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Rectal Bioavailability of Delta-9-Tetrahydrocannabinol From Various Esters

MAHMOUD A. ELSOHLY,*‡ THOMAS L. LITTLE, JR.,* AHMED HIKAL,*† ERNEST HARLAND,* DONALD F. STANFORD‡ AND LARRY WALKER*

**Research Institute of Pharmaceutical Sciences and †Department of Pharmaceutics School of Pharmacy, University of Mississippi, University, MS 38677 and ‡ElSohly Laboratories, Incorporated, 1215½ Jackson Avenue, Oxford, MS 38655*

ELSOHLY, M. A., T. L. LITTLE, JR., A. HIKAL, E. HARLAND, D. F. STANFORD AND L. WALKER. *Rectal bioavailability of delta-9-tetrahydrocannabinol from various esters.* PHARMACOL BIOCHEM BEHAV **40**(3) 497–502, 1991.—The bioavailability of delta-9-tetrahydrocannabinol (Δ^9-THC) from suppository formulations containing several polar esters was studied. The esters tested were the hemisuccinate, N-formyl alaninate, N-methyl carbamate, and methoxy acetate. These esters were administered to monkeys in both lipophilic and hydrophilic suppository bases, namely, Witepsol H15 and polyethylene glycol, respectively. Each suppository contained a dose equivalent to 10 mg Δ^9-THC. Blood samples were analyzed for both Δ^9-THC and its carboxylic acid metabolite (11-nor-Δ^9-THC-9-COOH) using gas chromatography/mass spectrometry. The data showed that, with the exception of the hemisuccinate, no Δ^9-THC or its metabolite was detected in the blood samples using the Witepsol H15. Using polyethylene glycol, low levels of Δ^9-THC and its metabolite were detected in blood for all esters tested. The levels, however, were lower than those observed with Δ^9-THC hemisuccinate using Witepsol H15. Subsequent studies in the conscious dog using the hemisuccinate in Witepsol H15 showed 67% bioavailability of Δ^9-THC with a linear response in the dose range equivalent to 5–20 mg of Δ^9-THC. No significant bioavailability differences were found when Δ^9-THC hemisuccinate ester was administered in various lipophilic bases (Hydrokote 25, Kaomel, Suppocire AIML, and Witepsol H15).

Bioavailability of THC THC esters Suppositories

DELTA-9-TETRAHYDROCANNABINOL (Δ^9-THC) has been reported to be effective as an antiemetic agent in patients receiving cancer chemotherapy (7). Several studies have been carried out to establish both safety and antiemetic efficacy of the drug which have been summarized in a recent review (1). The drug has since been approved by the Food and Drug Administration (FDA) for this indication and is currently available under the trade name Marinol. However, the oral absorption of Δ^9-THC was reported (4) to be slow and erratic with low bioavailability value ($6 \pm 3\%$). In addition, it was noted that the absorption of Δ^9-THC from the gastrointestinal tract was influenced by fasting or food deprivation which was found to decrease the rate of absorption of the drug from sesame oil (6).

In an attempt to search for another formulation to effect better bioavailability of Δ^9-THC, Perlin et al. (5) examined its absorption from different suppository formulations and concluded that it would not be absorbed from either lipophilic or hydrophilic bases. However, in a previous communication, we reported 13.5% bioavailability of Δ^9-THC from a suppository formulation containing the prodrug Δ^9-THC-hemisuccinate in monkeys (2). This publication reports on the bioavailability of Δ^9-THC from various polar esters in both monkeys and dogs.

METHOD

Δ^9-THC Esters

The following esters were prepared:

1. Δ^9-THC-hemisuccinate was prepared by reaction of Δ^9-THC with succinic anhydride in pyridine followed by chromatography of the reaction product on silica gel column where the hemisuccinate ester was isolated as a light yellow viscous liquid.
2. Δ^9-THC-hemiglutarate was prepared as previously outlined for the hemisuccinate except that glutaric anhydride was used for the reaction with Δ^9-THC.
3. Δ^9-THC-methoxy acetate was prepared as before except that methoxy acetylchloride was used.
4. Δ^9-THC-N-formyl alaninate was prepared by reaction of Δ^9-THC with N-formyl alanine in dry ether using DCCI as a coupling reagent.
5. Δ^9-THC-N-methyl carbamate was prepared by reaction of Δ^9-THC with N-methyl isocyanate.

The chemical structures of all compounds prepared were verified using both proton NMR and mass spectrometric analysis.

The following compounds were obtained from the National Institute on Drug Abuse, Research Technology Branch, Rock-

TABLE 1

MEAN CONCENTRATION* OF Δ^9-THC AND ITS ACID METABOLITE IN PLASMA FOLLOWING ADMINISTRATION OF DIFFERENT ESTERS IN WITEPSOL H15 SUPPOSITORIES

	Ester (equivalent to 10 mg Δ^9-THC)							
	Hemisuccinate Conc (ng/ml)		N-Formyl Alaninate Conc (ng/ml)		N-Me-Carbamate Conc (ng/ml)		Methoxy Acetate Conc (mg/ml)	
Time (h)	THC	THC-COOH	THC	THC-COOH	THC	THC-COOH	THC	THC-COOH
0	0	0	0	0	0	0	0	0
0.5	15	0	0	0	0	0	0	0
1.0	26	0	0	0	0	0	0	0
2.0	46	9	0	0	0	0	0	0
4.0	10	28	0	0	0	0	0	0
6.0	13	27	0	0	0	0	0	0
8.0	13	22	0	0	0	0	0	0
24.0	14	12	0	0	0	0	0	0

*The data are the mean values from two monkeys. Since there was no evident absorption of the other esters, the experiment was discontinued after two rounds of a randomized 4×4 design.

ville, MD: Δ^9-THC, Δ^9-THC-5′-$^2H_3$, ll-nor-Δ^9-THC-9-COOH, and 11-nor-Δ^9-THC-9-COOH-5′-$^2H_3$

Suppository Preparation

The following suppository bases were used in this study:

1. Witepsol Hl5: A mixture of mono-, di-, and triglycerides of saturated vegetable fatty acids (C_{10}–C_{18}) with a melting range of 33.5–35.5°C, obtained from Huls Petrarch Systems, Bristol, PA.

2. Hydrocote 25: A mixture of the higher-melting fractions of coconut and palm kernel oil with 0.5% lecithene with a melting range of 33.6–36.3°C obtained from Capital City Products Company, Columbus, OH.

3. Kaomel: A fractionated hydrogenated triglycerides mixture with a melting range of 35–38°C, obtained from Durkee Foods, Rockville Center, NY.

4. Suppocire AIML: A eutectic mixture of mono-, di-, and triglycerides from natural vegetable oils with a melting range of 33–35°C, obtained from Gattefosse Corporation, Elmsford, NY.

5. Polyethylene glycol mixture: A mixture of PEG-3350 (25%) and PEG-600 (75%), a commonly used water solvent base obtained from Sigma Chemical Company, St. Louis, MO.

Suppositories were prepared by dispersing the test ester in the molten base followed by pouring the mixture into an aluminum suppository mold. Each suppository (approximately 1.9 g) was made to contain a known amount of the ester equivalent to 10 mg Δ^9-THC. Also suppositories of Δ^9-THC in Witepsol Hl5 were made to contain the equivalent of 5, 10, and 20 mg of Δ^9-THC.

Animal Studies

1. *Monkeys*: Four male cynomolgus monkeys (4.5–5.3 kg) were used in a 4×4 crossover design with a two-week washout period between drug administrations. Animals were fasted over-

TABLE 2

MEAN CONCENTRATION* OF Δ^9-THC AND ITS ACID METABOLITE IN PLASMA FOLLOWING ADMINISTRATION OF DIFFERENT ESTERS IN PEG SUPPOSITORIES

	Ester (equivalent to 10 mg Δ^9-THC)							
	Hemisuccinate Conc (ng/ml)		N-Formyl Alaninate Conc (ng/ml)		N-Me-Carbamate Conc (ng/ml)		Methoxy Acetate Conc (mg/ml)	
Time (h)	THC	THC-COOH	THC	THC-COOH	THC	THC-COOH	THC	THC-COOH
0	0	0	0	0	0	0	0	0
0.5	3	1	1	9	0	0	0	0
1.0	9	3	5	17	1	0	1	0
2.0	6	13	6	22	5	0	3	10
4.0	6	13	3	34	7	0	3	16
6.0	6	9	5	37	10	3	3	14
8.0	2	7	4	40	9	0	2	40
24.0	0	6	0	6	0	0	1	12

*The data are the mean values of three monkeys for each ester. The data corresponding to the fourth monkey were discarded because of apparent gross contamination of the plasma samples.

TABLE 3

MEAN CONCENTRATION* OF Δ^9-THC IN PLASMA FOLLOWING ADMINISTRATION OF THE HEMIGLUTARATE ESTER IV AND IN WITEPSOL H15 SUPPOSITORIES

Time (min)	2.64 mg Ester in 0.5 ml Ethanol IV Conc (ng/ml)	13.2 mg Ester in Witepsol H15 Suppository Conc (ng/ml)
0	0	0
5	614	NT
15	264	NT
30	191	5
60	100	14
90	56	NT
120	36	17
180	24	NT
240	17	13
360	7	10
480	0	8

NT: not tested.

*The data are the mean values of four monkeys for both suppository and IV doses.

night (water ad lib) prior to treatment and were anesthetized with ketamine (10 mg/kg IM). The monkeys were used in studies where the bioavailability of Δ^9-THC from different esters was compared.

2. *Dogs*: Four beagle dogs were used in this study and were allowed access to food and water ad lib and were not anesthetized. The dogs were used in studies comparing the bioavailability of Δ^9-THC from suppositories containing the hemisuccinate ester in various lipophilic bases and studying the correlation between the dose in the suppository and the blood levels of Δ^9-THC.

In all cases, a two-week washout period was allowed between dosing of the animals.

Blood Sampling

Blood samples were collected using heparinized syringes at 5, 10, 15, and 30 minutes and at 1, 2, 4, 6, and 8 hours following IV injections and at 0.5, 1, 2, 4, 6, and 8 hours after suppository dosing. A direct venus puncture was used for blood collection in the monkeys, while a peripheral venus catheter was employed for the dogs. Blood samples were centrifuged and plasma was separated and stored under freezer conditions (less than two weeks) until analysis.

TABLE 4

CONCENTRATION OF Δ^9-THC IN PLASMA FOLLOWING IV ADMINISTRATION OF 2.64 mg OF THE HEMISUCCINATE ESTER IN 0.5 ml ETHANOL IN DOGS

	Concentration (ng/ml)				
Time (min)	Animal 1	Animal 2	Animal 3	Animal 4	Mean
0	0	0	0	0	0
5	264	312	207	293	269
10	190	231	146	171	184
15	145	NA	100	126	124
30	95	111	50	77	83
60	49	61	30	22	41
120	19	27	16	9	18
240	7	7	NA	4	6
360	3	NA	NA	0	2

NA: not analyzed.

TABLE 5

CONCENTRATION OF Δ^9-THC IN PLASMA FOLLOWING ADMINISTRATION OF 13.2 mg HEMISUCCINATE ESTER IN WITEPSOL H15 SUPPOSITORIES IN DOGS

	Concentration (ng/ml)				
Time (h)	Animal 1	Animal 2	Animal 3	Animal 4	Mean
0	0	0	0	0	0
0.5	118	189	68	94	117
1.0	152	115	120	94	120
2.0	131	120	89	60	100
4.0	71	76	55	37	60
6.0	34	50	52	42	45
8.0	24	42	37	34	34

Gas Chromatographic/mass Spectrometric Analysis of Plasma Samples

To 1.0 ml plasma in a 12 × 75 mm culture tube was added 2 ml of acetonitrile containing 100 ng/ml of Δ^9-THC-5'-$^2H_3$ (used as internal standard). The tube was vortexed for 30 seconds and then centrifuged for 5 minutes. The supernatant was transferred to a 13 × 100 mm culture tube, and the solvent was evaporated to approximately 1 ml under nitrogen at 55°C. The volume was then adjusted to 1 ml with distilled water. One milliliter of 2 N NaOH was added to each tube, and the tubes were placed in a 55°C water bath for 15 minutes. To each tube was added 3 ml of hexane:ethyl acetate (9:1). Each tube was vortexed for 2 minutes. The organic (top) layer was transferred to a 12 × 75 mm culture tube and the solvent evaporated. The residue containing Δ^9-THC and the internal standard was derivatized for GC/MS analysis as follows: To the residue in each tube was added 0.05 ml of N-(*tert*-butyldimethylsilyl)-N-methyl trifluoroacetamide (TBDMS). The tubes were stoppered and placed in an oven at 70°C for 15 minutes. The reagent was then evaporated under nitrogen at 55°C, the residue was dissolved in 0.02 ml of iso-octane, and one μl was injected into the GC/MS system.

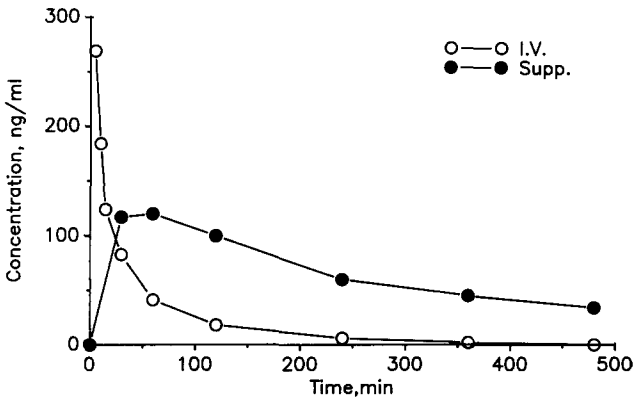

FIG. 1. Plasma concentration of Δ^9-THC vs. time curves following administration of Δ^9-THC-hemisuccinate IV (2.64 mg in 0.5 ml ethanol) or in suppository form (13.2 mg per suppository in Witepsol H15 base).

TABLE 6

BIOAVAILABILITY OF Δ^9-THC HEMISUCCINATE FROM DIFFERENT LIPOPHILIC SUPPOSITORY BASES IN DOGS

	Percent Bioavailability			
Animal No.	Witepsol H15	Hydrokote 25	Kaomel	Suppocire AIML
1	63.1	73.6	50.6	60.2
2	90.8	68.2	72.6	85.9
3	41.8	59.3	66.6	58.3
4	47.8	6.5*	41.4	26.8
Mean % Bioavailability				
	60.9 (±21.9)	51.9 (±30.8)	57.8 (±14.3)	57.8 (±24.2)

*There was indication that this dog expelled part of the suppository. Should the data from the animal be discarded, the mean bioavailability from Hydrocote 25 would be 67% (±7.2).

GC/MS analysis was carried out using a Hewlett Packard 5970B mass selective detector interfaced to an HP-5890 GC fitted with a 10 M × 0.18 mm DB-1 column (0.4 μ film). Injection was made in the splitless mode (30-s delay) with a column temperature programmed at 200°C (1 min) − 250°C at 20°/min. Ions at *m/z* 371 and 428 were monitored for Δ^9-THC and 374 and 431 *m/z* for the internal standard (TBDMS derivatives). Quantitation was based on ions at *m/z* 371 and 374. Calibration curves were prepared from 10 to 80 ng/ml Δ^9-THC in plasma.

For plasma samples where the analysis of Δ^9-THC acid metabolite was carried out, the basic aqueous layer following extraction of Δ^9-THC was used to extract the acid metabolite according to the procedure previously reported (2). In this case, 11-nor-Δ^9-THC-9-COOH-5′-$^2H_3$ was used as internal standard and was added to the initial acetonitrile solution.

Treatment of Data

Plasma concentrations were plotted vs time. Area under the curves $(AUC)_{0-8}$ from time zero to 8 hours was calculated using the trapezoidal rule (3). Bioavailability was calculated from the IV and suppository data and adjusted for the dose levels in both routes. IV data were fitted into a two-compartment model using PC NONLIN, and the estimated apparent volume of distribution was used to estimate the concentration at time zero (C_0) which was used in the calculations of the area under the curve.

TABLE 7

BIOAVAILABILITY OF Δ^9-THC FROM RECTAL SUPPOSITORIES CONTAINING THE HEMISUCCINATE ESTER IN WITEPSOL (5 mg EQUIVALENT DOSE)

	Concentration of Δ^9-THC in Plasma (ng/ml)				
Time	Dog No. 1 (Bk)	Dog No. 2 (R)	Dog No. 3 (G)	Dog No. 4 (B)	Mean
30 min	14	14	8	9	11
1 h	41	26	21	18	27
2 h	24	15	15	18	18
4 h	22	17	9	12	15
6 h	14	7	12	9	11
8 h	8	4	10	9	8

TABLE 8

BIOAVAILABILITY OF Δ^9-THC FROM RECTAL SUPPOSITORIES CONTAINING THE HEMISUCCINATE ESTER IN WITEPSOL (10 mg EQUIVALENT DOSE)

	Concentration of Δ^9-THC in Plasma (ng/ml)				
Time	Dog No. 1 (Bk)	Dog No. 2 (R)	Dog No. 3 (G)	Dog No. 4 (B)	Mean
30 min	73	ND	60	46	60
1 h	139	110	ND	87	112
2 h	104	97	153	ND	118
4 h	82	38	80	63	66
6 h	69	32	83	ND	61
8 h	52	ND	101	ND	77

ND: not analyzed.

RESULTS AND DISCUSSION

In a previous publication we reported that Δ^9-THC could be made bioavailable from suppository formulation when introduced in the form of its hemisuccinate ester (2). This study was designed to investigate the bioavailability of Δ^9-THC from suppository formulations containing other polar esters of the drug. The esters examined were the methoxy acetate, the N-formyl alaninate, the N-methyl carbamate, and the hemiglutarate. In a 4×4 crossover design, the bioavailability of the hemisuccinate ester was compared to that of the methoxy acetate, N-formyl alaninate, and N-methyl carbamate when all esters were administered in a lipophilic base (Witepsol H15) and also in a hydrophilic base (polyethylene glycol) in the monkey. There was no measurable Δ^9-THC or its acid metabolite from esters other than the hemisuccinate when administered in a lipophilic base (Table 1). On the other hand, when the esters were administered in a hydrophilic base (Table 2), there was significant bioavailability from the N-formyl alaninate and to a lesser degree from N-methyl carbamate and methoxy acetate. The Δ^9-THC blood levels, however, were not as high as those seen following the administration of the hemisuccinate in a lipophilic base. The low blood levels of Δ^9-THC and its metabolite following administration of the hemisuccinate in polyethylene glycol suppositories was partially attributed to the hydrolysis of the hemisuccinate ester in this hydrophilic base. The data shown in Tables 1 and 2, there-

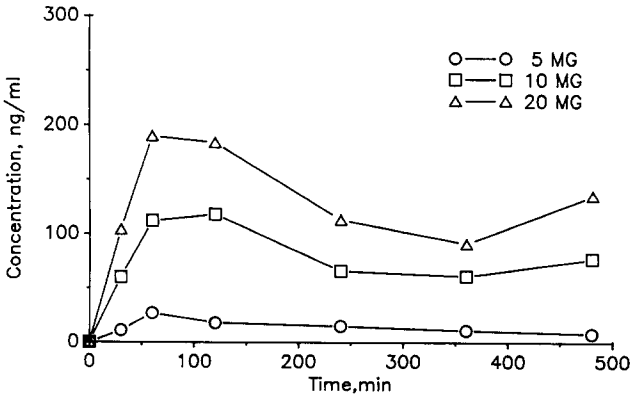

FIG. 2. Plasma Δ^9-THC concentration vs. time curves following the administration of Δ^9-THC-hemisuccinate in doses equivalent to 5, 10, and 15 mg of Δ^9-THC in Witepsol H15 suppositories.

TABLE 9

BIOAVAILABILITY OF Δ^9-THC FROM RECTAL SUPPOSITORIES CONTAINING THE HEMISUCCINATE ESTER IN WITEPSOL (20 mg EQUIVALENT DOSE)

	Concentration of Δ^9-THC in Plasma (ng/ml)				
Time	Dog No. 1 (Bk)	Dog No. 2 (R)	Dog No. 3 (G)	Dog No. 4 (B)	Mean
30 min	188	48	77	103	104
1 h	184	51	358	165	190
2 h	148	78	177	332	184
4 h	109	59	133	149	113
6 h	76	85	111	ND	91
8 h	171	99	115	154	135

ND: not analyzed.

fore, suggested that among the four esters studied, Δ^9-THC-hemisuccinate showed the highest blood levels of Δ^9-THC when administered in Witepsol H15. Since the hemisuccinate ester has a terminal carboxylic acid group, other esters with the same function, such as the hemiglutarate ester, were investigated to study the effect of the length of the ester side chain on the bioavailability of Δ^9-THC. Δ^9-THC-hemiglutarate was prepared and was administered to monkeys, both as an IV solution and in the form of suppositories in Witepsol H15 base, to determine the bioavailability of Δ^9-THC from this formulation. Table 3 shows the mean concentration of Δ^9-THC in plasma following the administration of the hemiglutarate ester by both routes. The data show that, although the hemiglutarate ester resulted in reasonable blood levels of Δ^9-THC, the levels were not as high as those seen with the hemisuccinate ester. The bioavailability of Δ^9-THC from the hemiglutarate ester was approximately 7% compared to 13.5% from the hemisuccinate ester in the same formulation.

These data suggested that the best ester to effect bioavailability of Δ^9-THC from a suppository formulation is the hemisuccinate ester from a lipophilic base. However, the overall low bioavailability noticed with the monkeys could be attributed to one or both of the following reasons: 1) the fact that the monkeys had to be anesthetized during the study which might have affected the rectal absorption process by some unknown mechanism, and 2) the fact that in many cases the suppositories might have been partially expelled since there has always been an indication of leakage around the anal area. Therefore, it was determined to proceed with the study using beagle dogs which were trained to accept the insertion of a suppository and collection of blood samples in the conscious state.

Bioavailability of Δ^9-THC From the Hemisuccinate Ester Suppositories in Dogs

Four dogs were administered Δ^9-THC-hemisuccinate IV (2.64 mg in 0.5 ml ethanol per dog) and in Witepsol H15 suppositories (13.2 mg per suppository per dog). Tables 4 and 5 show the plasma Δ^9-THC concentration data from individual dogs in the IV and suppository studies respectively, while Fig. 1 shows the Δ^9-THC concentration vs. time curve using the mean blood levels from both studies. Based on these data, the bioavailability of Δ^9-THC from suppositories containing the hemisuccinate ester in Witepsol H15 was calculated to be 67.3% using the trapezoidal rule.

Bioavailability of Δ^9-THC From the Hemisuccinate Ester Administered in Different Lipophilic Bases

In order to select the most efficient base in effecting bioavailability of Δ^9-THC from suppository formulations containing the hemisuccinate ester, four lipophilic bases, including Witepsol H15, were studied in dogs. In a 4×4 crossover design, the dogs received 13.2 mg of Δ^9-THC-hemisuccinate (equivalent to 10 mg Δ^9-THC) in one of the following suppository bases: Witepsol H15, Kaomel, Suppocire AIML, and Hydrokote 25. Table 6 shows the calculated bioavailability of Δ^9-THC for the individual animals from the above-mentioned bases. The mean percent bioavailability was calculated for each base and was found to range from 52–61% among all bases. It must be mentioned that the relatively low bioavailability observed with Hydrokote 25 (52%) could be explained as a result of expulsion of part of the suppository by one of the dogs. Should the data from this dog be discarded, the bioavailability calculated based on three dogs would be 67%.

Effect of the Dose of Δ^9-THC-Hemisuccinate on the Δ^9-THC Blood Levels

Since Witepsol H15 was used as the base in several studies, and since there was no significant difference in bioavailability from various lipophilic bases, a study was initiated to determine the effect of the Δ^9-THC-hemisuccinate dose in suppository on blood levels of Δ^9-THC. The dogs were administered suppositories containing the hemisuccinate ester equivalent to 5, 10, and 20 mg Δ^9-THC per suppository. Tables 7–9 show the Δ^9-THC plasma levels for the individual dogs for different dose levels while Fig. 2 shows the Δ^9-THC plasma concentrations vs time curves for the three dose levels. It is evident that the blood levels of Δ^9-THC are dependent on the dose of the hemisuccinate ester in the suppository.

CONCLUSION

It is concluded from these studies that rectal administration of Δ^9-THC-hemisuccinate in lipophilic suppository bases results in high bioavailability of the parent drug Δ^9-THC and that blood levels are dependent on the dose of the ester in the suppository. Since there was no significant difference in bioavailability from various lipophilic bases, the most appropriate base to be selected for a final product would be the one which results in the highest stability of the final product. Work is in progress to ascertain the stability of Δ^9-THC-hemisuccinate in various lipophilic suppository bases.

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