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Development and Characterization of Oro Dispersible Films of Bilastine

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Abstract:

The aim of this research work was to develop oro-dispersible films of Bilastine, with the goal of achieving a fast onset of action to improve the management of allergic rhinitis. Using the solvent-casting method, sixbatches were formulated of oro-dispersible films, by using HPMC K4M, HPMC K100 as film-forming polymers. Various evaluation parameters such as thickness, weight variations, folding endurance, surface pH, disintegration, drug content, and in-vitro drug release were evaluated for all formulated batches. Among the formulated variations, F2 exhibited exceptional characteristics, lower disintegration time of only 18 seconds. Moreover, it demonstrated the highest drug release, with an impressive 95.32% of the drug being released within just 30 minutes, surpassing the performance of the other formulations. Thus, F2 was selected as the optimized formulation. Analysis through FTIR indicated that there were no significant interactions between the drug and the polymers used in the optimized formulation. In conclusion, the development of oro-dispersible film of Bilastine represents a promising approach for the treatment of allergic rhinitis. These films offer the advantage of rapid dissolution, leading to enhanced therapeutic efficacy.

Keywords: Mouth Dissolving Films, Bilastine, Allergic rhinitis

Introduction:

Oral film technology was initially created in the late 1970s to address the difficulties faced by elderly and young patients who have trouble swallowing tablets and capsules. However, it has gained popularity in the pharmaceutical industry due to its numerous advantages, including increased durability, rapid release, precise dosing, and ease of administration.[1-5] The oral route of drug delivery is preferred for its cost-effectiveness and convenience, leading to high patient adherence, especially among the elderly and pediatric populations. Nevertheless, the challenge of swallowing difficulties necessitates the development of innovative and safer drug delivery systems such as oral strips and buccal films.[6-10]

Fast-dissolving films have become increasingly popular as an alternative to fast-dissolving tablets because they quickly dissolve upon contact with wet surfaces like the tongue, eliminating the need for additional liquids. This convenience not only provides a marketing advantage but also enhances patient compliance. Furthermore, the drug is directly absorbed into the systemic circulation, bypassing degradation in the gastrointestinal tract and the first-pass effect. These advantages have contributed to the widespread acceptance and popularity of this formulation, particularly among pediatric and geriatric patients and individuals with a fear of choking. Oral thin films are now approved and utilized as a technique for achieving systemic distribution of active pharmaceutical ingredients (APIs) in over-the-counter (OTC) medications and some prescription treatments.[11-14]

Fast-dissolving oral films are formulated using hydrophilic polymers that dissolve rapidly on the tongue or buccal cavity, facilitating drug delivery to the systemic circulation upon contact with liquid. The user applies the film on or under the tongue (sublingual) or along the inside of the cheek (buccal) for oral administration. These films are typically postage stamp-sized, with a similar shape and thickness. By bypassing first-pass metabolism through this drug delivery method, the medication's bioavailability is enhanced. A major challenge in developing fast-dissolving oral films lies in taste masking, as medications administered in the oral cavity should have an acceptable taste. Taste plays a crucial role in the development of oral pharmaceuticals, particularly in pediatric medicine, as it influences patient acceptance, compliance, and the market success of oral formulations regardless of the administration mode.[14-19]

Materials:

Bilastine is obtained from Concept Pharma Aurangabad. HPMC (K4M, K15) was obtained by Research-lab fine chemicals industries in Mumbai, along with Mannitol and Aspartame. Polyethylene glycol is sourced from Gateefoseeas, a company located in Mumbai. Citric Acid is supplied by Thomas Baker Pvt. Ltd, based in Mumbai. Finally, Vanillin is sourced from Ranbaxy Fine Chemicals Limited, located in New Delhi.

Pre-formulation Study

Characterization of Bilastine :

Description: Color and physical form of Bilastine were checked visually.

Solubility: Solubility of Bilastine was checked in water and different pH buffers (pH 1.2, 4.5, 6.8, and 7.4).

Melting Point: The melting point of Bilastine was determined by introducing a small amount of the substance in a capillary attached to a graduated thermometer, and constant heat was applied with the assembly suspended in a melting point apparatus. The temperature at which the substance melted was noted.

Spectroscopy

Determination of λ max of Bilastine:

Weigh accurately 10 mg of Bilastine, transfer it into a 100 mL volumetric flask, and make up the volume to 100 mL with phosphate buffer (pH 6.8). From this solution, 1 mL was withdrawn and added to a 10 mL volumetric flask and diluted up to 10 mL with phosphate buffer (pH 6.8). Finally, the sample was scanned in the range of 200-400 nm. The wavelength of the maximum absorption was noted, and the UV spectrum was recorded.

Standard Calibration Curve of Bilastine in Phosphate Buffer (pH 6.8):

Accurately weigh 100 mg of Bilastine and add it to a 100 mL volumetric flask. Make up the volume to 100 mL with phosphate buffer (pH 6.8) (1000 µg/mL). From this solution, 10 mL was withdrawn and added into a 100 mL volumetric flask, and the volume was made up to 100 mL with phosphate buffer (pH 6.8) (100 µg /mL). This solution was used as the stock solution. From the stock solution, 2,4,6,8,10,12 and 14 mL of solution was withdrawn and added into a 10 mL volumetric flask and finally diluted up to 10 mL with phosphate buffer (pH 6.8). The absorbance was measured for each solution at 280 nm using a UV-Visible spectrophotometer. The graph was plotted for absorbance vs. concentration.

Formulation of Oro-dispersible Films:

Dose Calculation

The drug to be loaded in the film was determined by the dose of the drug and the drug loading in the glass plate was determined by the area of the glass plate.

Preparation of films by solvent casting method:

All the ingredients were weighed accordingly. The polymer was dissolved in ethanol. The drug mannitol, citric acid and vanillin were dissolved separately in ethanol. Then polymer solution added to drug solution and plasticizer (PEG-400) added then stirred for 15 minutes to produce a clear solution, which kept aside for 15 minutes to get bubble free solution. Then solutions were casted slowly with continuous flow on glass plate to prevent formation of bubbles then it kept for drying. The dried films were gently separated from glass plate and evaluated.

Formulation design:

Oro-dispersible oral films were prepared using various grades of HPMC as polymer.

Sr.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Bilastine	20	20	20	20	20	20
2	HPMC K4M	25	30	35	-	-	-
3	HPMC K15	-	-	-	25	30	35
4	PEG 400 (ml)	0.03	0.03	0.03	0.03	0.03	0.03

5	Aspartame	5	5	5	5	5	5
6	Mannitol	10	10	10	10	10	10
7	CitricAcid	5	5	5	5	5	5
8	Vanillin	1.5	1.5	1.5	1.5	1.5	1.5
9	Ethanol(ml)	q.s	q.s	q.s	q.s	q.s	q.s

Results and Discussion:

Standard calibration curve of Bilastine

Concentration	Absorbance
0	0
2	0.1758
4	0.2987
6	0.4168
8	0.5284
10	0.6594
12	0.7648
14	0.8704

Table 1: Calibration Curve of Bilastine

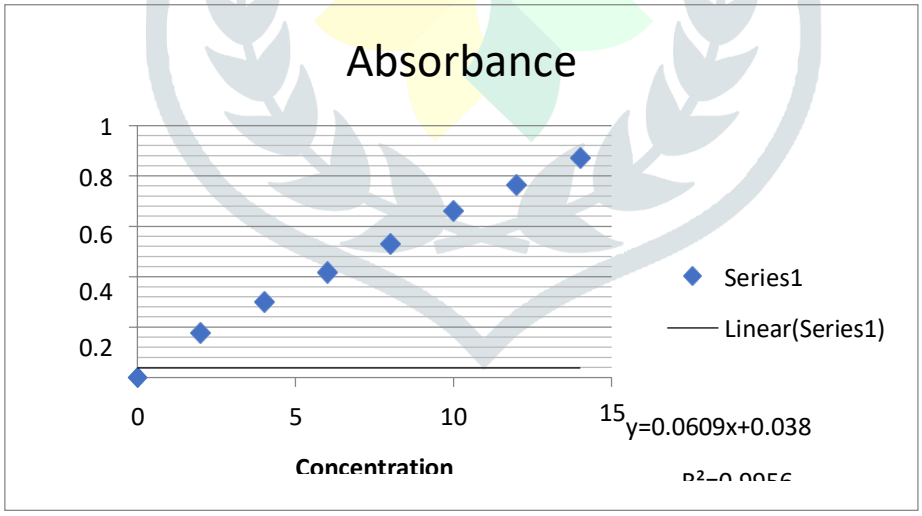

Fig 1: Calibration Curve of Bilastine

Evaluation:

Formulation Batch	Appearance	Tack Test	Film Thickness (mm)	Tensile Strength(Kg/mm)
F1	Transparent	Non Tacky	0.7±0.04	0.216±0.004

F2	Transparent	Tacky	0.9±0.10	0.220±0.002
F3	Transparent	Non Tacky	1.3±0.21	0.221±0.006
F4	Transparent	Non Tacky	0.7±0.10	0.410±0.002
F5	Transparent	Tacky	1.0±0.06	0.416±0.002
F6	Transparent	Non Tacky	1.1±0.24	0.421±0.004

Table 2: EvaluationofFilmsfor,AppearanceTacktest,Thickness andTensile Strength

PhysicalAppearanceandSurfaceTextureofOro-dispersiblefilms:
TheseparameterswerecheckedsimplywithvisualinspectionofOro-dispersiblefilmandbyfeelortouch.TheobservationsuggeststhatOro-dispersiblefilmsarehavingsmoothsurfaceandtheyareelegant enough to see.

TackTest
All Strips were evaluated for tack test out of that only F2 and F5 batches were found to betacky and other batches were found to be non-tacky The tack test of all Oro-dispersible oral filmsisgiven in abovetable.

TensileStrength:
Tensile strength was found to increase with increase in concentration of the polymers. Tensilestrengthrangeof thefilmsvaried fromto 0.216±0.004 to0.516±0.002for HPMCfilms.

ThicknessofOro-dispersiblefilms:
The thickness of Oro-dispersible Films were measured using screw gauge and the averagethickness of Oro-dispersible film given in above Table The thickness of Oro-dispersible filmpreparedwithHPMCK4,K15,respectively.

ThicknessofOro-dispersiblefilmswasfoundbetween 0.7±0.04to1.3±0.25.

Batch	DisintegrationTime (sec)	Folding Endurance	% Drug Content	WeightVariation (mg)	pH
F1	22.6±0.24	77 ±0.24	95.43±0.38	4.5±0.09	6.36
F2	18.3±0.26	90 ±0.38	98.47±0.27	6.7±0.08	6.61
F3	19.3±0.64	80 ±0.51	89.12±0.28	7.9±0.21	6.83
F4	23.23±0.12	86 ±0.24	96.54±0.98	5.5±0.11	6.81
F5	21.01±0.37	82 ±0.45	92.12±0.44	7.1±0.24	6.68
F6	22.77±0.39	81 ±0.54	90.25±0.16	6.5±0.42	6.90

Table 3:Evaluationparameterofformulationbatches.

DisintegrationTimeofOro-dispersiblefilm:

Strip of 2 x 2 cm^2 size taken and disintegration time checked visually. In each case three Oro-dispersible films were used and the average drug content was calculated, the results were shownin abovetable.

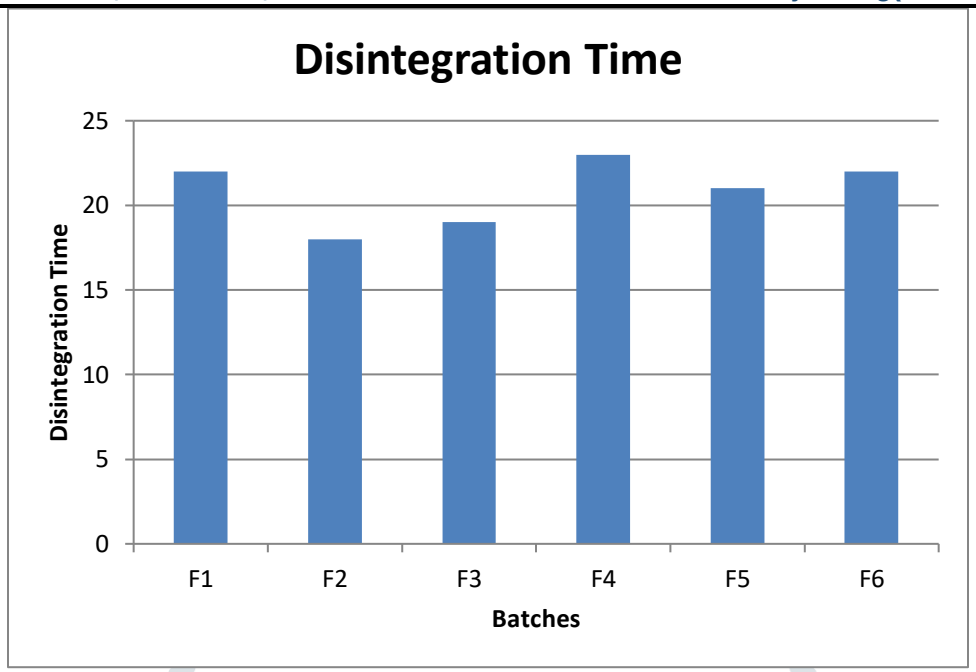

Fig3:DisintegrationTimePreparedFilms

Disintegrationtimes of Oro-dispersible films werefoundbetween18.3 ±26 to 23.23 ±0.12.

FoldingEnduranceofOro-dispersiblefilms:

ThefoldingenduranceofOro-dispersiblefilmwasdeterminedbyrepeatedlyfoldingasmallfilmof Oro-dispersible film at same place till it broke and the average folding endurance of all FilmsgiveninTablewhichrangesbetweenin tablesinbetweenrange74±0.24to82±54.

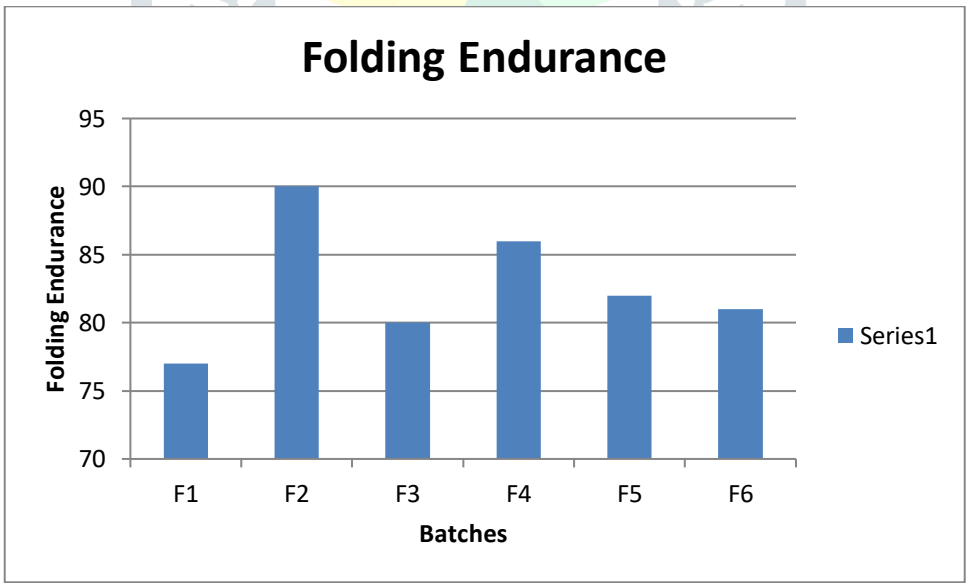

Fig 4 :FoldingEnduranceOfPreparedFilms

DrugContentUniformityofOro-dispersibleFilms:

In each case three Oro-dispersible films were used and the average drug content was calculated,the results were shown in above table. The drug was dispersed in the range of 89.12±0.14 to98.47±0.12.SuggestingthatdrugwasuniformlydispersedinOro-dispersiblefilms.TheS.D.valuecalculated for such formulation is very less which suggest that the results are reproducible

andaccuracyin themethod used to prepareOro-dispersiblefilms.

WeightVariationofOro-dispersiblefilms:

Weight of Oro-dispersible Films was determined using digital balance and the average weights of oro-dispersible films were given in above table. The weight variation of formulated films inbetween 4.5±0.09to 7.9±0.57.

SurfacepHofOro-dispersibleFilms:

The surface pH was noted by pH meter near the surface of Oro-dispersible film and allowing toequilibrate for 1 min and the surface pH of Oro-dispersible films was given in above table thesurfacepH ofOro-dispersiblefilm wasfound tobein-between 6.36to 6.81pH (n=3).

In-VitroDissolutionStudiesOfBilastine:

Time	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	22.64	25.98	20.35	23.98	21.55	20.25
10	39.71	45.24	34.58	39.32	34.25	32.32
15	55.47	68.87	59.37	55.74	53.35	51.25
20	72.24	89.68	85.87	84.93	83.25	78.35
25	82.98	97.26	90.29	87.16	85.32	84.35
30	92.46	98.58	95.24	96.32	91.25	93.35

Table4 :In-VitroDissolutionstudiesofBilastine

Allvaluesexpressedasmean±SD(n=3),F=Formulationbatch

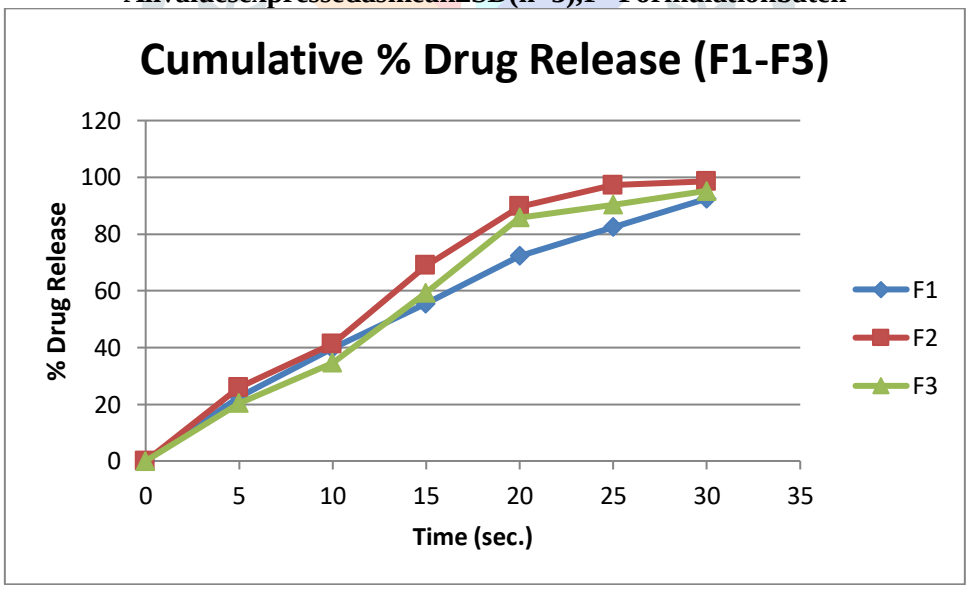

Fig5:Cumulative%DrugReleaseFromF1-F3

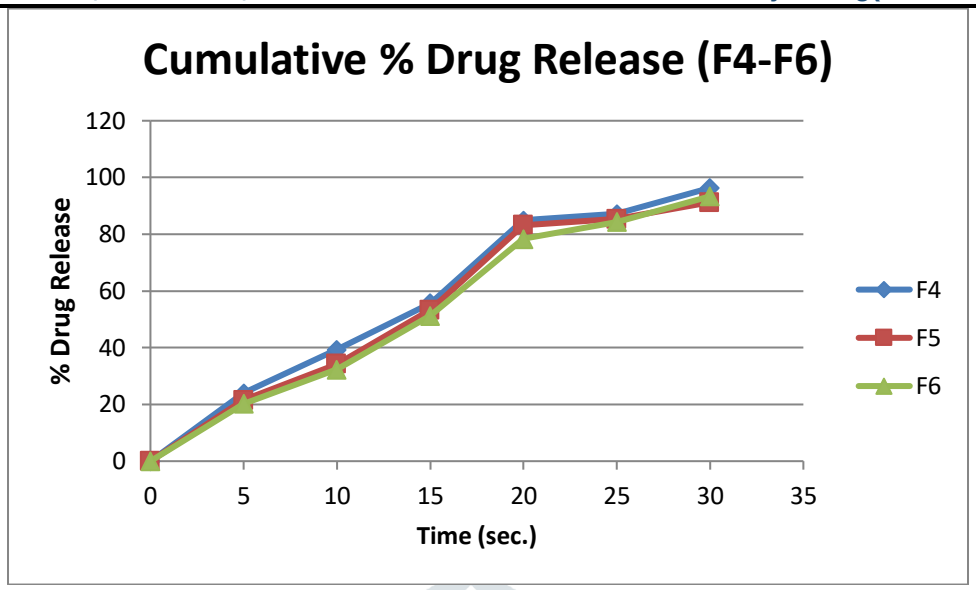

Fig6:Cumulative%DrugReleaseFromF4-F6

In these all aspects the formulation F2 satisfied all the pharmaceutical parameters of mouthdissolvingfilms,andappearstogivebettertherapeuticeffects,withdisintegrationtime18.23±0.12seconds 98.58 %drugrelease.

StabilityStudies

Stability studies for the optimized formulation (F4) was carried out in order to determine thephysical stability of the formulation. The results were shown in there was no significant changeintheparameterswhichareevaluatedduringthestudyperiod in the accelerated conditions

EvaluationParameters	0Days	30Days	60Days
Thickness	0.9	0.9	0.9
WeightVariation	0.79	0.79	0.76
FoldingEndurance	14.24	14.24	13.51
SurfacepH	6.8	6.7	6.7
DisintegrationTime(Sec)	17.23	16.57	16.21
% Drug Content	96.54	96.45	96.31
Visual Inspection	Transparent	Transparent	Transparent
% Drug Release	98.58 ±0.21	96.11±0.47	91.84±0.24

Table10:ParametersstudiesonF2formulationbeforeandafterstabilitystudy

There were no considerable changes in physical parameter of film such as Thickness, Weightvariation, Folding endurance, Disintegration time, % Drug content of formulation F2 before andafter accelerated stabilitystudy.

Summary

Bilastineisthedrugsusedinallergicrhinitiswhichisverycommon.The absolute bioavailability of Bilastine is approximately 61%.To overcome the above-mentioned problems an attempt was made to developand to improve the solubility of drug and reduce side effects, it was attempted todevelopOro-dispersiblefilmsusingdifferentfilmformingpolymers.FTIRspectroscopic studies were carried out in order to establish compatibility between drugand excipients. The results were concluded that there were no chemical interactionsbetweendrugandthe excipientsused,sotheycouldbeusedfortheformulationofOro-dispersiblefilms.

Total9formulationsofmouthdissolvingfilmsweredevelopedusingvariousexcipientswhich were found to be compatible using FTIR of films.

Formulations were preparedusingthreedifferent polymerssuch as HPMCK4M, HPMC K15.

FilmswereevaluatedforqualitycontroltestssuchasAppearance,Tacktest,Thickness,Tensile strength, disintegration time, folding endurance,% Drug content, Weightvariation,in-vitrodissolution, Comparisonwithmarketed productandstabilitystudy.

The thickness of formulations was between 0.7±0.04 to 1.3±0.21. Tensile Strength ofall 9 formulations was found to be in between 0.0216±0.004 to 0.516±0.002. TheDisintegrationtimeoftheformulationswasfoundtobebetween18.23±0.12to34.78±0.97.

ThesurfacepHofallformulationswasfoundtobeinbetween6.36to6.81.TheFoldingenduranceoftheformulationswasfoundtobeinbetween77±0.26to90 ±0.54The%drug content of all the formulations was found be in between 90.25±0.28 to 98.47 ±27.TheWeightvariationoftheformulationswasfoundtobeinbetween4.5±0.09to7.9 ± 0.57.

InthiseallaspectstheformulationBatchF2satisfiedallthepharmaceuticalparametersofmouth dissolvingfilms.So, the F2 batchwas selectedas optimizedbatch.

Conclusion

Overall,thisstudy successfully developedOro-dispersiblefilmsforBilastine, which showed desirable physical characteristics and drug content. Thefindings suggest that the formulation approach using these film-forming polymers canbeapromisingstrategytoenhancethesolubilityandminimizesideeffectsofthedrugin thetreatmentofallergicrhinitis.Furtherinvestigations,including invivostudiesandclinical trials, may be warranted to assess the efficacy and safety of these formulationsfor potential therapeutic applications.

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