Original Research Article

Factorial analysis of the binding properties of acetylated ginger starch in metronidazole tablet formulations

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Abstract

Introduction: The delivery of drug is often affected by formulation processes and the excipients used in the formulation.

Materials and Methods: A 2^3 factorial analysis was used in this study to evaluate the effect of acetylated ginger starch (AGS) (*Zingiber officinale*) as a binder in metronidazole tablets, in comparison to corn starch (CS) BP. The individual and interacting effects of variables (binder type X_1, binder concentration X_2, and compression pressure X_3) used on tablet properties such as friability, crushing strength, crushing strength friability ratio (CSFR), disintegration and crushing strength friability/disintegration time ratio (CSFR/DT) were determined. The effect of these binders on the granule properties using Hausner's ratio, Carr's index (CI), angle of repose, and densities as response parameters was also determined.

Results: Granules prepared with AGS had high densities and small granule sizes when compared with those containing CS. Granules containing CS have better flow properties. X_1 (binder type) has a significant effect on the crushing strength of the tablet. It also had the highest effects on CSFR and CSFR/DT. The combination of X_1X_3 had the highest effect on crushing strength and DT.

Conclusion: This study shows that, in formulations, care must be taken in choosing the excipients and the process parameters required for the formulation since these can affect the delivery of the drug individually or in combination. AGS could be useful as a binder when a tablet with low crushing strength and fast disintegration is desired.

Keywords: Acetylated ginger starch, binder, factorial analysis, metronidazole, tablet

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INTRODUCTION

Drug delivery is the method by which a pharmaceutical compound is administered to humans or animals to achieve a therapeutic response.[1] Different formulation variables such as excipients and formulation methods or parameters have been shown to affect the delivery of drugs.[2,3] Excipients can be obtained from natural sources such as starch,[4] gums,[5] and cellulose.[6]

Starch is one of the most widely used excipients in pharmaceutical formulations because of its versatility, abundance, biodegradable nature, and relatively nontoxic property. In addition to these, starch can be modified relatively easily to improve its functionality in drug formulations. Such modifications include gelatinization,[7] acetylation,[8,9] and acid modification.[10] Modification of starches has been shown to improve their solubility,

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viscosity, shear strength, and rate at which drugs are released from them.

In this study, metronidazole was chosen as the drug because of its poor compressional property. It requires excipients such as binder to improve its compressional properties. Acetylated ginger starch (AGS) was evaluated as a binder in metronidazole tablet formulation using 2^3 factorial analysis.

MATERIALS AND METHODS

Materials

The materials used were metronidazole BP (Medical export Co., Ltd., England), corn starch (CS) BP, magnesium stearate (Loba Chemie PVT Ltd., Mumbai, India), and lactose (Ind-Swift Labs Ltd, Parwanoo, India). Ginger starch obtained from *Zingiber officinale* rhizomes was purchased from a local market in Ibadan, Nigeria. All the other materials used were of analytical grades.

Methods

Extraction of ginger starch

Rhizomes of ginger (*Z. officinale)* were washed with water, peeled, and weighed. The peeled ginger was washed with distilled water and reduced to smaller pieces using a local blending mill. The ground ginger mass was soaked with enough quantity of water and left for about 5–6 h. This was then washed thoroughly with water onto a clean muslin cloth into a collecting vessel to release the starch granules. The content of the collecting vessel was allowed to settle for some hours and the water was decanted. This was repeated for the next 2 days ensuring that water was changed each day. After the 3rd day, the settled starch was scrapped off and placed on a clean tray to dry in the oven at about 60–70°C. The dried starch was milled by triturating in a mortar.

Acetylation of ginger starch

The method described by Sodhi and Singh[11] was used to prepare the AGS. Exactly 35 g of ginger starch was weighed into a beaker containing 100 mL of distilled water; the slurry formed was constantly stirred for about 30 min. The slurry was adjusted to pH 8.0 with NaOH. After adjusting the pH, 1.2 g of acetic anhydride was added and the reaction was allowed to proceed for another 5 min. The slurry was adjusted to pH 4.5 with 0.5M HCl, filtered through No. 1 Whatman filter paper. The residue was washed for four times with distilled water for complete removal of acid that may be present in it. The residue was air-dried at room temperature.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) spectrum of the ginger starch was recorded with a Perkin Elmer RXI spectrophotometer (Connecticut, USA). The dry starch powder was mixed with potassium bromide (KBr) and pressed into pellets. The spectrum was obtained by scanning between 4000 and 500/cm. This was done for native and acetylated starch.

Preparation of metronidazole granules

About 200 g of the basic formulation containing metronidazole (60% w/w), CS (10% w/w), and lactose (30% w/w) was dry mixed for 5 min in a planetary mixer (model A 120, Hobart Manufacturing Co., UK) and moistened with water or appropriate amount of cornstarch mucilage or AGS mucilage (1%–5% w/v) to produce granules containing different concentrations of the binders [Table 1]. Massing was continued for 5 min, and the wet masses were granulated by passing them through a 1.4-mm mesh sieve. The sieved mass was then dried in a hot air oven at 60°C for 3 h after which it was re-sieved through a 1.0-mm mesh sieve.

Granule size distribution

The granule size was determined by sieve analysis method. The sieves were arranged in descending order of aperture size with the receiver at the bottom of the stack. About 100 g of granules was weighed into the upper sieve and covered. The sieves were stacked on a sieve shaker and shaken for 5 min after which granules retained on each sieve were carefully weighed.

Determination of bulk density

Exactly 20 g of each granulation was weighed into a 100 mL measuring cylinder. The cylinder was then tapped 3 times on a horizontal surface, and the volume occupied by the granules was read to the nearest 0.5 mL. Bulk density was recorded in g/mL and calculated as follows.

$$\text{Bulk density} = \frac{\text{Weight in grams}}{\text{Volume in mL}}$$

The procedure was done in triplicate.

Determination of tapped density

About 20 g of each granulation was weighed and transferred into a 100 mL measuring cylinder. The cylinder was tapped 100 times on a horizontal surface, and the

Table 1: Formula for formulations

	Composition				
	0	1	2	3	5
Metronidazole (%)	60	60	60	60	60
CS (%)	10	10	10	10	10
Lactose (%)	30	29	28	27	25
Binder (%)	0	1	2	3	5

CS: Corn starch

volume occupied by the granules was recorded. Tapped density was calculated as follows:

$$\text{Tapped density} = \frac{\text{Weight in grams}}{\text{Volume in mL}}$$

The procedure was done in triplicate.

The percentage compressibility was calculated from the following relationship:

$$\%\ \text{compressibility} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Hausner's ratio (HR) was calculated from the following relationship:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Determination of particle density

The particle density of the granules was determined by the liquid pycnometer method using xylene as the displacement fluid. An empty 50 mL pycnometer bottle was weighed (w), and then filled to overflowing with xylene and the excess xylene was wiped off. The bottle with the xylene was weighed again (w_1). A 2 g weight of the sample was weighed (w_3) and quantitatively transferred into the pycnometer bottle. The excess xylene was wiped off and the bottle was weighed again (w_4). The particle density was calculated from the following equation:

$$Pt = w_2\, w_3/50\ (w_3 - w_4 + w_2 + w)$$

w_2 is the weight of xylene alone, i.e., $w_1 - w$

Determination of flow rate

A cylindrical funnel with a large stem was clamped to a retort stand. About 20 g of granules was weighed and allowed to flow through the funnel. The time taken for the granules to flow through the funnel was recorded. The determinations were done in triplicates and repeated for each batch.

$$\text{Flow rate} = \frac{\text{Massof granules}(g)}{\text{Time taken}\ (s)}$$

Determination of angle of repose

A funnel was attached to a retort stand, at a height of about 2.3 cm from the tile on the horizontal surface. The dry granules from each granulation batch were passed through the funnel and a heap was formed. The height and the radius of the heap were determined. The procedure was determined in triplicates.

Angle of repose (tan ø) = H/r

Where, H = Height of the heap

r = Radius of the heap

Compression of metronidazole granules

About 500 mg metronidazole compacts were produced using a hydraulic press (Carver laboratory press Inc., USA) machine fitted with 10.5-mm flat-faced punches at varying predetermined pressures. The punches and die were lubricated with a 1% w/v magnesium stearate dispersed in acetone. After compressing the tablets, their weights and thickness were determined to within ±1 mg and ± 0.01 mm, respectively, and stored over silica gel for 24 h to prevent false values.

Evaluation of tablet properties

Uniformity of weight

Twenty tablets were selected randomly from each batch and weighed individually on a Mettler Toledo electronic balance (Zurich, Switzerland). The average weight was calculated to determine the weight uniformity.

Determination of tablet hardness

Five tablets from each batch were selected, the crushing strength of the tablets was determined by placing each tablet between the anvil of the tablet tester, and the force required to break the tablets into two was recorded.

Determination of tablet friability

Twenty tablets from each batch were weighed and placed in the tablet compartment of a friabilator (DBK friability test apparatus) and rotated at 25 rpm for 4 min. Friability was calculated as the percent weight loss as in the following equation:

$$\text{Friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

Determinations were done in triplicates.

Determination of tablet disintegration time

The British Pharmacopoeia[12] method was used. Five tablets per batch were selected and placed in the disintegration test apparatus (DBK tablet disintegration test apparatus) with discs. The disintegration medium was distilled water maintained at a temperature of 37°C ± 0.5°C. The time taken for each tablet to disintegrate was recorded and the average was calculated.

Factorial analysis

2^3 factorial analysis was carried out using Minitab®17. The independent process parameters such as binder type, binder concentration, and compression pressure as well as the levels at which they were used are shown in Table 2.

Table 2: Granule properties

Binder	Concentration of binder (%w/w)	Bulk density (g/ml)	Tapped density (g/ml)	CI (%)	HR	Particle density	Angle of repose (°)	Flow rate (g/s)	Granule size (μm)
Control	0.0	0.472±0.0	0.531±0.0	11.03±1.3	1.12±0.0	1.522±0.0	44.76±0.5	2.64±0.1	700
CS	1.00	0.425±0.0	0.465±0.0	8.60±0.0	1.09±0.0	1.477±0.0	45.66±0.3	2.11±0.1	640
	2.00	0.476±0.0	0.504±0.0	5.54±0.5	1.06±0.0	1.434±0.1	46.22±0.8	1.86±0.0	718
	3.00	0.433±0.0	0.492±0.0	11.99±0.6	1.14±0.0	1.515±0.0	44.24±0.5	2.57±0.1	520
	5.00	0.423±0.0	0.462±0.0	8.44±0.6	1.09±0.0	1.532±0.0	44.42±1.1	2.09±0.3	319
AGS	1.00	0.421±0.0	0.563±0.0	25.22±5.2	1.34±0.1	1.547±0.0	45.62±1.1	1.87±0.3	460
	2.00	0.462±0.0	0.678±0.1	31.85±7.3	1.47±0.2	1.543±0.0	47.37±1.1	3.48±0.2	270
	3.00	0.414±0.0	0.519±0.0	20.03±4.9	1.25±0.1	1.511±0.0	45.75±1.6	1.34±0.3	580
	5.00	0.469±0.0	0.667±0.0	29.68±2.8	1.42±0.1	1.431±0.0	45.72±0.4	1.04±0.1	210

CI: Carr's index, HR: Hausner's ratio, CS: Corn starch, AGS: Acetylated ginger starch

Statistical analysis

Student's *t*-test at 95% confidence interval with $P \leq 0.05$ was used to compare the effects of the various parameters on the response factors.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

The FTIR of native and AGS is shown in Figure 1a and b. With acetylation, the peak at 1602/cm shifted to a more intense peak at 1645/cm (stretching c = o). The peak 1012/cm also shifted to a more intense peak at 1023/cm which could be related to the amorphous form of starch.[13] New peaks were observed at 1451/cm and 858/cm. The absence of peak between 1850 and 1760 shows that acetic anhydride is absent in the product.[14] This shows that the starch was fully washed of unreacted acetic anhydride which may serve as an impurity in the starch.

Granule properties

Four common methods of testing powder flow are compressibility index (CI) or HR, angle of repose, flow through an orifice, and shear cell.[15] The granule properties of AGS and CS are shown in Table 2. There was a significant difference between the bulk and tapped densities of AGS granules which led to high Carr's index/CI and HR value. CI is a measure of bridge strength and stability, and HR is a measure of interparticulate friction.[16] The CI for AGS granules was 20.03–31.85 while HR was 1.25–1.47. These values are between fair-to-poor range on the scale while the CI and HR values for CS granules ranged between excellent and good.[15] Angle of repose is not an intrinsic property of the powder since the method used to form the cone affects the value. The angle of repose for all the granulations was 44.24–47.37 [Table 2], which is between passable and poor. Particle size and density have been shown to affect the flow properties of powders.[17] Large particle size and high density have been reported to result in improved granule flow.[18] CS with higher granule sizes has better flow when compared with AGS. The particle density of granulations containing AGS was higher than those with CS at low concentrations (1%–2% w/w).

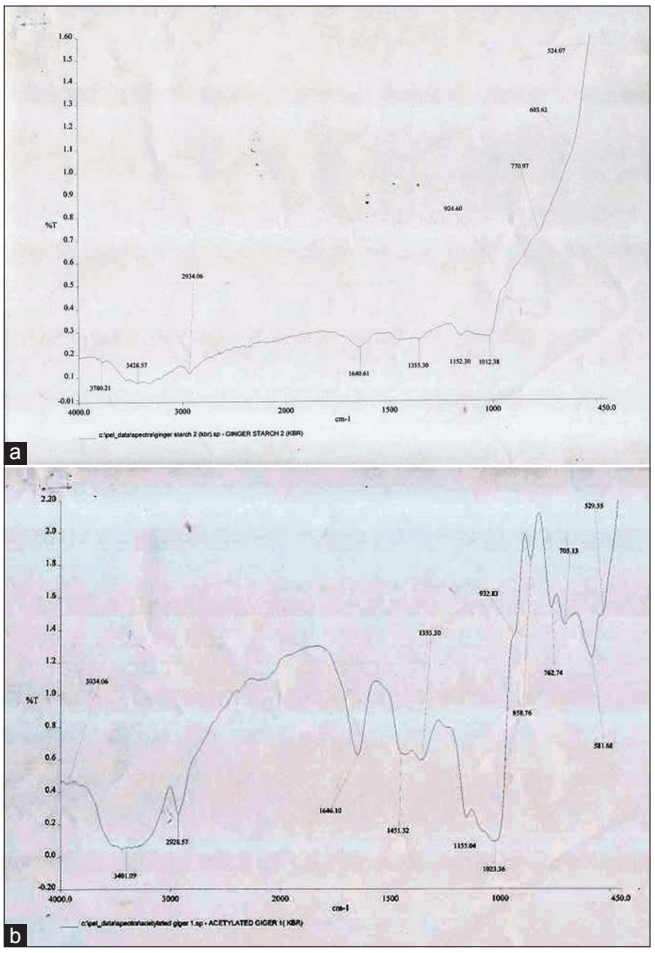

Figure 1: (a) Fourier transform infrared spectroscopy of native ginger starch. (b) Fourier transform infrared spectroscopy of acetylated ginger starch

Factorial analysis of tablets

The independent process parameters such as type of binder (X_1), binder concentration (X_2), and compression pressure (X_3) and their levels are shown in Table 3. The qualitative effects of the three parameters on the response variables such as crushing strength, friability,

crushing strength friability ratio (CSFR), disintegration and crushing strength friability/disintegration time ratio (CSFR/DT) studied are shown in Table 4. The individual coefficients of the variables on tablet properties are shown in Table 5. The ranking of the variables on crushing strength and CSFR was $X_1>X_3>X_2$. For friability it was $X_3>X_2>X_1$, ranking on disintegration was $X_3>X_1>X_2$, and CSFR/DT was $X_1>X_2>X_3$ [Table 5]. A positive value of this response shows a synergistic/increased effect while negative value indicates that the variable has an antagonistic effect/decreased effect on the response. Binder type had the highest effect on crushing strength of the tablets. Changing binder from CS to AGS gave a significant ($P < 0.05$) decrease in crushing strength which is a measure of tablet strength.[19] Dense hard granules require high compression pressure to form a hard compact tablet.[20] This could have been responsible for the low crushing strength and high friability when binder type was changed from CS to AGS. Changing binder from CS to AGS had a positive effect on friability, i.e., increase in friability and a negative effect on disintegration, i.e., decrease in DT.

Compression pressure had the highest effect on disintegration [Table 5]. This could be due to the reduction in porosity leading to increase in interparticulate bonding between the granules.[21] The DT of the tablets increased as observed from the positive sign [Table 5]. It has been shown that a porous structure is needed for water uptake during disintegration.[22] Increasing compression pressure from 28.28 MNm^{-2} to 169.68 MNm^{-2} reduced porosity of the tablets, thereby reducing water uptake thus leading to increase in DT.

The antagonistic effect of changing binder from CS to AGS is shown in Figure 2. The contour plots of the independent variables on crushing strength, CSFR, and CSFR/DT are shown in Figures 3 and 4.

The effects of the combination of the variables on the interaction coefficient values are shown in Table 6. The ranking of the interaction effects on crushing strength was $X_1X_3>X_2X_3>X_1X_2$, on friability was $X_1X_3=X_2X_3>X_1X_2$, on CSFR was $X_1X_2>X_1X_3>X_2X_3$, on DT was $X_1X_3>X_1X_2>X_2X_3$, and on CSFR/DT was $X_1X_2>X_2X_3>X_1X_3$. The combination of binder type and compression pressure had the highest effect on friability, crushing strength, and disintegration of the tablets. Changing compression pressure from low to high would affect the tablet compact, while the binder type could affect the packing of granules during compression. This packing

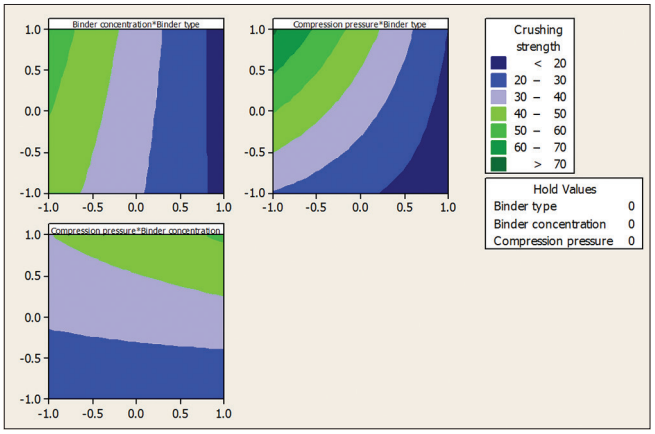

Figure 2: Contour plots of effects of independent variables on crushing strength of tablets

Table 3: Independent process parameters and their levels

Independent process parameters	Associated variable	Lower level (coded −1)	Higher level (coded +1)
Binder type	X_1	CS	AGS
Binder concentration	X_2	1% w/w	5% w/w
Compression pressure	X_3	28.28 MNm^{-2}	169.68 MNm^{-2}

CS: Corn starch, AGS: Acetylated ginger starch

Table 4: Values of crushing strength, friability, disintegration time, crushing strength friability ratio, and crushing strength friability ratio/disintegration time for tablets for factorial experimental design

Batch number	Binder type (X_1)	Binder concentration (X_2)	Compression pressure (X_3)	Crushing strength	Friability	DT	CSFR	CSFR/DT
1	−1	−1	−1	30.2	0.97	0.37	31.13	84.14
2	+1	+1	+1	19.54	0.77	0.15	25.38	169.2
3	+1	−1	−1	15	0.91	0.36	16.48	45.78
4	+1	+1	−1	12.38	1.03	0.16	12.02	75.13
5	−1	+1	−1	28.86	0.52	0.26	55.5	213.46
6	−1	+1	+1	82.62	0.20	0.48	413.1	860.62
7	+1	−1	+1	19.54	0.62	0.33	31.52	95.52
8	−1	−1	+1	59.84	0.87	0.63	68.78	168.06

−1: Low values, +1: High values, DT: Disintegration time, CSFR: Crushing strength friability ratio

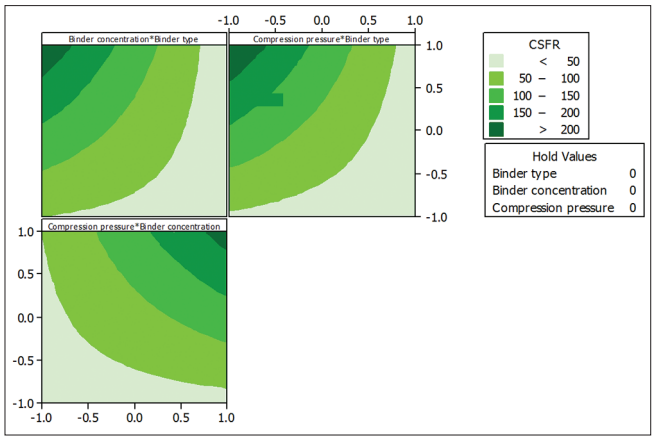

Figure 3: Contour plots of effects of independent variables on crushing strength friability ratio of tablets

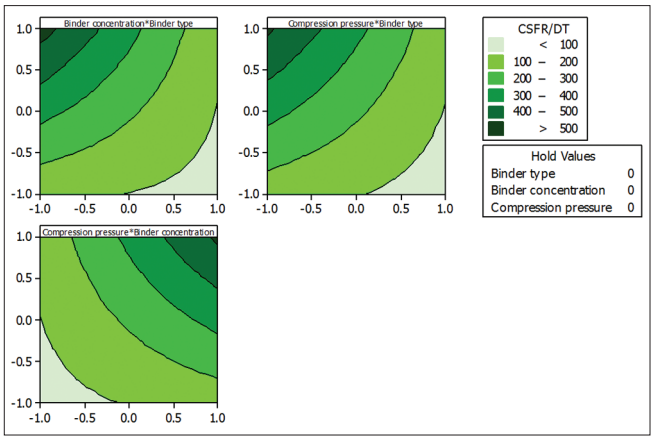

Figure 4: Contour plots of effects of independent variables on crushing strength friability ratio/disintegration time of tablets

Table 5: Individual coefficients of the variables on tablet properties

Factor	Coefficient	Crushing strength	Friability	DT	CSFR	CSFR/DT
X_1	Effect	−16.88	0.096	−0.093	−60.39	−117.6
	P	0.031	0.200	0.052	0.237	0.199
X_2	Effect	2.35	−1.06	−0.08	0.237	115.6
	P	0.674	0.182	0.06	0.361	0.205
X_3	Effect	11.89	−0.12	0.56	52.96	109.4
	P	0.084	0.161	0.09	0.290	0.226

DT: Disintegration time, CSFR: Crushing strength friability ratio

Table 6: Interaction coefficients of the variables on tablet properties

Factor	Coefficient	Crushing strength	Friability	DT	CSFR	CSFR/DT
X_1X_2	Effect	−3.01	0.17	−0.015	−47.41	−89.9
	P	0.464	0.113	0.295	0.448	0.398
X_1X_3	Effect	−8.96	−0.02	−0.065	−45.86	−73.4
	P	0.185	0.695	0.073	0.458	0.461
X_2X_3	Effect	3.34	−0.02	−0.003	39.78	75.9
	P	0.431	0.586	0.795	0.503	0.450
$X_1X_2X_3$	Effect	−2.69	0.03	0.008	−40.20	−64.9

DT: Disintegration time, CSFR: Crushing strength friability ratio

is dependent on the granule shape, size, and density. The combination of binder type and concentration had the highest effect on CSFR and CSFR/DT.

CONCLUSION

AGS produced in this study conferred good tableting properties on metronidazole tablets. AGS produced tablets with low crushing strength and low DT. The 2^3 factorial analysis showed that the type of excipients and the interactions of some of the variables had effect on the properties of the metronidazole tablet. Hence, excipients and the compression pressure to be used must be carefully chosen. From this study, it can be concluded that AGS could be useful as a binder in the formulation of metronidazole tablet.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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