using an effervescence method with sodium bicarbonate, along with SSG and other excipients resulted in fast disintegration of the tablet formulation. Formulation CP-OPT was found to be an optimum formulation with a DT of 8.216 ± 0.7 s, drug content of 100.08 ± 0.8%, and drug release percentages of 76.47 ± 0.2% and 86.56 ± 0.8% at 5 and 10 min, respectively. The optimization process was made easier by Design Expert software, providing a solution of optimized formulation with a desirability score of 0.832.

The application of Quality by Design principles coupled with the Design of Experiment allowed a better understanding of the critical variables that affect the tablet's quality attributes.

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