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FORMULATION AND EVALUATION OF METOPROLOL SUCCINATE TRANSDERMAL PATCHES

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Abstract:

Bioadhesive systems provide intimate contact between a dosage form and the absorbing tissue, which may result in high concentration in a local area and hence high drug flux through the absorbing tissue. Example : Transdermal Drug Delivery system. The present study was carried out to investigate the Transdermal release of Metoprolol Succinate by Solvent Casting method using different polymers. From the results, it was found the liberation of drug from the formulations. All the Transdermal patches Pre-formulation and Post-formulation patches were found to be within the limits. Among all the formulations, F6 (with Sodium alginate, Gelatin, PVP K30, HPMC K4M, SLS, Urea, Tween 80 and Glycerine) emerged to be the best one, because, it exhibits the maximum percentage drug release of 98.15%. In-vitro kinetics for F6 showed that the drug mechanism was found to be Non-Fickian diffusion.

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INTRODUCTION:

Bioadhesion:

Bioadhesion includes cell-to-cell adhesion, bacteria binding to surfaces, adhesion to mucous membranes and the use of adhesive materials in medical treatments. Bioadhesive systems provide intimate contact between a dosage form and the absorbing tissue, which may result in high concentration in a local area and hence high drug flux through the absorbing tissue. Example : Transdermal Drug Delivery system. [1]

Transdermal drug delivery system (TDD):

TDD is defined as self-contained, discrete dosage forms which ,when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery can achieve systemic treatment of diseases via the transdermal route. It offers the advantages of avoiding hepatic first-pass effect, good patient compliance and decreased dosing frequency. The outer most level, the epidermis, consists of a specific constellation of cells known as keratinocytes, which function to synthesize keratin, a long, threadlike protein with a protective role.

The skin consists of three main layers:

- Epidermis
- Dermis
- Hypodermis[2]

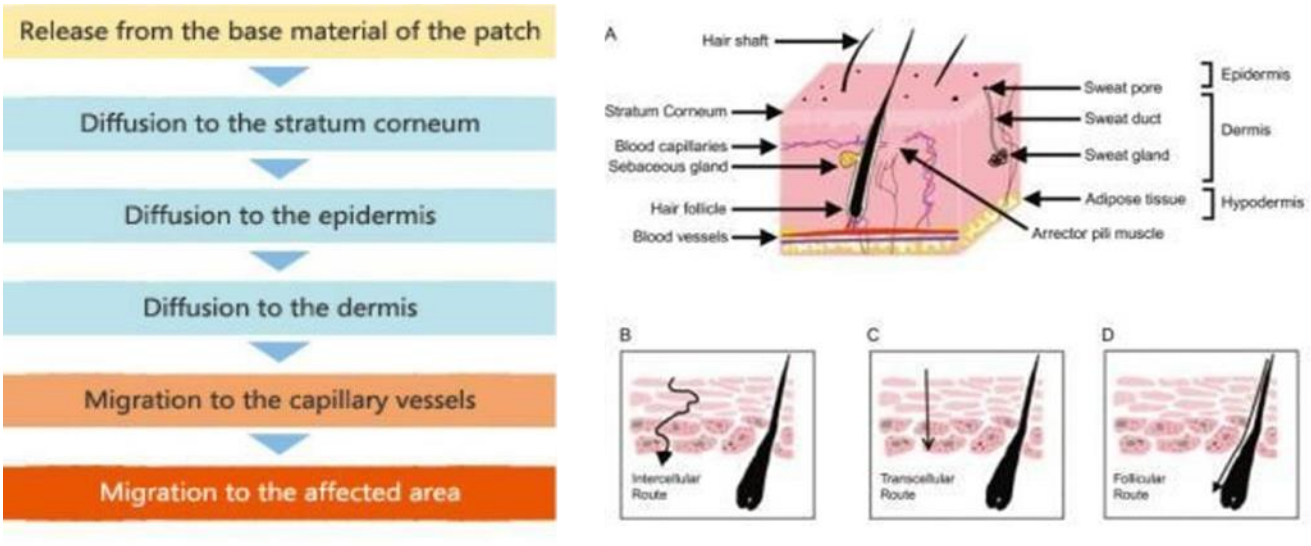


Figure-1: a) Mechanism of Transdermal Patches **b) Permeation of drug across the skin**

There are many anti-hypertensive and Anti-anginal drugs, Metoprolol Succinate is widely used, which is a beta-blocker that affects the heart and circulation (blood flow through arteries and veins). Metoprolol Succinate is used to treat angina (chest pain) and hypertension (high blood pressure). It is also used to lower your risk of death or needing to be hospitalized for heart failure.6 Metoprolol succinate undergoes hepatic metabolism or first pass metabolism in the liver. The plasma half life ranges from 3 to 7 hours. In order to increase rapid absorption and show rapid onset of action, this drug is formulated as Transdermal patches by bypassing first pass metabolism. [3]So, the aim of the present work is to formulate and evaluate metoprolol succinate in- order increase the bioavailability.

1. Selection of Drug
2. Review of Literature.
3. Procurement of drug and other suitable excipients.
4. FT-IR studies for drug and excipients compatibilities.
5. To formulate and evaluate Metoprolol succinate patches using various polymers.
6. Pre-formulation studies

Physiochemical evaluation of drug molecule:

1. Description
2. Solubility
3. Melting point
4. Hygroscopicity
5. Flow properties

Compatibility studies of drug molecule with excipients:

1. Non-thermal methods
2. Spectroscopic Technique

Post formulation studies: Weight variation test, thickness of the patch, measurement of folding endurance, drug entrapment efficiency, in-vitro release studies, kinetic studies and stability studies.

MATERIALS AND METHODS:

Table-1: Materials [4]

Sl. No	Category	Materials	Supplier
1.	Drug	MetoprololSuccinate	InterMed factory, Chennai
2.	Polymers	HPMC(K_4M)	HIMedia Laboratories.Pvt.Ltd.
		PVP(K_{30})	HIMedia Laboratories.Pvt.Ltd
		Gelatin	SDFCL, SdfiNE-CHEM LIMITED, Mumbai
		SodiumAlginate	SDFCL, SdfiNE-CHEM LIMITED, Mumbai
		Urea	Nice Chemicals.Pvt Ltd.
3.	Permeation Enhancers	Sodium lauryl sulpahte	HIMedia Laboratories.Pvt.Ltd
		Tween 80	SDFCL, SdfiNE-CHEM LIMITED, Mumbai
4.	Lubricant and Plasticizer	Glycerin	SDFCL, SdfiNE-CHEM LIMITED, Mumbai
5.	Solvent	Ethanol	Changshu Hongsheng FineChemical Co.,Ltd.

Table-2: Instruments [5]

S.No	Instruments Used	Manufactrers/Source
1.	Electronic Balance(Model-IN-201L)	INFRA DIGI^{TM,} CHENNAI
2	Heating Mantle	AARSON SCIENTIFIC WORKS
3	Magnetic Stirrer	AARSON SCIENTIFIC WORKS
4	Petri Dishes	BOROSIL®
5	U.V Spectrophotometer	LABINDIA Analytical(UV 3000^{+})
6	Hot Air Oven	Ashok united Scientific company
7	Measuring Cylinders (10,100ml)	Aarson^{TM}(AARSON SCIENTIFICWORKS)
8	Beakers (50,100,250ml)	BOROSIL®
9	Pipettes (1,5,10ml)	VENSIL
10	Test tubes	BOROSIL®
11	Spatula	Nsil Labs Glass Works Pvt.Ltd,Hyderabad.
12	Glass Rod	BOROSIL®

Formulation methodology:[6]
Metoprolol Succinate Transdermal Patches were Prepared by

1. Take required quantity of water in a boiling test tube then, add required amount of Sodium Alginate, and mix well under the heat.
2. Now, take a beaker, add the drug (Metoprolol Succinate) in few ml of water with the help of Spatula with constant stirring and pou
3. Add the remaining polymers l i ke Hydroxyl propyl m ethyl cellulose (HPMC), Povidone K30(PVPK30), Gelatin and permeation e
4. Add Plasticizer like Glycerin.
5. Lubricate the Petridish with Glycerin and Pour the above solution into the Petridish.
6. Then, Keep the petridishes containing the solution in Hot Air Oven at 50oc or at room temperature for 24 hours.
7. This Petriplates are allowed to rest until the patches are completely Dried.
8. Peel off the patches from respective petridishes and wrap them with aluminium foil.
9. Finally, Store them in Desiccator for further evaluation studies.

Ingredients	Formulations					
	F1	F2	F3	F4	F5	F6
MetoprololSuccinate	0.45g	0.45g	0.45g	0.45g	0.45g	0.45g
Sodium Alginate	0.7g	0.7g	0.5g	0.7g	0.4g	0.5g
Gelatin	0.7g	0.5g	0.3g	0.7g	2g	0.5g
PVP K_{30}	0.2g	0.2g	0.2g	0.2g	0.15g	0.2g
HPMC K_4M	0.1g	0.1g	0.050g	0.1g	0.1g	0.1g
Sodium Laurylsulphate	0.04g	0.04g	-----	0.04	0.04g	0.04g
Urea	0.2g	0.2g	-----	-----	-----	0.2g
Tween 80	2 Drops	2 Drops	-----	2 Drops	1 drop	3 drops
Glycerin	2 Drops	2 Drops	2 Drops	2Drops	1 drop	3drops
water	40 ml	40 ml	40 ml	40 ml	40 ml	40ml

Preparation of Buffer Solution (Phosphate Buffer, pH-7.4): [7]
Potassium Dihydrogen Phosphate 0.2M: dissolve 6.8g of potassium dihydrogen phosphate in water and dilute with water to 250 ml.

Sodium Hydroxide 0.2M: Dissolve 1.6g of sodium Hydroxide in water and dilute with water to 200ml.

Phosphate Buffer Solution: Place 250ml of 0.2M potassium dihydrogen Phosphate and 195.5ml of0.2M sodium hydroxide in a 1000 ml volumetric flask and make up the volume up to 1000ml.

Preparation of Standard solution of Metoprolol Succinate: A solution of 25mg of Metoprolol Succinate was prepared by dissolving in 100 ml of distilled water from which 4 ml was withdrawn in separate volumetric flask and diluted to 100 ml with phosphate buffer, pH -7.4 to produce 10µg/ml concentration and absorbance at 274 nm.

Preparation of working solution: From Standard solution, 4 ml, 8 ml, 12 ml, 16 ml, 20ml, 24 ml were withdrawn in separate volumetric flasks and diluted to 100 ml with Phosphate buffer, pH-7.4 to produce 10 µg/ml, 20 µg/ml, 30 µg/ml, 40 µg/ml, 50 µg/ml, 60 µg/ml concentrations respectively. The solutions were analyzed by U.V. Spectrophotometer at 274nm and results were recorded, compared with standard. The calibration graph was plotted as concentration on X-Axis v/s absorbance on Y- Axis.

Pre-Formulation Studies [8]
A) Physiochemical evaluation of a drug molecule
• Description
• Solubility
• Melting point

• Hygroscopicity
• Flow properties
1. Bulk density
2. Tapped density
3.Angle of repose
4.Compressibility index (CI) and Hausner's (HR) ratio -

B) Compatibility studies of the drug molecule with Excipients
• Non thermal methods
• Spectroscopic technique i.e., FTIR studies was carried out.

Post- formulation studies of Metoprolol Succinate Transdermal Patches [9]:

1. Weight variation test
2. Drug entrapment efficiency
3. Thickness of the patch
4. Measurement of folding endurance:
5. In vitro diffusion release studies: In vitro drug release study was carried out using a Franz diffusion cell. The effective diffusion area was 2 cm2. The receptor compartment (400 ml) was filled with phosphate buffer, pH 7.4.The patches were applied under occlusion on the dialysis membrane fitted between the donor and receptor compartments of the diffusion cell. The drug release was performed at 37 ± 0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from receptor medium were withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer, pH 7.4. The amount of metoprolol succinate released into the receptor medium was quantified by using UV–visible spectrophotometer at 274 nm against a blank.
6. Kinetic studies: The cumulative amount of Metoprolol Succinate released from the formulated Patches at different time intervals were fitted in to several kinetic models such as Zero order kinetics, First order kinetics, Higuchi model and Korsemayer-peppas model to characterize mechanism of drug release.
7. Stability studies: Metoprolol Succinate and the effect of carriers after storing at different Temperature and Relative Humidity for 15 days stability studies were carried out. About 25mg of equivalent of metoprolol succinate formulation were taken in well closed containers from ideal batches and stored separately at 400C ± 20C/75% RH± 6% (Accelerated testing) and 300C±20C / 60% RH ± 5% (Alternate testing). From these, Samples equivalent to 25 mg of metoprolol Succinate was removed at the interval of 5,10,15 days and analyzed the drug content and diffusion studies Spectro photometrically at 274nm.

RESULTS:

Table-3: Calibration curve of metoprolol succinate

Calibration curve of metoprolol succinate			
S.no.	**Conc.(µg/ml)**	**Absorbance**	**Average Slope**
0	0	0	0.9935
1	10	0.148	
2	20	0.253	
3	30	0.389	
4	40	0.525	
5	50	0.693	
6	60	0.876	

Pre-formulation studies:

Table-4: Physico-chemical Properties

S. No	DESCRIPTION	RESULTS
1.	Colour	White Crystalline Powder
2.	Odour	Odourless
3.	Taste	Bitter

Table-5: Solubility

Raw Material(API)	RESULTS
Metoprolol Succinate	Water:- Freely Soluble Methanol:- soluble Ethanol:- Sparingly Soluble I sopropanol:-Slightly soluble Acetone:- Practically Soluble

Table-6: Melting Point

Raw Material(API)	Melting Point
Metroprolol Succinate	$120^{o}c$

Table-7: Hygroscipicity

Raw Material(API)	Result
Metroptrolol Succinate	Non-Hygroscopicity

Table-8: Flow properties

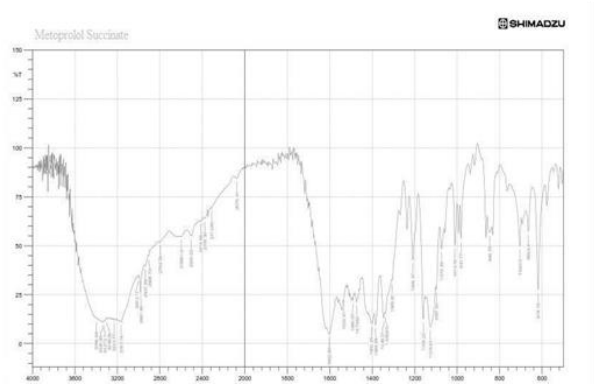
Raw Material(API)	Bulk Density (g/ml)	Tapped Density (g/ml)
Metoprolol Succinate	1.25	1.42

Table-9: Angle of repose, Compressibility Index & Hausner's Ratio:

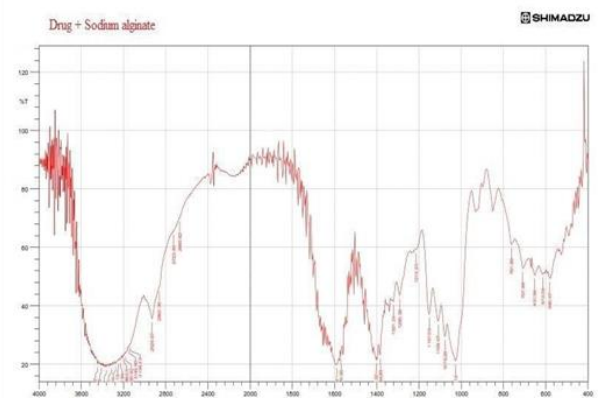
raw material(api)	Angle of repose	CompressibilityIndex	Hausner's Ratio	Flow Property
Metroprolol Succinate	33.42^{o}	11	1.136	Good

FTIR Spectra: Figure-1

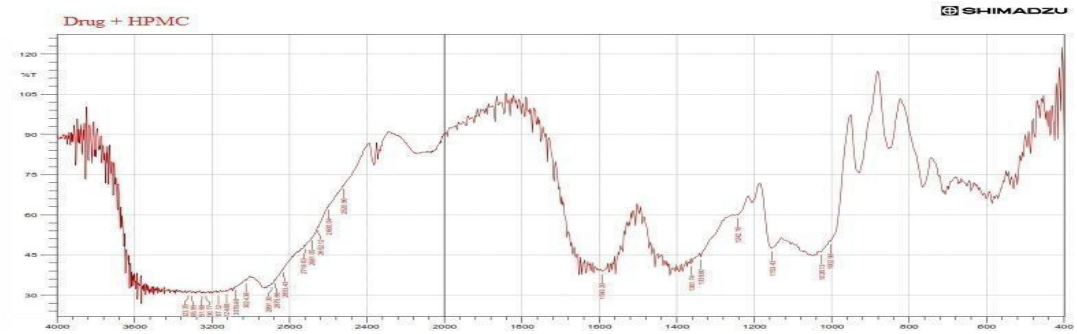
Metoprolol Succinate



Drug+ Sodium alginate



Metoprolol pmc:



Spectrum of pure drug Metoprolol Succinate was compared with spectrum of Metoprolol succinate with excipients. The disappearance or shifting of Metoprolol succinate peak with the following functional groups in any of the spectra studied.

Hydroxy group (O-H between 3650 cm-1 - 3200cm-1)

Amine (2o amine between 3500cm-1 - 3300 cm-1), (1oamine between 1500cm-1-1655cm-1) Amide(C-H between 3300cm-1-2700cm-1), (CH2 CH3 between 1350 cm-1-1470cm-1) Ether(C=O between 1780 cm-1 & 1650 cm-1 and (C-O between 1250cm-1 & 1050 cm-1) Alkene(C=C between 1680cm-1-1600cm-1)

There was no interference to the drug and Excipients and concluded that peaks of Hydroxyl group, Amine, Ether, Amide and alkene lied in the appropriate peak ranges.

It was concluded that ingredients used are compatible with one another in our Compatible studies.

Table-10: Post formulation studies

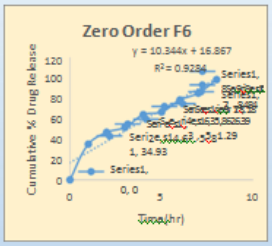
Formulations	Thickness (mm)	Weight variations(mg)	Folding endurance
F1	0.92	89.2	Less than 200
F2	0.95	90.1	Less than 150
F3	0.88	92.3	Less than 100
F4	0.92	94.1	Less than300
F5	0.88	96.5	Less than 250
F6	0.94	97.6	300

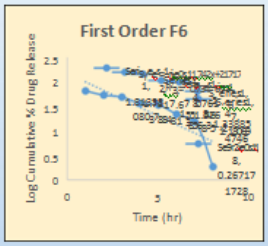
Table-11: % drug release

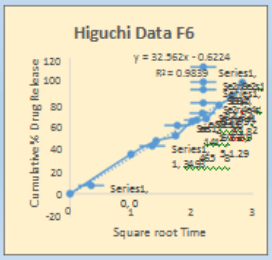
Formulation	Percentage Drug release							
	TIME(HOURS)							
	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr
F1	18.29%	23.29%	28.26%	34.59%	43.73%	54.86%	69.87%	79.85%
F2	19.96%	31.60%	42.94%	48.10%	59.64%	67.98%	86.50%	96.48%
F3	26.61%	29.94%	41.35%	46.51%	58.04%	64.80%	79.85%	91.49%
F4	14.97%	24.95%	35.59%	42.94%	51.29%	61.55%	66.39%	69.87%
F5	48.24%	51.57%	34.15%	62.82%	29.82%	79.52%	83.17%	88.17%
F6	34.93%	46.58%	51.29%	63.82%	66.39%	78.18%	84.84%	98.15%

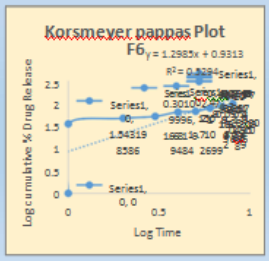
Table-12: Kinetic studies

Zero order		First order		Higuchi Data		Korsmeyer Pappas data	
Time	%CDR Release	Time(h)	Log % CDR Remaining	Sqrttime	% CDR	log time	Log % CDR Release
1	34.93	1	1.813380807	1	34.93	0	1.543198586
2	46.58	2	1.727703884	1.41	46.58	0.301029996	1.668199484
3	51.29	3	1.68761813	1.73	51.29	0.477121255	1.710032699
4	63.82	4	1.558468563	2	63.82	0.602059991	1.8049568
5	66.39	5	1.526468512	2.23	66.39	0.698970004	1.822102669
6	78.18	6	1.338854746	2.44	78.18	0.778151250	1.893095666
7	84.84	7	1.180699201	2.64	84.84	0.845098040	1.92860066
8	98.15	8	0.267171728	2.82	98.15	0.903089987	1.991890304









'n' exponent value of F6 from Korsemeyer-Peppas kinetics studies was found to be 0.64 which is in the limit of Non-Fickian diffusion mechanism.

Table-13: Stability studies

Formulation	Percentage of entrapment efficiency					
	Day intervals					
	5thday		10thday		15thday	
	40°C±75%RH	30°C±60%RH	40°C±75%RH	30°C±60%RH	40°C±75%RH	30°C±60%RH
F1	79.85%	79.82%	79.70%	79.45%	79.36%	78.20%
F2	96.48%	96.40%	96.36%	96.24%	96.18%	95.80%
F3	91.49%	91.45%	91.38%	91.27%	90.56%	90.14%
F4	69.87%	69.79%	69.69%	69.52%	69.36%	68.32%
F5	88.17%	88.09%	88.2%	87.92%	87.88%	86.52%
F6	98.15%	98.13%	98.12%	98.11%	98.10%	97.9%

DISCUSSION:

Totally 6 (n=6) formulations were prepared with Metoprolol Succinate powder equivalent to 25mg of Metoprolol Succinate, prepared separately in a Solvent casting method.

Pre formulation parameters like Bulk density, Tapped density, Angle of repose, Compressibility index and Hausner's ratio indicated all formulations showed good flow properties. [10]

Pre formulation compatibility studies concluded that there was no Excipient - Excipient and Drug-Excipient interaction and concluded that both were physically and chemically stable.

Transdermal patches were prepared and were evaluated for post Formulation parameters like Thickness, Weight variation, Folding endurance, swelling index, Drug Entrapment efficiency and Diffusion parameters.

The release profile of the formulations was compared with standard. Among the formulations, F1 had shown a release of 79.85%, F2 had shown 96.48%, F3-91.49%, F4-69.87%, F5-88.17%and F6-98.15%. Formulation F6 had matched the standard release profile. F6 showed higher drug release of 98.15%. [11]

Different model independent approaches (Zero order, First order, Higuchi and Korsemeyer-Peppas plots) were performed for Diffusion profile comparison of all Transdermal patches. Diffusional exponent 'n' and mechanism of diffusional release from Transdermal patches indicates that the drug release mechanism was found to be Anomalous transport (Non- fickian diffusion). [12]

The Transdermal patches were packed and subjected to stability studies at 400 C and 75% RH and 300 C and 60% RH. Samples were analyzed at regular intervals and found that no significant changes observed in any of the studied parameters during the study period, thus it could be concluded that formulation F6 said to be stable. [13]

From the study, it might be concluded that the Metoprolol Succinate Transdermal patches 25mg can be prepared as release formulations compared to conventional dosage forms to treat Hypertension, CAD, Angina.

CONCLUSION:

The present study was carried out to investigate the Transdermal release of Metoprolol Succinate by Solvent Casting method using different polymers. From the results, it was found the liberation of drug from the formulations. All the Transdermal patches Pre-formulation and Post-formulation patches were found to be within the limits. Among all the formulations, F6 (with Sodium alginate, Gelatin, PVP K30, HPMC K4M, SLS, Urea, Tween 80 and Glycerine) emerged to be the best one, because, it exhibits the maximum percentage drug release of 98.15%. In-vitro kinetics for F6 showed that the drug mechanism was found to be Non-Fickian diffusion.

Finally, It was proven that the Formulation and Evaluation of Metoprolol Succinate by Solvent Casting method was a promising technique to prepare Transdermal patches to treat hypertension, which may increase patient compliance and decreased reactions in GIT. This technique was simple, Cost effective, Stable and easy to scale up.

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