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Formulation and Evaluation of Fexofenadine HCL Oral Dispersable Tablets

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***Abstract*: Fexofenadine chloride is an anti-histamine drug used in the treatment of hayfever and allergies symptoms. its oral absorption is 33% and having 14.4 hrs of half-life and belongs to BCS class II drug., a favourable formulation which can enhance solubility and dissolution rate of this model drug may help effectively in the treatment of bacterial infections. Efficiency and bioavailability of poorly soluble drug Fexofenadine HCL through solid dispersion technique using HP Beta cyclodextrine and beta cyclodextrine. the evaluation parameters and method of preparation of physical mixtures and solid dispertions of Fexofenadine HCL by solvent evaporation was explained. Charecterization in solid state was done by various analytical techniques such as FT-IR studies.**

***Keywords*: Solid dispersion, Hydriphillic carrier, FT-IR, Spectroscopy, HP beta cyclodextrine.**

1. Introduction

Solid dispersion (SD) is one of such methods and it involves a dispersion of one or more active ingredients in an inner carrier or matrix in solid state prepared by melting, dissolution in solvent or melting solvent method.

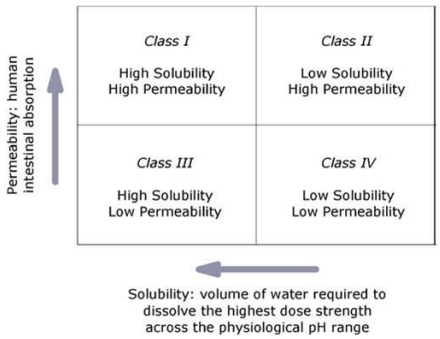


Fig. 1. Biopharmaceutical classification system chart

Noyesh- Whitney equation provides some hints as to how the dissolution rate of even very poorly soluble compounds might be improved to minimize the limitations to oral Availability[2].

$$\frac{dc}{dt} = \frac{AD(Cs - c)}{h}$$

Where,

dC/dt - is the rate of dissolution,

A - is the surface area available for dissolution,

D - is the diffusion coefficient of the compound,

Cs- is the solubility of the compound in the dissolution medium,

C - is the concentration of drug in the medium at time t and

h - is the thickness of the diffusion boundary layer adjacent to the surface of the dissolving compound.

To increase the dissolution rate from equation the following approaches are available.

- To increases the surface area available for dissolution Decreasing the particle size of drug.
- Optimizing the wetting characteristics of compound surface.
- To decrease the boundary layer thickness.
- Ensure sink condition for dissolution.
- Improve apparent solubility of drug under physiologically relevant conditions.

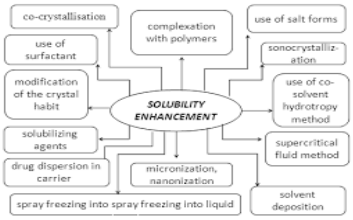


Fig. 2. Summarizes the various formulation and chemical approaches that can be taken to improve the solubility or to increase the available surface area for dissolution

The solid dispersion (SD) technique has often proved to be the most successful in improving the dissolution and bioavailability of poorly soluble drugs because it is simple, economic, and advantageous.

A. Classification of solid dispersion

Based on their molecular arrangement, six different types of solid dispersions can be distinguished.

1. Eutectic mixtures
2. Amorphous precipitation in crystalline matrix
3. Solid solution
4. Continuous solid solutions
5. Discontinuous solid solutions
6. Subsitutional solid dispersions

B. Methods of preparation of solid dispersions

Various methods used for preparation of solid dispersion system. These methods are given below:

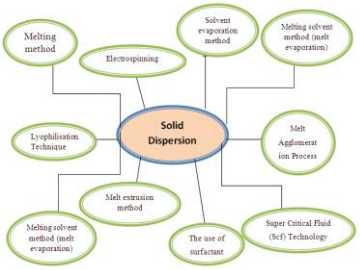


Fig. 3. Schematic representation of various methods of solid dispersions

1. kneading method
2. Solvent evaporation method
3. Melting solvent method (melt evaporation)
4. Melt extrusion methods
5. Lyophilization techniques
6. Melt agglomerations Process
7. The use of surfactant
8. Electrospinning
9. Super Critical Fluid (SCF) technology

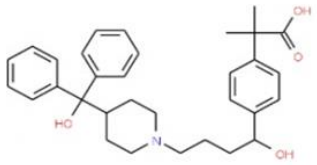
2. Drug Profile

A. Drug

Fexofenadinehydrochloride

Fexofenadine hydrochloride (Allegra) is an antihistamine drug used in the treatment of hayfever and similar allergy symptoms. It was developed as a successor of an alternative to terfenadine. Fexofenadine, like other second and third-generation antihistamines, does not readily pass through the blood-brain barrier, and so causes less drowsiness than first-generation histamine-receptor antagonists.

Structure:



Application: A metabolite of ofterfenadine, a H1-Histamine receptor antagonist

CAS Number: 83799-24-0

Molecular Weight: 501.66

Molecular Formula: $C_{32}H_{39}NO_4$

Appearance: Powder

Physical State: Solid

Solubility: Soluble in Methanol

Storage: Store at -20° C

Melting Point: 193-196° C

IUPAC Name

2-(4-{1-hydroxy-4-[4-(hydroxydiphenylmethyl)piperidin-1-yl]butyl}phenyl)-2-methylpropanoic acid.

Pharmacology

Indication: For management of Seasonal allergic rhinitis

Pharmacodynamics:

Fexofenadine is a second-generation, long lasting H1-receptor antagonist (antihistamine) which has a selective and peripheral H1-antagonist action.

Mechanism of action

Like other H1-blockers, Fexofenadine competes with free histamine for binding at H1-receptors in the GI tract, large blood vessels, and bronchial smooth muscle.

Protein binding: 60%-70%

Metabolism: Approximately 5% of the total dose is metabolized, by cytochrome P450 3A4 and by intestinal microflora.

Half-life: 14.4 hours

Toxicity: Side effects include dizziness, drowsiness, and dry mouth.

B. Polymer profile

HP β-Cyclodextrins

Chemical Names:

HYDROXYPROPYLbeta-CYCLODEXTRIN;2-Hydroxypropy-.beta.-cyclodextrin;2-Hydroxypropylether-b-cyclodextrin; AKOS015901120; AN-13194 More...

Molecular Formula: C54H102O39

Molecular Weight: 1375.371 g/mol

β–Cyclodextrin

Synonyms: β-Cyclodextrin, β-Cycloamylose,β-Dextrin, Cycloheptaamylose; Cycloheptaglucan, Cyclomaltoheptose.

Nonproprietary names BP: Betadex PhEur: Betadexum USPNF: Betadex

Chemical name and CAS registry number: β-Cyclodextrin [7585-39-9]

Empirical formula and molecular weight: β-Cyclodextrin C42H70O35= 1135

3. Methodology

Material

Table 1
List of chemicals used

SN o.	Materials	Manufacturer
1.	FEXOFENADINE HCL	DR. REDDYS
2.	HP β Cyclodextrin	S.D FINE CHEMICALS
3.	β Cyclodextrin	S.D FINE CHEMICALS
4.	Methanol	S.D FINE CHEMICALS

A. Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance.

Definition: It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients.

Objective: Overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms.

The following preformulation studies were carried out for Fexofenadine,

a) Determination of melting point of Fexofenadine HCL
b) Solubility studies
c) Drug– excipient compatibility studies

Experimental Methods:

Preparation of solid dispersions of fexofenadine HCL:

There are several carriers, which have been reported for the preparation of solid dispersions by using β Cyclodextrin, HP β Cyclodextrin using solvent evaporation method.

a. Solvent evaporation method:

In solvent evaporation method, the drug and carriers were mixed in 1:0.25, and 1:0.5 ratios in Methanol. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100. And now the obtained product was collected and stored in desiccators.

Formulation code	Drug: polymer	Drug : polymer ratio
F1	Fexofenadine HCL: HP β Cyclodextrin	1:0.25
F2		1:0.5
F3	Fexofenadine HCL: β Cyclodextrin	1:0.25
F4		1:0.5

Evaluation of Solid Dispersions:

Prepared polymer drug conjugates were evaluated by

1) Estimation of drug content
2) Entrapment efficiency
3) *In- vitro* dissolution studies

Kinetics of drug release

The mechanism of drug release for the Fexofenadine HCL solid dispersions was determined using zero order and first order.

The results of in vitro release profile obtained for all the formulations were plotted in modes of data treatment as follows:

1. Zero – order kinetic model – Cumulative % drug released versus time.
2. First – order kinetic model – Log cumulative percent drug remaining versus time.

Formulation of fexofenadine HCL tablets:

Equivalent weight of Fexofenadine HCL was added with suitable excipients and the tablets were formulated by direct compression according to the formulae given in the table

All the ingredients were passed through # 60 mesh sieve separately.

	F1	F2	F3	F4	F5	F6
Fexofenadine HCL(mg)	30	30	30	30	30	30
Lycoat(mg)	3	5	7	-	-	-
SSG (mg)	-	-	-	3	5	7
Aspartame(mg)	60	60	60	60	60	60
MCC(mg)	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Magnesium Stearate(%)	3	3	3	3	3	3
Talc(%)	3	3	3	3	3	3
TOTAL(mg)	150	150	150	150	150	150

Precompression Parameters

Method Preparation of Mixed Blend of Drug and Excipients

All the materials were passed through sieve no. 80. Required quantity of each ingredient was taken for each specified formulation (Mentioned in Table) and all the ingredients were subjected to grinding to a required degree of fineness (except magnesium stearate and talc). The powdered blend was evaluated for flow properties as follows.

Angle of repose

Angle of repose is determined by using funnel method.

$\theta = \tan^{-1} (h / r)$

Bulk density

$$D_b = \frac{M}{Vo}$$

Where, M is the mass of powder, V0 is the bulk volume of the powder

Tapped density

$$D_T = \frac{M}{Vt}$$

Where, M is the mass of powder, V_T is the tapped volume of the powder

Compressibility index

Carr'sIndex(I)=(TappedDensityBulkDensity)/(TappedDenity) x100

Hausner's Ratio

Hausner's ratio is an indirect index of ease of powder

$$\text{Hausner's Ratio} = \frac{\text{BulkDensity}}{\text{Tapped Density}}$$

Where D_t is tapped density and D_b is bulk density

Evaluation of tablets

Post compression parameters

Weight variation test

Tablet hardness

Tablet friability

% Friability = [(W1-W2)100]/W1

Where, W1= Weight of tablet before test, W2 = Weight of tablet after test.

In-Vitro Disintegration time

Thickness and Diameter

Drug content uniformity

Dissolution studies

4. Results and Discussion

A. *Preformulation studies*

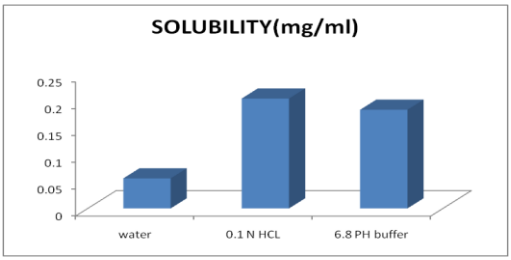
Determination of melting point

The melting point of Fexofenadine HCL was found to be 193-196° C which was determined by capillary method.

Solubility

Solubility of Fexofenadine HCL was carried out at 25^{0}C using 0.1 N HCL, 6.8 phosphate buffer, and purified water.

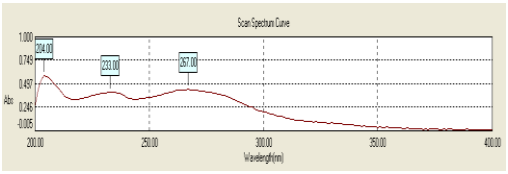
S.No.	Medium	Solubility(mg/ml)
1	water	0.056
2	0.1 N HCL	0.205
3	6.8 PH buffer	0.184



Solubility studies of Fexofenadine HCL

Analytical method development by U.V. Spectroscopy:

UV Scan Spectrum of Fexofenadine HCL



Calibration curve data of Fexofenadine HCL

Concentration(µg/ml)	Absorbance
0	0
100	0.131
200	0.236
300	0.342
400	0.456
500	0.575
600	0.674

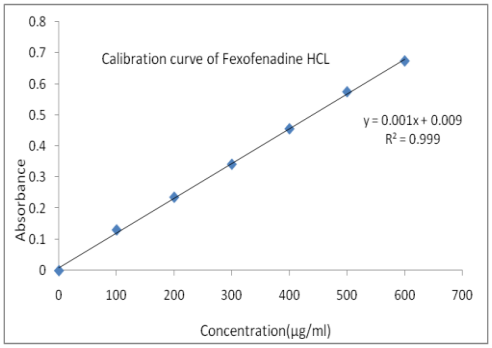


Fig. Calibration curve of Fexofenadine HCL

Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of pure drug with that of various excipients used in the formulation.

Form. code	Entrapment efficiency
SF1	73.21
SF2	78.52
SF3	88.75
SF4	96.75

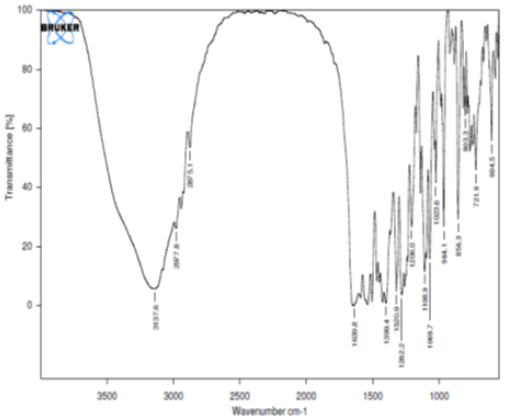


Fig. IR spectrum of Fexofenadine HCL Optimised Formulation

Discussion: Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug (Fexofenadine HCL) and optimized formulation (Fexofenadine HCL: excipients) which indicates there are no physical changes.

Drug content uniformity for solid dispersions by solvent evaporation method

Table
Drug content uniformity for solid dispersions by solvent evaporation method

Form.code	%drug content
SF1	69.64
SF2	76.21
SF3	85.82
SF4	89.76

Discussion: % drug content values of all the formulation (SF1-SF4) were in the range of 69.64-89.72.

Table
Entrapment efficiency of solid dispersions by solvent evaporation method

Form. code	Entrapment efficiency
SF1	73.21
SF2	78.52
SF3	88.75
SF4	96.75

Discussion: The entrapment efficacy of the formulated solid dispersions was found to be in the range of 73.21-96.75%respectively.

Invitro drug release studies of solid dispersions
Solvent Evaporation Method
Invitro drug release studies for formulations (SF1-SF4)

S. No.	Time (Min)		Percentage drug release		
		1:0.25 (SF1)	1:0.5 (SF2)	1:0.25 (SF3)	1:0.5 (SF4)
0	0	0	0	0	0
1	15	32.78	35.12	37.26	42.86
2	30	39.92	39.98	41.22	56.85
3	45	47.36	49.82	52.82	63.28
4	60	56.28	58.22	61.21	72.48
5	75	64.86	74.86	78.36	80.21
6	90	74.16	78.21	81.16	88.96

Discussion: which shows at the end of 90 mins the formulation SF1 releases 74.16, formulation SF2 releases 78.21, formulation SF3 releases 81.16, formulation SF4 releases 88.96%.

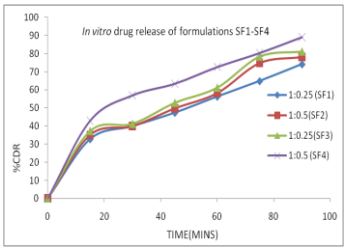


Fig. *Invitro* drug release profile for drug: H P β Cyclodextrin(SF1-SF2) & β Cyclodextrin (SF3-SF4)

B. *Evaluation of tablets*

Discussion:

The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

C. *Post Compression parameters*

All the batches of tablet formulations were characterized for official evaluation parameters like Weight variation, Hardness, Friability, Tablet thickness and drug content and results are shown in the table.

Discussion:

Hardness of the tablet was acceptable and uniform from batch to batch variation, which was found to be 3.68 – 4.28 kg/cm^2.All the formulations passed the weight variation test as the % weight variation was within the pharmacopoeial limits of the tablet weight. Friability values were found to be less than 1% in all the formulations F1 – F6 and considered to be satisfactory ensuring that all the formulations are mechanically stable

Drug content uniformity of formulations:

The prepared formulations were analysed for drug content and the data is reported in below Table. The drug content was found to be within the limits which show that the drug was uniformly distributed in all the formulations.

Table
Drug content uniformity of formulations F1-F6

Tablet formulation	% of drug content
F1	95.96
F2	97.65
F3	99.62
F4	98.02
F5	98.71
F6	98.16

Discussion: % drug content values of formulation F1 is 95.96%, F2 is 97.65 %, F3 is 99.62 %, F4 is 98.02%, F5 is 98.71%, F6 is 98.16%. The drug content values for all the formulations (F1-F6) was found to be in the range of 95.96-99.62%

Dissolution studies of the tablets:

The prepared tablets were subjected to dissolution studies in order to know the amount drug release. As the concentration of polymer increased, the drug release decreased.

Table
Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Bulk density	Tapped density (mean±SD)	Angle of repose	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±1.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±1.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±1.96	1.18±0.05

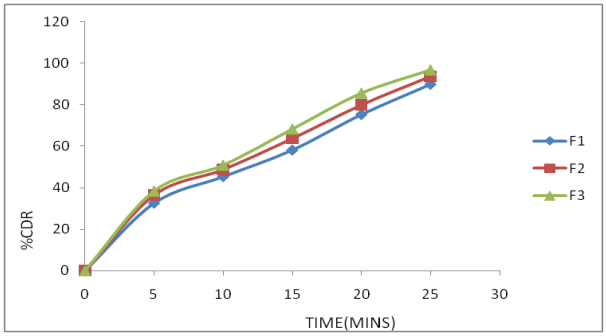
Table
Characterization Fexofenadine HCL tablets

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kp)	Friability (%)	Disintegrating time(sec)
F1	151.2±0.02	3.4±0.02	3.6±0.01	0.68±0.02	32.18±0.02
F2	149.3±0.06	3.5±0.04	4.2±0.03	0.62±0.06	31.16±0.05
F3	148.4±0.07	3.7±0.06	3.5±0.02	0.79±0.08	30.36±0.06
F4	151.6±0.04	3.4±0.01	3.9±0.01	0.65±0.02	32.08±0.08
F5	149.2±0.03	3.2±0.01	3.7±0.01	0.59±0.08	34.29±0.02
F6	149.8±0.02	3.5±0.02	4.1±0.06	0.48±0.06	32.12±0.07

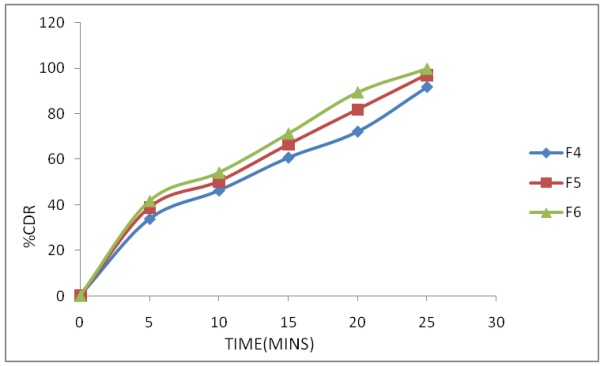
Table
% Cumulative drug release of formulations F1-F6

Time (Min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	33.81	38.77	41.65	32.54	36.41	38.38
10	46.29	50.28	54.17	45.30	48.71	50.85
15	60.80	66.48	71.31	58.12	63.64	68.23
20	72.25	81.85	89.46	75.23	79.84	85.53
30	91.87	97.17	99.82	89.78	93.59	96.74

In vitro drug release of F1-F3



In vitro drug release of F4-F6



Drug release kinetics:
Zero order plot of (F6):

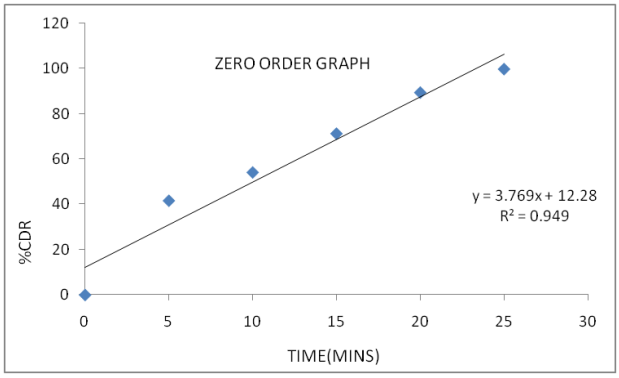
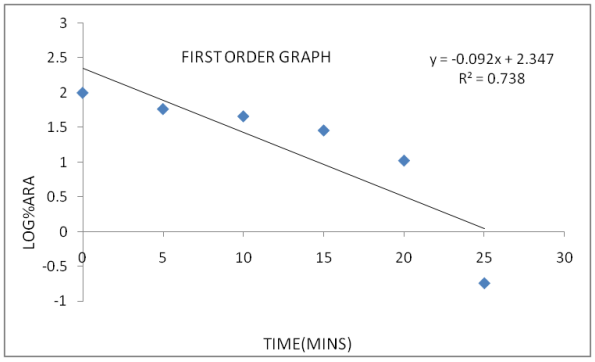


Table
Order of kinetic values of Formulation F3

order of kinetics	Zero Order	First Order
Regression values	0.949	0.738

First order plot of (F6):



Discussion:

The drug release from the tablets was explained by using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation F6 follows Zero order kinetics

5. Conclusion

Dispersions were evaluated and results was explained in above mentioned data.

The following conclusions were drawn from the present investigations.

- From the Solubility studies in various buffers we can say that 0.1 N HCL solution has more solubility when compared to other buffer solutions for Fexofenadine HCL.
- The melting point of Fexofenadine HCL was found to be 193-196° C which was determined by capillary method.
- Form the drug excipient compatibility studies we observe that there are no interactions between the pure drug and optimized formulation (drug + excipients) which indicates there are no physical changes.
- All the formulations of Fexofenadine HCL were prepared solvent evaporation and method.
- All the prepared solid dispersions were evaluated for drug content and entrapment efficiency.
- The invitro dissolution studies of Fexofenadine HCL was performed.
- From the optimized formulation of the solid dispersions (i.e., SF4) weight equivalent of Fexofenadine HCL was used along with the superd is integrants like SSG and Lycoat.
- Pre compession and Post compression evaluation studies were performed.
- The better drug relase with lycoat(7mg) with 99.82% of drug release at the end of 25mins.
- Drug release kinetics of the optimized formulation shows zero order drug release.

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