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RESEARCH ARTICLE

Development and Characterization of Transdermal patches of Propanalol Hydrochloride for the prophylaxis of Migraine

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Abstract:

The purpose of the research work to developed to developed transdermal system containing drug propanolol HCl for prophylaxis of migrane with different ratio of polymers like Ethylecellulose (EC) , Polyvinyl Pryrrolidone (PVP) and Polyvinyl alcohol (PVA) by the solvent evaporation technique. The formulated trandermal patches were evaluated with thickness, moisture uptake, tensile strength, percent elongation, folding endurance, drug content and weight variation test. All prepared formulation indicated good physical stability. Invitro permeation study was performed in franz diffusion cell. The formulation Propaderma (PVA:PVP;2:1) showed best in-vitro skin permeation through rat skin (Wister alibino rat) as compare to other formulation. The results followed in kinetic profile. The release profile of formulation F1 (r^2 = 0.990 for higuchi) indicated that the permeation of drug from the patches was governed by a diffusion mechanism. Hence by going through all the results of study one can deduce there is infect a scope for this propanalol transdermal patch in market for patients suffering from migraine.

Key words: Propanolol HCl, transdermal patches, prophylaxis of migrane, in-viro permeation study.

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INTRODUCTION:

Transdermal drug delivery patches have been in the market for over a decade.[1] Transdermal drug delivery system (TDDS) is to delivery of drugs into systemic circulation at a predetermined rate with no or minimal (statistically insignificant) interior intra-patient variation in transdermal absorption (TA).[2] Therefore the rate limiting step in TA is provided by TDDS rather than skin. Several TDDS have been developed and introduced into the market place since introduction of scopolamine in 1981. The early thinking of TDDS providing optimum therapy with no and/or minimal side effects has changed during the last 15 years. One of the main reasons for reasonable success of TDDS is due to patient convenience and compliance.[3-4]

Propanolol HCl hydrochloride is a non-specific beta-adrenergic blocking agent in the my-ocardium, bronchi, and vascular smooth muscle. Propranolol HCl does not have any intrinsic sympathomimetic activity (ISA).[5] additionally; propranolol HCl possesses membrane-stabilizing effects (quinidine-like) affecting the cardiac action potential and direct myocardial depressant effects. Propranolol is well absorbed after oral administration, but a rapid first-pass effect through the liver reduces systemic bioavailability to approximately 2-27%, thereby explaining the significant difference between oral and intravenous dosages.[6]

The objective of the research was to development of novel drug delivery system that is a transdermal patch of Propanalol HCl for the prophylaxis of Migraine. The attempt of this study is to increase patient compliance by decreasing the frequency of dosing. The disease like prophylaxis, patient has to take drug in regular intervals and missing dose leads to lower levels of plasma drug and leading to therapeutic failure. Thus, there is a need of a device which could release the drug in a predetermined rate and maintaining the plasma level inside therapeutic range for a longer period ,and hence it is transdermal system which could release drug in predermined rate and extent thereby decreasing the frequency of dosing and providing a controlled and sustained release via polymer matrix. Another aspect of this study is to produce a transdermal patch which is not significantly irritating to skin as it could directly affect the patient acceptability.

The physicochemical properties of propranolol HCl, its half-life of 3 to 5 hours, and its low molecular weight of 295.81 make it a suitable candidate for administration by the transdermal route.[7]

Material and Method:

Propranolol hydrochloride was obtained as a gift sample from Zydus Cadila (Ahmedabad, India). Ethylecellulose, Polyvinyl Pryrolidone, Polyvinyl alcohol was purchased from Himedia laboratory, Mumbai, India. Propylene glycol and Dimethyl Sulfuoxide was purchased from Rankem RFCL Ltd. (New Delhi). Other chemical was purchased from local Market.

Formulation of drug incorporated transdermal patches.

The matrix type Transdermal Patches containing Propanalol HCL were prepared solvent evaporation method[8] using different ratio of Ethylcellulose, Polyvinyl Pryrolidone, Polyvinyl alcohol. The polymers in different ratio were dissolved in the respective Solvents. Then the drug was added slowly in the polymeric solution and stirred on the magnetic stirrer to obtain a uniform solution and polyethene glycol was used as plasticizers. Solution was clear and homogeneous. Then the solution was poured on the a flat squared shaped aluminium foil coated glass moulds having surface area of 25 cm^2 and dried at the room temperature for 24 hrs for solvent evaporation. Then the patches were cut in square shape. Drug incorporated for each 1x1 cm^2 patch was 14 mg. the formulation table is given in Table 1.

Table 1: Different formulas for formulations

Formulations	Polymer EC:PVP	Polymer PVA:PVP	Plasticizer (in mg) P.E.G - 400	Solvent (10 ml)	Drug (in mg)
PROPADERMA -1	4 : 1	-	120	WATER	350
PROPADERMA -2	3 : 2	-	120	WATER	350
PROPADERMA -3	1 : 1	-	120	WATER	350
PROPADERMA -4	-	2 : 1	120	CHLOROFORM	350
PROPADERMA -5	-	1 : 1	120	CHLOROFORM	350
PROPADERMA -6	-	3 :2	120	CHLOROFORM	350

Evaluations

a. Physical evaluations

1. Thickness[9]

The thickness of films was measured by Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

2. Moisture uptake[10]

The percent moisture absorption test was carried out to check the physical stability and integrity of the films at high humid conditions. In the present study the moisture absorption capacities of the films were determined in the following manner. The films were placed in the dessicator containing saturated solution of aluminium chloride, keeping the humidity inside the dessicator at 79.5 % R.H. After 3 days the films were taken and weighed the percentage moisture absorption of the films was found.

3. Tensile Strength[9,11]

The tensile strength was determined by the apparatus designed as shown in fig-1. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 10mm length and 5mm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2 minutes to calculate formula is give as. {(Weight at break/a.b) x (1+DL/L)},Where a,b,L are thickness, width, and length respectively and DL is change in length.

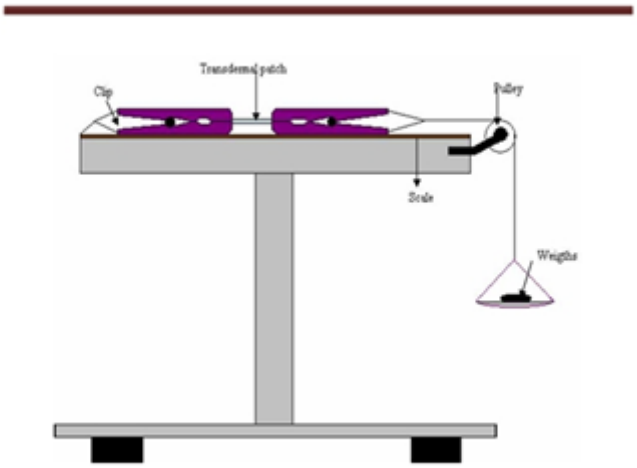

Figure 1: Assembly for % elongation

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4. Percent elongation[12]

The Percentage elongation at break was measured by formula given below.

$$\text{Strain (E)} = \frac{\text{Total elongation}}{\text{Original length}} \times 100 = \frac{L - L_0}{L_0} \times 100$$

5. Folding endurance

A strip of 2cm x2cm ($4cm^2$) was subjected to folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported.[13]

6. Drug content

The patch of total area of $1cm^2$ was cut and dissolved in 100 ml phosphate buffer in 100ml volumetric flask and shaken for 4 hrs in magnetic stirrer. Then 1 ml was withdrawn from the solution and diluted. The absorbance of the solution was taken at 283.6nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.[14]

7. Weight variation

The set of three patches of diameter of 1 $cm^2$was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.[9]

Diffusion-studies[15]

Preparation of skin

A full thickness of skin was excised from dorsal site of dead rat and skin was washed with water. The fatty tissue layer was removed by using nails of fingers. The outer portion with hairs was applied with depilatory and allowed to dry. With the help of wet cotton the hairs were scrubbed and washed with normal saline solution. The skin was kept in normal saline solution in refrigerator until skin was used for diffusion study. Prior to use, the skin was allowed to equilibrate with room temperature. Then skin was mounted between donor and receptor compartment of cell. The skin was clamped in such a way that the dermal side will be in contact with receptor medium.

Diffusion cell

The diffusion studies were done to get an idea of permeation of drug through barrier from the transdermal system. In vitro studies are also done for TDDS development. Usually, two types of diffusion cells are used as horizontal and vertical. The Franz and Keshary Chien (K-C) type of diffusion cells are of horizontal type of cells. In this work, K-C type of diffusion cell was used. Diffusion cells generally comprise two compartments, one containing the active Compartment (donor compartment) and the other containing receptor solution (receptor compartment), separated by barrier i.e. Rat abdominal skin. The cell consisted of sampling port and temperature maintaining jacket. The outlet and inlet was connected with latex tube so the jacket had stagnant water inside and heat was provided by hot plate. The stainless steel pin was used to stir the receptor solution using magnetic stirrer. The rat abdominal skin was placed on receptor compartment and both compartments held tight by clamps.

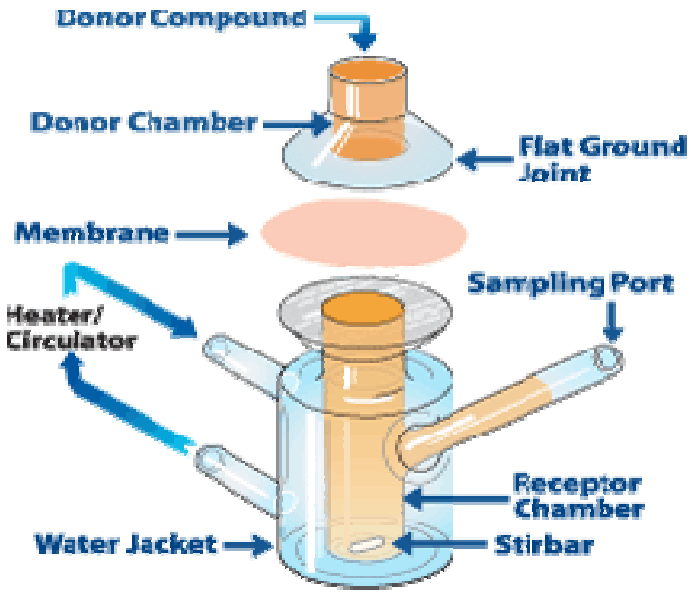

Figure-2: Diffusion Cell.

Method

Phosphate buffer pH 7.4 was used as receptor solution. The volume of diffusion cell was 10 ml and stirred with bent stainless steel pin. The temperature was maintained at 37 ± 1°C with the help of hot plate. The diffusion was carried out for 10 hours and 1 ml sample was withdrawn at an interval of 1 hour. The same volume of phosphate buffer pH 7.4 was added to receptor compartment to maintain sink conditions and the samples were analyzed at 305.5nm. Other designs of diffusion cells that are in existence include Valia-Chien (V-C) cell, Ghannam-Chien (G-C) cell, Jhawer-Lord (J-L) Rotating disc system, etc.

Skin Irritation Studies

Patches were applied to the shaved skin on the side of the back of rabbit and secured using adhesive tape. On other back side of the rabbit, control patch (without drug) was secured in a similar way. The animal was observed for any sign of reteam or edema for a period of 48 hrs.[16]

Kinetic Studies

To know the mechanism of drug release from this formulations, the data were treated according to First order, Higuchi's equation and zero order Patterns.

Results and Discussion:

The matrix type Transdermal Patches containing Propanalol HCL were prepared solvent evaporation method using different ratio of Ethylecellulose, Polyvinyl Pryrrolidone, Polyvinyl alcohol along with the plasticizer PEG 400 (Table 1). Prepared transdermal patches were evaluated for physiochemical properties like stickiness, flexibility, smoothness, folding endurance, weight variation and mechanical properties like thickness uniformity, moisture uptake test, tensile strength, modulus of elasticity and percentage elongation at break, . No amount of constriction in the placebo and medicated transdermal films ensured their 98-100 % flatness. Thus these formulations can maintain a smooth and uniform surface when applied on skin. Results are shown in Table 2 and 3.

Table 2: Physicochemical properties of the prepared Transdermal patches

Formulation code	Stickiness	Flexibility	Smoothness	Folding endurance	Weight(mg) AM±SD
Propaderma -1	Non-Sticky	Flexible	Smooth	130-150	30.12±1.1
Propaderma -2	Non-Sticky	Flexible	Smooth	130-150	32.32±0.6
Propaderma -3	Non-Sticky	Flexible	Smooth	130-150	31.47±1.1
Propaderma -4	Non-Sticky	Flexible	Smooth	130-150	36.12±1.5
Propaderma -5	Non-Sticky	Flexible	Smooth	130-150	34.38±.0.8
Propaderma -6	Non-Sticky	Flexible	Smooth	130-150	33.72±1.2

*n=3 determination

The thickness of the films varied from 0.321±0.032 to 0.351±0.56mm. The values obtained for all the formulations are given in the table 5. The formulation PROPADERMA- 2 (EC: PVP 3:2) showed lowest percent moisture absorption than other formulations. This might be because of the hydrophobic nature of ethyl cellulose polymer. The values for the moisture uptake have been given in the table 5. The tensile strength was found to be in the range of 0.379 to 0.548 the formulation Propaderma - 0.548 showed the best tensile strength. The values for all the patches are tabulated in the table 5. The % elongation was found to be in the range of 73 to 86%. The formulation Prop derma – 5 showed minimum % elongation among all the other patches. The results obtained for all the formulations is tabulated in the table10. The folding endurance was found to be in the range of 130 – 150.The values for all six formulations is given in the table 5. This data revealed that the patches had good mechanical strength along with flexibility. The weight variation was to be in the range of 30.12±1.1 to 36.12±1.5. The drug content was in the range of 90.35 to 95.92 %.

Table 3: Mechanical Properties of Transdermal Patches

Formulation Code	%Moisture Absorption	Thickness (mm)AM±SD	%Elongation	Tensile strength (kg/mm^2)	Percentage Drug content
Propaderma -1	3.26	0.325±0.01	76.3	0.379	90.71
Propaderma-2	3.07	0.334±0.02	84.2	0.456	91.85
Propaderma-3	3.76	0.321±0.03	78.4	0.548	95.92
Propaderma-4	5.18	0.327±0.04	82.1	0.388	94.35
Propaderma-5	4.82	0.338±0.02	73.2	0.493	92.22
Propaderma-6	5.32	0.351±0.05	85.5	0.380	90.35

*n=3 determination

The rat skin was used to carry out the study. The formulation Propaderma4 (PVA:PVP; 2:1) showed drug diffusion for 24 hours was 52.80 % for *in-vitro*, hence best formulation. The % drug diffusion for six formulations is given in the table 4. Where the Formulations {PD-(1-6)} are denoted as Series (1-6).

Table 4(a): In-vitro % drug Release

Time	PD- 1	PD-2	PD-3	PD-4	PD-5	PD-6
0	0	0	0	0	0	0
2	12.54	10.76	9.70	14.45	12.56	10.74
4	15.43	14.31	10.88	18.22	15.78	13.34
6	19.50	17.57	14.75	21.84	19.45	16.41
8	23.32	21.64	18.38	25.97	23.63	19.15
10	29.74	26.80	21.36	30.23	27.28	22.87
12	33.78	32.76	24.95	33.75	32.35	24.97
16	39.43	41.79	31.41	41.28	36.87	30.62
24	47.87	49.65	37.87	52.80	43.27	38.65

Table 4(b): R^2 Value for all Transdermal Patches

Formulation	PD-1	PD-2	PD-3	PD-4	PD-5	PD-6
ZERO ORDER	0.936	0.960	0.952	0.947	0.910	0.942
FIRST ORDER	0.973	0.980	0.967	0.982	0.952	0.968
HIGUCHI MODEL	0.982	0.959	0.973	0.985	0.990	0.988

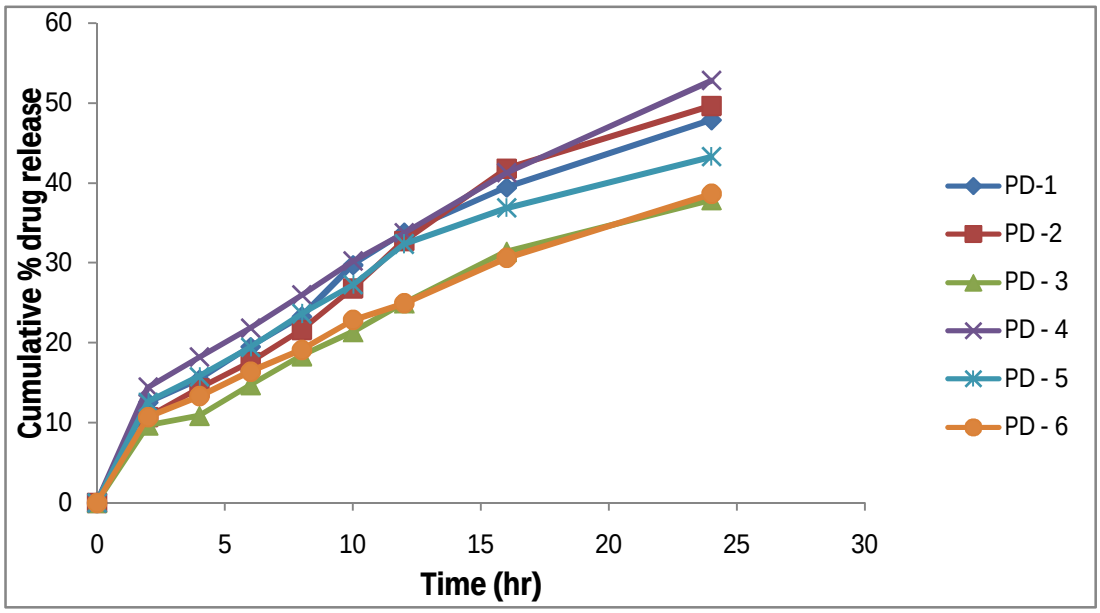

Figure: 17 In -vitro Zero Order Plot

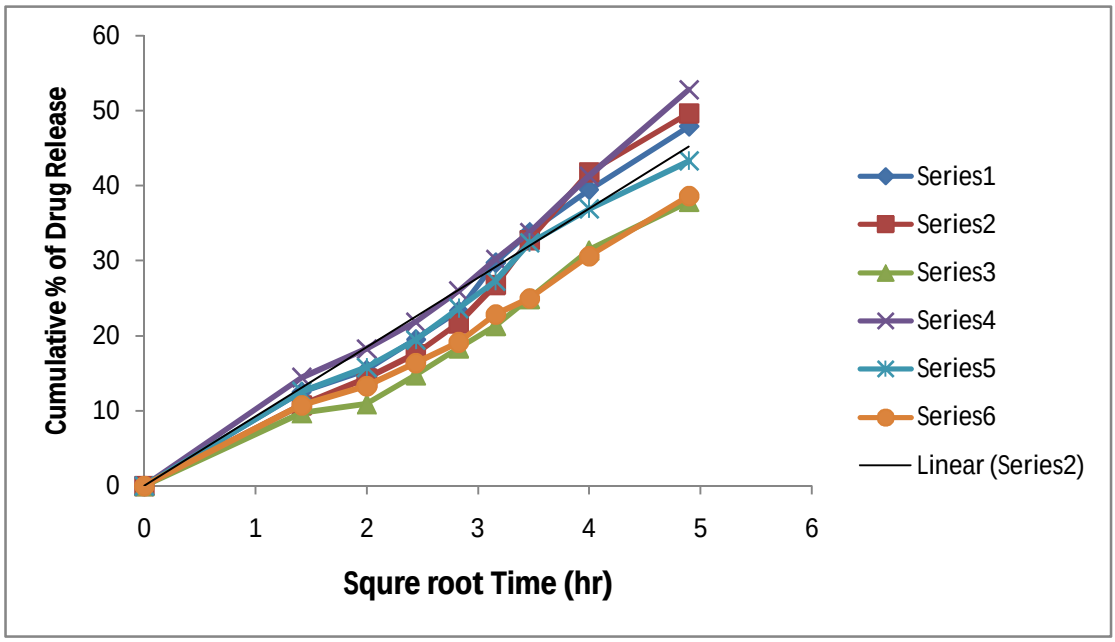

Figure: 18 In-vitro Highuchi Model Plot

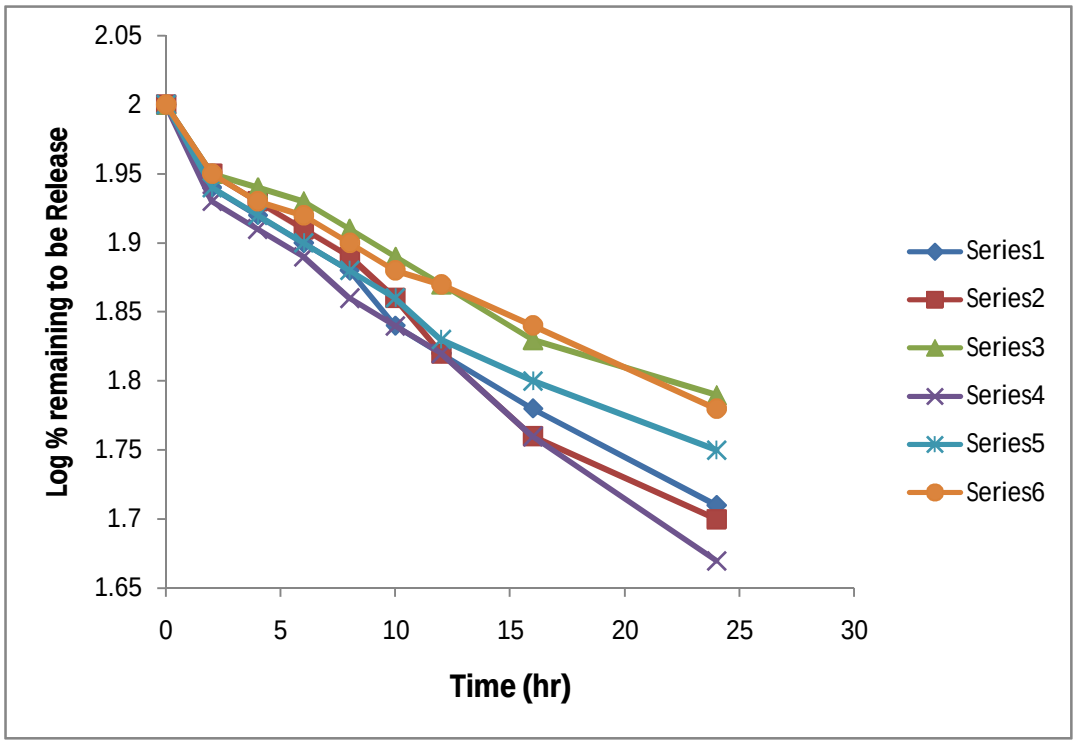

Figure: 19 In-vitro First order Plot

The drug-release mechanism was studied by comparing the respective correlation coefficients for different release models (Table 4 (b). It was observed that the drug release was diffusion controlled in the Transdermal formulation.

The release mechanism was studied by comparing the values of correlation coefficients, and the drug release was found to be controlled by diffusion of drug through the transdermal patches. The Higuchi model was found to be the best fitted for drug release from propanolol HCl transdermal patches formulations.

Conclusion:

This study highlights the formulation and evaluation of transdermal patch of Propanalol for prophylaxis of Migrane. Low molecular weight, good permeability and shorter half-life of made it a suitable drug candidate for the development of transdermal patches. In this work an attempt was made to formulate and evaluate TDDS for sustained release Propanalol HCl by solvent casting method. Characterization, identification of drug, reformulation Studies, formulation and evaluation have been completed and has been discussed in results and discussion.

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