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Formulation and Evaluation of Transdermal Patch of Apremilast

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ABSTRACT: This research aimed to design and assess a transdermal patch for delivering Apremilast.The formulation incorporated Eudragit S100 and HPMC E50 LV as base polymer, with PEG 400 serving as a plasticizer. Preformulation studies revealed no intraction between the drug and excipients, as validated by IR spectroscopy. The linearity curve for UV analysis is also estabilished. A total of nine trial formulation (A1-A9)with different polymer concentrations were developed. These patches were clear,smooth and displayed consistent weight and thickness.Surface ph ranged between 6.8 and 7.1 and drug content, folding endurance and elongation were within acceptable standards. Initially, individual polymer formulations (either HPMC or Eudragit S100) did not achieve the target drug release profile. However the combination of both polymers resulted in improved performance. Among them A8 formulation exhibited optimal drug release and favourable characteristics ,leading to its selection as the optimized batch. Further optimization was conducted using 3^2 factorial design, with HPMC E50 and Eudragit S100 as independent variables while measuring the drug release at 1 hr and folding endurance as dependent variables. The S8 formulation proved to be the most effective, with stability testing affirming its reliability.

KEYWORDS: Transdermal patch, Apremilast

I. INTRODUCTION

The goal of any drug delivery system is to transport a therapeutic dose of medication to the intended site within the body and maintain the necessary drug concentration. Medication can be delivered through the various routes including oral, parentral, nasal, transdermal, rectal, intravaginal and ocular. Among all of them, oral route is most widely used due to its ease and conveniencs. However, it has limitations, such as undergoing first-pass metabolism and degradation in the gastrointestinal tract due to enzymes and ph variations.To overcome these issues, innovative drug delivery systems, particularly controlled release systems, have been developed. These systems use natural or synthetic polymers that interact with the drug, allowing it to be released in a controlled and predictable manner. The introduction of transdermal drug delivery systems (TDDS) marked a significant advancement in controlled drug delivery technology. It becomes a great field of interest.

TDDS are self contained, discrete dosage forms which when applied to the intact skin; deliver the drug, through the skin at control rate to the systemic circulation. The concept of drug absorption through the skin was first proposed by Stoughton in 1965. The U.S.FDA approved the first transdermal patch, Transderm-SCOP, in 1979 for prevention of nausea and vomiting. In Transdermal drug dilevry system (TDDS) the drug is mainly deliverd through the skin using a medicated adhesive patch. This patch adheres to the skin and facilitates the transport of the drug into the bloodstream. Today, Transdermal patches are widely accepted for delivering many drugs to the systemic circulation in order to achieve a desired pharmacological outcome.

The effectiveness of this method is reflected in the approval of over 35 transdermal dryg delivery products in the United States. This products are used to treat a variety of medical conditions, including hypertention, angina, menopause-related symptoms, chronic pain, nicotine addiction, male hormone deficiency and more recently for contraception and manging urinary incontinence.

Transdermal medication delivers a steady infusion of a drug over an extended period of time. Transdermal drug delivey can increase the therapeutic value of many drugs by avoiding specific problems associated with the drug e.g., gastrointestinal irritation, low absorption, decomposition due to hepatic first pass effect, formation of metabolites that cause side effects , short half life necessitating frequent dosing etc.

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Skin As Site For Transdermal Drug Administration

The skin of an average adult body covers a surface area of approximately two square meters and receives about one- third of the blood circulating through the body. Structurally, the skin is a complex, multi layered oragan composed of various histological layers. It is typically divided into three main tissue layers: The Epidermis,

Dermis and Hypodermis (as illustrated in Figure 1.1)

On a microscopic level , the epidermis consists of five sub-layers , with the stratum corneum forming the outer most barrier. This layer directly interfaces with the external environment. Each square centimetre of human skin, on average contains 40-70 hair follicles and 200-250 sweat glands. Despite their abundance, these skin appendages make up only about 0.1 % of skin total surface area.

Even though the foreign agents, especially the water soluble ones , may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendages route of percutaneous absorption has, at steady state, a very limited contribution to the overall kinetic profile of transdermal permeation. The primary mechanism for transdermal drug delivery, especially for neutral molecule, is passive diffusion through the intact stratum corneum in the spaces between follicles.

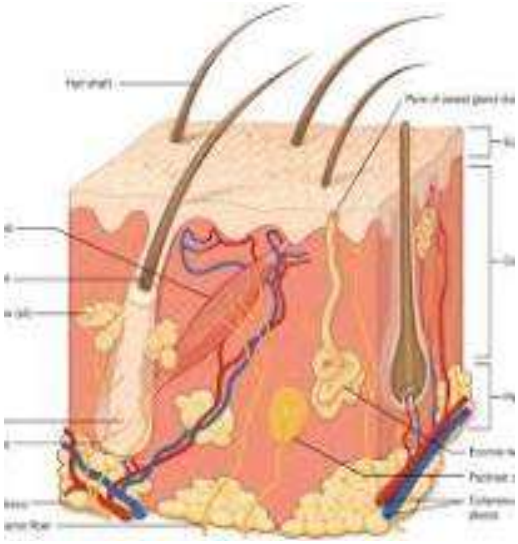

Figure 1.1 Cross section of skin

BASIC COMPONENTS OF TDDS

The component of TDDS include;

1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients

a.) Adhesives
b.) Backing membrane

MATERIALS AND METHOD

Materials

Apremilast pure grade was graciously provided as gift sample from Torrent Research Center, Ahmedabad. HPMC E50, Eudragit S100 polymers obtained from Chemdyes corporation Ahmedabad. Propylene glycol, PEG 400 obtained from Seva fine chemicals , Ahmedabad. All the materials and powders were stored under vaccum at room temperature.

Solubility enhancement of Apremilast

Preparation of Cyclodextrin inclusion complex

Drug with β-CD in different ratio, 1:0.25, 1:0.5, 1:0.75, and 1:1 molar ratio was taken. First cyclodextrin is added to the mortar, small quantity of 50% ethanol is added while triturating to get slurry like consistency. Then slowly drug is incorporated into the slurry and trituration is further continued for one hour. Slurry is then air dried at 25°C for 24 hrs, pulverized and passed through sieve no.100.

Preparation of Transdermal patch by solvent casting method

Polymers in combination were accurately weighed and dissolved in respective solvent and the casted in an anumerated falt bottom petri dish. These blank patches were allowed to dry overnight at room temperature.

The Apremilast patches were formulated using solvent evaporation method, by dissolving weighed quantity of drug in required volume of acetone in a beaker. The selected concentrations of polymers were dissolved in 10 ml of distilled water in another beaker.

To this beaker, add the acetone solution containing drug. Keep the beaker on thermostatically controlled magnetic stirrer which is maintained at 37 ±0.5 °C. The required quantity of plasticizer is added drop wise to the beaker while stirring is continued until the drug is dispersed with polymer. The solution was poured into petri dish; an inverted funnel was placed over the petridish to prevent fast evaporation of the

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solvent and the films were allowed to dry overnight at room temperature.

Then the patches were cut into 2×2 cm^2 and packed in an aluminium foil and stored in desiccators for further use.

Table 1: Formulation table

Ingredient/ patch(mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9
Apremilast Solid dispersioneq.	10	10	10	10	10	10	10	**10**	10
HPMCE50	50	100	150	-	-	-	50	**75**	100
EudragitS100	-	-	-	50	100	150	100	**75**	50
PEG400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	**0.5**	0.5
Acetone(ml)	-	-	-	10	10	10	10	**10**	10
Water(ml)	10	10	10	10	10	10	10	**10**	10

EVALUATION

Appearance

This transdermal patches were visually inspected to assess their overall appearance. Obsevations focused on characteristics such as colour, smoothness, flexibility, tranperancy, and any sign of physical imperfections like cracks or air bubbles. These attributes were recorded to ensure consistency and uniformity across all patches.

Thickness

The thickness of each transdermal patch was measured using a digital vernier calliper, which had a minimum precision of 0.01 mm. Measurements were taken at three separate locations on each patch to ensure uniformity. The average thickness and standard deviation (SD) were calculated to determine the consistency of the film across different areas.

Weight variation

To evaluate the uniformity in weight, square samles (4 cm^2 each) were cut from three different section of the film. The weight of each sample was recorded and the variation in weight among the three was analyzed. This test ensured that the drug was uniformly distributed throughout the film. The weight of each film was taken and weight variation was calculated.

Folding Endurance

Folding endurance was determined by repeated folding of the patch at the same place till the strip breaks. The number of times the patch is folded without breaking was computed as the folding endurance value. This test evaluated how well the patch could withstand repeated folding, thereby indicating the strength of polymer and effectiveness of the plasticizer. Three samples of each patch type were tested to determine an average value.

Surface pH

The surface pH of the transdermal patches was determined to ensure skin compatibility. A small amount of distilled water was used to moisten the patch, and the pH was measured by placing a calibrated pH meter electrode directly onto the surface. Measurements were done in triplicate for accuracy and the average value along with standard deviation was recorded.

Drug Content

Pieces of 2×2 size were cut from each type of formulation and put in 100 ml of phosphate buffered saline pH 7.4 solution. The contents were magnetically stirred for 2 hours. The solution was then filtered through What man filter paper and diluted suitably with phosphate buffer saline pH 7.4. The solution was then analysed for its absorbance at 231 nm using plecbo patch as blank. The determination was carried out in triplicate for all the formulations and average with standard deviation was recorded.

Percentage Elongation

The elasticity of the patch was assessed by determining its percentage elongation. The patch was stretched until it reached its brecking point, and the change in length was recorded. The percentage elongation was calculated using the formula:

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Percentage Elongation= (L1-L2/L1)x 100
Where,
L1 is the final length of each patch
And L2 is the initial length of each patch

In Vitro Diffusion Study

In Vitro Drug Diffusion studies was carried out using the 20 ml Franz diffusion cell. The synthetic membrane was used as a skin. The membrane was stabilized before mounting to remove the soluble components. The membrane was mounted between the donor and receptor compartments. The receptor compartment was filled with 20ml of isotonic phosphate buffer of pH 7.4 which was maintained at 37 ± 0.2^{o}C and hydrodynamics were maintained using magnetic stirrer. One patch of dimension 2cm×2cm was previously moistened with a few drops of pH 7.4 phosphate buffer and placed in donor compartment. 1 ml samples from receptor compartment were withdrawn at suitable time interval of 1, 2, 3, 4, 6 and 8 hours which was then replaced with 1ml of pH 7.4 phosphate buffer. The percentage of drug permeated was determined by measuring the absorbance in UV Visible spectrophotometer at λmax of 231 nm.

Stability study

Stability study was carried out at 40^{0}C/75% RH condition for 1 month. Each piece of the patch from the optimized formulation was packed in butter paper followed by aluminum foil. After 1 month, the patches were evaluated for the physical appearance, drug content and diffusion study.

DRUG EXCIPIENTS COMPATIBILITY STUDY

FTIR Study

FTIR Study of Pure API powder and the final formulation physical mixture was done. The results are attached here. From the below results it can be concluded that no any interaction was found between the selected drug and Excipient used.

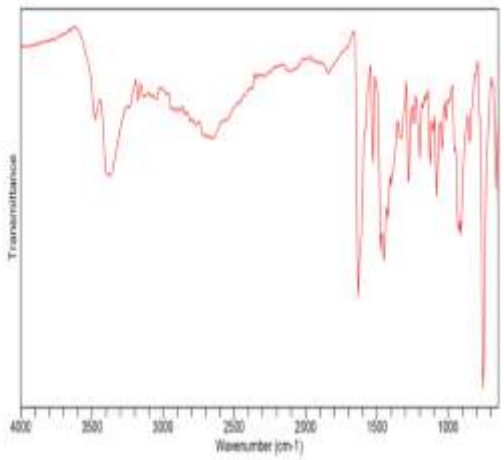

Figure 2: FTIR Spectra of Pure Drug

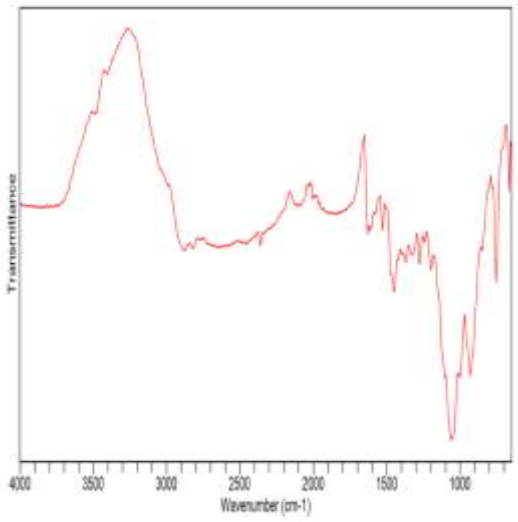

Figure 2.1:FTIR Spectra of physical mixture

Evaluation of Transdermal Patches

Formulation and development of transdermal patches has been initiated to achieve the targeted objectives. The development batches were taken using HPMC E50 and Eudragit S100 as matrix forming polymers. The evaluation parameters were checked and recorded as below;

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Table 2: Evaluation of trial batches of Transdermal patch

Batch	Surface	Transparency	Stickiness
A1	Smooth	Non-Transperent	Non-Sticky
A2			
A3			
A4			
A5			
A6			
A7	Rough		
A8			
A9			

Based on the above weight variation, thickness and surface pH results, it was observed that the all A1-A9 batches were found satisfactory in terms of weight variation test.

Table 2.1 : Evaluation of trial batches of transdermal patch

Batch	Drug Content(%) ± SD	Folding Endurance ±SD	%Elongation
A1	95.2 ± 3.1	59 ± 10	2.6 ± 1.1
A2	96.1 ± 2.5	72 ± 12	3.9 ± 1.4
A3	94.4 ± 3.6	91 ± 14	4.1 ± 1.3
A4	95.5 ± 3.3	102 ± 15	5.6 ± 2.4
A5	94.2 ± 3.9	114 ± 12	6.8 ± 3.2
A6	96.5 ± 1.8	130 ± 16	7.2 ± 2.2
A7	97.9 ± 1.3	149 ± 18	10.3 ± 3.3
A8	98.2 ± 1.1	169 ± 14	12.5 ± 3.9
A9	95.7 ± 2.8	150 ± 13	14.8 ± 4.4

Based on the above results of drug content, folding endurance and % elongation, it was observed that all A1-A9 batches were well within acceptable range of drug content.

The % elongation of all batches was recorded in the above table. Based on % elongation results, it was noted that the elasticity of the film was increased with the increase in amount of polymer.

Folding endurance of the A1 to A9 batches were found satisfactory. Higher the amount of polymer gives the higher value of folding endurance. Polymers in combination gives high folding endurance as compared to single polymer. However, the Eudragit S 100 gives more folding endurance as compared to HPMC polymer.

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Table 2.2 : Evaluation of trial batches of transdermal patch

Batch	Weight variation (mg)±SD	Thickness (mm) ± SD	SurfacepH ± SD	%Moisture Absorption	%Moisture loss
A1	85.2±3.9	0.21 ± 0.05	7.1 ± 0.2	6.7	2.3
A2	134.2±4.1	0.25 ± 0.03	6.9 ± 0.4	6.5	3.1
A3	182.1±4.5	0.31 ± 0.04	7.0 ± 0.3	6.3	2.9
A4	86.1±2.6	0.22 ± 0.09	7.2 ± 0.4	7.1	3.5
A5	135.2±4.8	0.24 ± 0.02	7.1 ± 0.2	7.5	3.8
A6	181.3±3.9	0.30 ± 0.03	7.0 ± 0.2	7.8	4.1
A7	185.2±3.1	0.21 ± 0.06	6.9 ± 0.3	7.2	4.0
A8	187.2±3.6	0.26 ± 0.04	6.9 ± 0.2	7.9	4.6
A9	184.1±3.2	0.32 ± 0.02	6.8 ± 0.4	7.6	4.9

Based on the above weight variation, thickness and surface pH results, it was observed that the all A1-A9 batches were found satisfactory in terms of weight variation test.

The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory.

Further, the surface pH of the patches was found between 6.8 to 7.2 and it is acceptable.

Evalution of drug release

Drug release study of all 9 batches was performed to identify the good polymer and plasticizer combination. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 8 hours.

Hence the combination of these two polymers are taken and found better results than the single polymers.

Among all batches, A8 batch which contains HPMC and Eudragit S100 as matrix polymers and PEG 400 as plasticizer gives more than 90% drug release within 8 hours.

Hence the desired drug release was expected from HPMC and Eudragit S100 polymers combination. The results were recorded in below table and the comparison also showed in below figure.

Table 2.3 : Evaluation of drug release profile of trial batches of transdermal patch

Time (Hrs.)	1	2	3	4	6	8	10	12
A1	8.8	13.5	16.4	21.5	46.8	70.8	89.9	96.9
A2	10.5	14.7	29.8	40.3	61.8	79.9	88.2	97.7
A3	28.5	32.3	50.2	68.0	72.3	81.2	89.4	98.9
A4	30.2	46.7	66.7	75.3	87.5	93.4	96.7	98.2
A5	26.7	50.9	62.9	73.5	81.6	89.3	94.9	97.7
A6	22.8	47.3	59.2	69.6	78.5	86.7	95.2	98.6
A7	18.9	42.1	54.6	65.9	71.2	80.3	91.4	98.5
A8	**21.6**	**45.9**	**58.6**	**68.2**	**73.3**	**85.6**	**92.5**	**99.7**
A9	26.5	48.3	61.3	71.3	77.8	89.3	98.2	98.8

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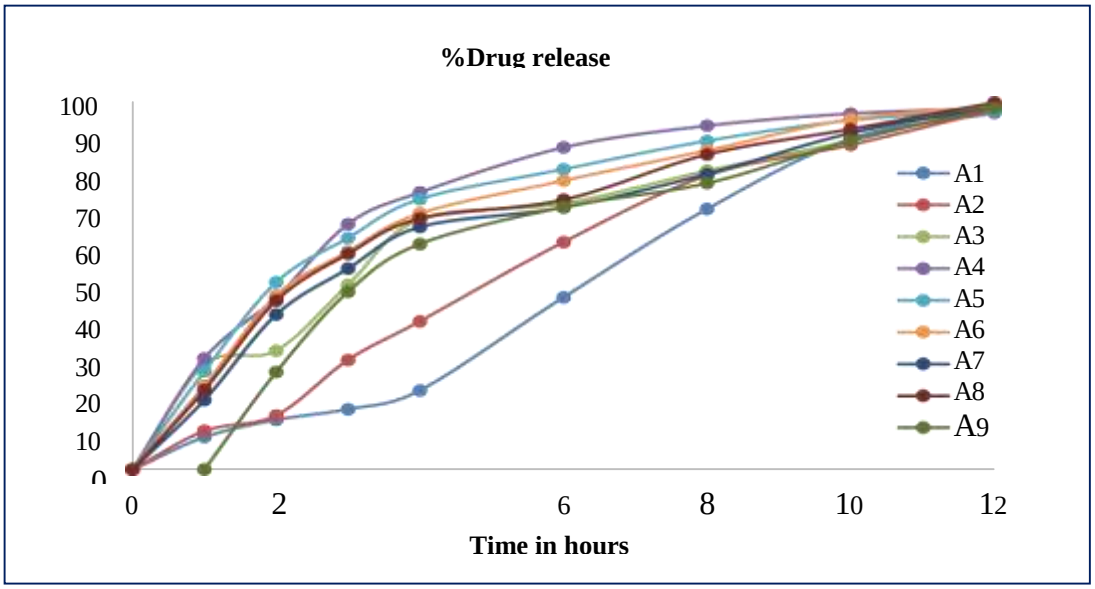

Figure 2 : Dissolution study of A1 to A9 Batches

Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters. Hence, the A8 batch selected as optimized batch and factorial design application initiated.

Stability study

Stability study of final optimized batch S8 performed for 1 month at 40°C and 75% RH. Initial results and after 1-month results compared and found satisfactory. The batch was found stable during stability. The results were recorded in below table.

Table 2.4 Stability study data of batch S8

Parameter	Initial	After 1 Month
Appearance	Smooth,Non-Transparent	Smooth,Non-Transparent
Average Weight (mg)	176 ± 3.1	175 ± 3.6
Thickness(mm)	0.27 ± 0.04	0.27 ± 0.05
Folding Endurance	235 ± 14	231 ± 15
%Drug Content	98.8 ± 1.6	98.6 ± 1.9
%Drug release after 12 hour	99.2 ± 3.5	99.0 ± 3.8

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Evaluation of Cyclodextrin Inclusion Complexes

Phycical appearance

Table 3: Phyicical appearance of different Cyclodextrin Inclusion Complexes

Sr. No.	Ratios	Colour	Odour
1.	1:0.25	White powder	Odourless
2.	1:0.5		
3.	1:0.75		
4.	1:1		

Table 3.1 Drug content of different Cyclodextrin Inclusion Complexes

Sr.No.	Ratios	% Drug content
1.	1:0.25	96.8 ± 0.5
2.	1:0.5	98.2 ± 0.8
3.	1:0.75	95.6 ± 0.9
4.	1:1	97.7± 0.4

Table 3.2 Drug release of Cyclodextrin Inclusion Complexes

Ratio	% Drug Release in min			
	15	30	45	60
Pure Drug	13.4	28.7	32.8	34.6
1:1	14.8	29.7	37.6	48.2
1:1.5	16.7	30.1	39.7	56.9
1:1.75	15.8	31.4	35.7	62.3
1:2	**22.9**	**52.47**	**77.8**	**98.4**

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Above three parameters of Cyclodextrin Inclusion Complexes checked and concluded that in all ratios, white free flowing odourless mixture obtained which have drug content range 95 % - 98%.

Also, the dissolution data shows that compare to pure drug and others ratios, 1:2 ratio of drug and Cyclodextrin Inclusion Complexes give good drug release which one is desirable for our future formulation development.

So, it was concluded that 1:2 ratio of Cyclodextrin Inclusion Complexes was optimized .

Ratio	Solubility(mg/ml)
Pure Drug	0.013
1:1	0.08
1:1.5	0.2
1:1.75	0.6
1:2	**0.9**

II. CONCLUSION

The aim of the present investigation was to develop and evaluate transdermal patch of Apremilast. Formulation development of Apremilast Transdermal patch was initiated using Eudragit S100 and HPMC E50 LV as matrix controlling polymer for matrix type Transdermal Patch. PEG 400 was selected as plastsizer. Preformulation study was performed to check the drug excipient compatibility. The IR spectra of Drug and final formulation found satisfactory. There is no any interaction between drug and excipients. Trials A1-A9 was initiated using different concentration of polymers in the formulation. The prepared patches were transparent and smooth in surface. The weight variation was found well within acceptable range. The thickness of patches was found uniform in nature and the variation is found satisfactory. Further, the surface pH of the patches was found between 6.8 to 7.1 and it is acceptable. The drug content, folding endurance and % elongation results of A1-A9 batches were found well within acceptable range. Initially the trial batches were taken with a single polymer like HPMC and Eudragit S100. The drug release was not achieved as per the target drug release profile for 12 hours. Hence the combination of these two polymers are taken and found better results than the single polymers. Based on the drug release data, it was observed that the A8 batch was the most satisfactory batch with respect to drug release and other parameters.S8 batch found stable during stability study. So A8 batch was our most satisfactory batch according to all the parameters.

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