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RESEARCH PAPER

Evaluation of Fast Disintegrants in Terfenadine Tablets Containing a Gas-Evolving Disintegrant

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ABSTRACT

Effects of four fast disintegrants on the dissolution of terfenadine tablets containing the gas-evolving disintegrant, $CaCO_3$, were evaluated. In addition, effects of presence of starch along with the fast disintegrants on the dissolution of the tablets were examined. Dissolution data were treated to give dissolution parameters which reflected efficiency of the disintegrant combinations. The four fast disintegrants improved disintegration/dissolution of the original formulation. The relative efficiency of improvement was in the order crospovidone > Ac-Di-Sol > Primojel > low substituted hydroxypropylcellulose. The presence of starch advertently affected the role of the fast disintegrants. Scanning electron microscope studies revealed that starch covered the drug-containing granules and other particles of the tablet. pH changes during dissolution of representative tablets in 0.1 N HCl solutions were determined at specific time intervals. The progressive decrease in rates of acid consumption as a function of the amount of starch, along with the SEM studies, suggested that a barrier existed around the tablet particles. The barrier was generated by the swelled starch grains and was responsible for the loss of the dissolution-improving capacity of the fast disintegrants. Furthermore, the barrier interfered with the diffusion of the hydronium ions and therefore, impaired the function of the disintegrant combination.

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INTRODUCTION

Starch, crosslinked starch, pregelatinized crosslinked starch, super disintegrants such as Explotab, and gas-evolving disintegrants such as calcium carbonate are among disintegrating agents currently used in pharmaceutical formulations. Several attempts were made to postulate mechanisms through which these disintegrants function. Normally, a combination of several processes such as swelling of disintegrant particles, capillary pressure effects, particle–particle bond-weakening, and air expansion are simultaneously working together to effect tablet disintegration (1–7). Gas-evolving disintegrants function through some of these processes by release of gases. However, release of gases to effect disintegration could be limited by the accessibility of water and other molecules from the dissolving medium to the disintegrant particles. Drugs or other excipients, which are hydrophobic and could be adsorbed on disintegrant surfaces, advertently influence the extent of hydration and the effectiveness of these disintegrants. Addition of fast disintegrants of high hydration capacity is reported to minimize this problem, and therefore, enhance dissolution. In the current investigation a tablet formulation containing $CaCO_3$ as a gas-evolving disintegrant was used to investigate the effects of the addition of four different types of fast disintegrants on the tablet disintegration/dissolution behavior. Terfenadine was chosen as the drug probe, because of its known strong hydrophic character and its ability to adsorb on surfaces (8). Effects of a combination of starch and fast disintegrants on the dissolution of the terfenadine formulation were also evaluated.

MATERIALS AND METHODS

Materials

Fast disintegrants were supplied as indicated: Primojel (PRJ) (Generichem Corp., Little Falls, NJ); Kollidon CL (Crospovidone, USP/NF, CPVP), (BASF, Germany); Ac-Di-Sol (ACDI) (FMC, Chicago, IL); and low substituted hydroxypropylcellulose, LHPC-LH21 (LPHC, Seppic, France). Other ingredients included Avicel PH 101 (FMC), Aerosil (Degussa, Germany), magnesium stearate (Merck, Germany), lactose, and maize starch (Roquette, France). Terfenadine and calcium carbonate were supplied by A.P.M. Co., Sult, Jordan.

Tablet Preparation

Terfenadine tablets were prepared according to the given basic formula (Table 1). Terfenadine (60 mg), maize starch (60 mg), and lactose (60 mg) were mixed in a planetary mixer (Erweka, Germany) for 15 min. Calcium carbonate (60 mg) were then added and further mixed for 20 min. Aqueous binding solution (equivalent to 70 mg solid polyvinylpyrrolidone [PVP]) was used to granulate the powder mix. The wet mass was passed through a 3.2-mm screen and then through a 2.5-mm screen (Erweka wet granulator). The granules were dried in a fluid-bed dryer (laboratory scale, Aeromatic, Switzerland) for 5 min then passed through a 1.6-mm screen and finally through a 1.0-mm screen. The resultant terfenadine granules were dried at 50°C for approximately 2.5 hr to achieve a moisture content of less than 1%. Dry granules were mixed with the extragranular excipients in a powder jar using a roller (Pascal Engineering, UK) for 20 min, then finally mixed with magnesium stearate for 5 min. A single-stroke tablet machine (Erweka Tablet Press, EKO) was used to compress the tablets using a 12-mm flat-face punch. Tablet weights and hardness were monitored during processing and were within acceptable limits. Tablet properties were as follows: weight 567 mg, diameter 12 mm, and tablet hardness of 17–19 kN.

Dissolution Studies

Dissolution runs were conducted using the USP paddle method rotating at 50 rpm in 1000 ml of 0.1 N HCl solution at 37°C. The drug was assayed spectrophotometrically by first derivative using a Beckman DU7 spectrophotometer (Beckman, Fullerton, CA) at λ 224 nm.

Relative rates of acid consumption by the calcium carbonate in tablets containing increasing amounts of starch was studied by monitoring changes in pH while tablets were dissolving. A Mettler DL 67 titrator equipped with a sensor, model DG 111-SC (Mettler Toledo, Switzerland), was used to automatically monitor the pH of the solution. In a typical run, a tablet was placed in 75 ml of 0.1 N HCl solution at room temperature, then stirred while pH values were recorded every 45 sec. Each run was carried out in duplicate and average of pH differences from zero time were calculated.

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was used to examine extent of coverage of outer surfaces of intact

Table 1

Basic Formula for Preparation of Terfenadine Tablets, 60 mg

Terfenadine granules (containing 60 mg TF, 60 mg calcium carbonate, 60 mg lactose, 70 mg PVP, and 60 mg maize starch)	310 mg
Calcium carbonate (extragranular)	25 mg
Avicel	24 mg
Aerosil	1 mg
Magnesium stearate	2 mg
Lactose powder, QS	205 mg
FD (replacing respective amount of extragranular lactose)	0–50 mg
MZ (replacing respective amount of extragranular lactose)	0–95 mg

QS: Quantity sufficient for manufacture; FD: fast disintegrant; MZ: maize starch.

tablets and interior of the divided tablets by starch grains. Tablets used in the investigation contained no starch, 47.5, and 95 mg of starch. Experiments were carried out using a Leitz 1000 A AMR scanning electron microscope (Leitz, Germany). Samples were prepared for examination by sputter coating with gold.

Treatment of Data

Dissolution data were treated according to the method described by Ibrahim et al. (9) to obtain the α- and τ-model parameters. The α parameter reflects the inherent ability of the tablet to break up and produce a certain population of dispersed granules. Higher α values indicate better disintegration patterns and more readily dissolving tablets. The τ parameter, conversely, is an estimate of the time required for the granules to lose physical integrity and liberate primary drug particles. A good dissolving tablet would be characterized by a high α value and a low τ value. The two parameters were applied to assess the relative efficiency of the disintegrating agents in improving tablet disintegration and dissolution. The following equations were used to calculate the α and τ parameters:

$$f_s(t) = \alpha\sqrt{t} - \beta + e^{-k_d \cdot t} \quad \text{for } 0 < t \leq \tau \qquad (1)$$

$$f_s(t) = f_s^{\tau} + (1 - f_s^{\tau}) \cdot \{1 - e^{-k_s \cdot (t - \tau)}\} \quad \text{for } t \geq \tau \qquad (2)$$

where $f_s(t)$ = fraction dissolved at time t; f_s^{τ} = fraction dissolved at $t = \tau$; k_d = first-order rate constant of disintegration of tablet; k_s = first-order rate constant of dissolution of primary drug particles; and β = constant.

RESULTS AND DISCUSSION

SEM Examination

SEM photographs of tablets containing no starch, 47.5, and 95 mg of starch are presented in Figs. 1, 2, and 3, respectively. These photos show microsurfaces

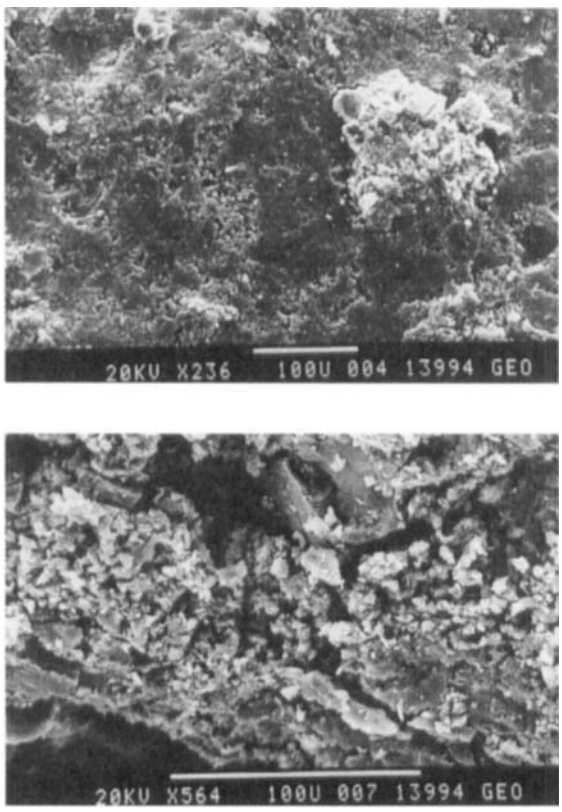

Figure 1. SEM photomicrographs of terfenadine tablets containing 0% starch: (a) tablet surface, (b) tablet interior.

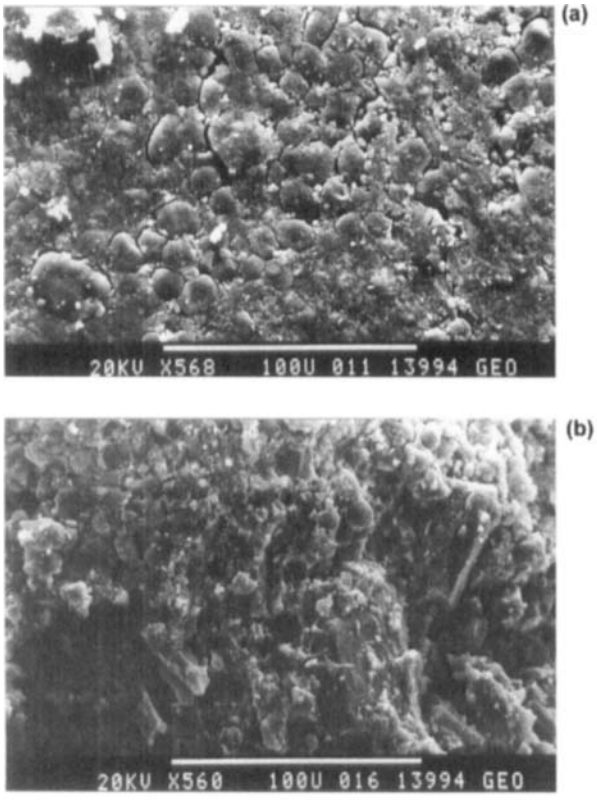

Figure 2. SEM photomicrographs of terfenadine tablets containing 47.5 mg starch: (a) tablet surface, (b) tablet interior.

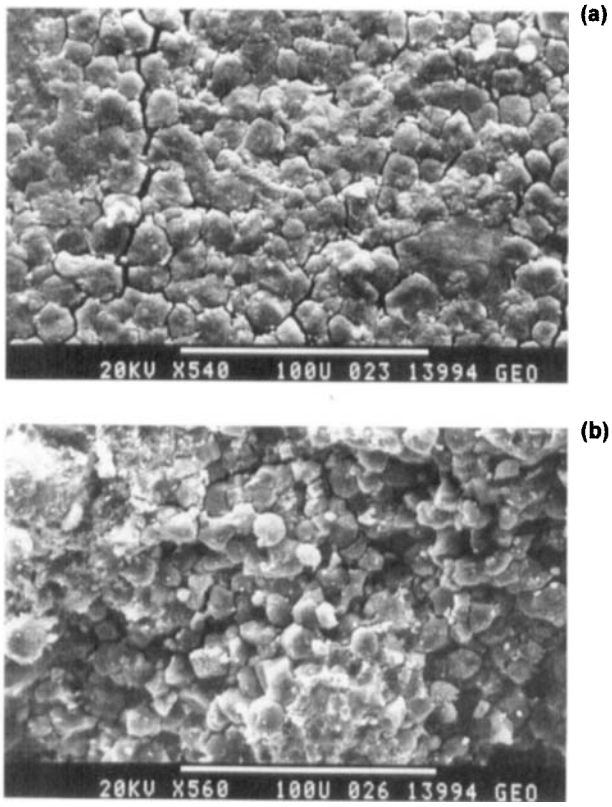

Figure 3. SEM photomicrographs of terfenadine tablets containing 95 mg starch: (a) tablet surface, (b) tablet interior.

of intact tablets and interiors of the divided tablets. Examination of Figs. 1–3 reveals that as the amount of starch was increased there was a gradual coverage of these surfaces with the more or less spherical starch grains. More specifically, Fig. 3, and to a lesser degree Fig. 2, presented surfaces effectively made of spherical starch grains. In contrast, photomicrographs of tablets containing no starch showed surfaces made of drug-containing granules and other excipients (Fig. 1). The significance of these observations is subsequently discussed in connection with the dissolution results.

Dissolution Studies

Effects of using a combination of each of the four fast disintegrants and the gas-evolving disintegrant on the disintegration/dissolution behavior of the terfenadine tablet are shown in Fig. 4. The addition of the fast disintegrants to the formulation improved both tablet disintegration and dissolution. As shown in Fig. 4(a), the time needed to achieve 50% dissolution was reduced with all four disintegrants. The rate at which t_{50} was reduced with the increase in the amount of the fast disintegrants was the highest with CPVP. Figure 4(b) shows plots of the dissolution parameters α and τ as a function of the amount of the fast disintegrant. As can be judged from these plots, presence of the fast disintegrants produced higher α values compared to the original formulation. These results suggest improved disintegration patterns and higher granule populations with each disintegrant combination. Moreover, the observed decrease in the τ value demonstrates the increased effectiveness of the disintegrant combinations in reducing the life-span of the granules compared to the gas-evolving disintegrant alone. These microeffects were reflected on the macrobehavior of the tablet as increased dissolution and lower t_{50} value at each disintegrant combination concentration. It is also apparent from Figs. 4(a) and (b) that these effects seemed to plateau at a certain disintegrant level depending on the characteristics of the fast disintegrant used.

The relative efficiency of the fast disintegrants in achieving higher α values and lower τ values compared

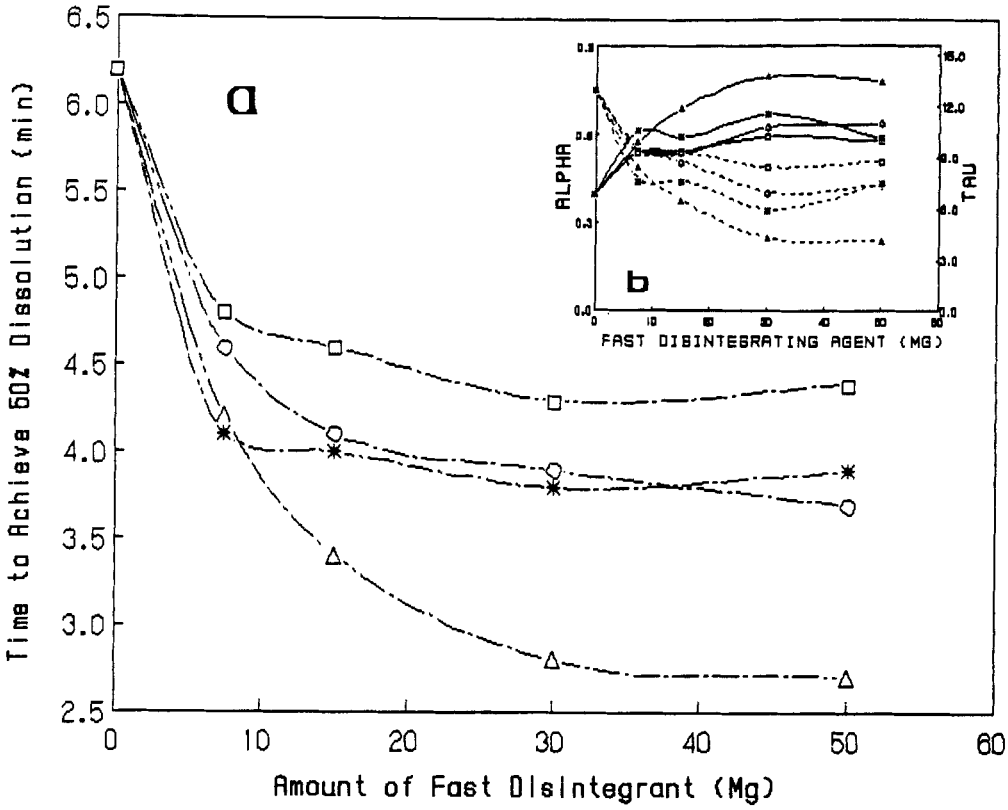

Figure 4. Effects of increased amounts of the fast disintegrants on dissolution (a) and the α and τ parameters (inset b) of terfenadine tablets Δ, CPVP; *, ACDI; ○, Primojel; □, LHPC; α values (—); τ values (- - - -).

to the original formulation was demonstrated in Fig. 5, curve I. When 30 mg of the fast disintegrant was used, the relative efficiency was in the order CPVP > Ac-Di-Sol > Primojel > LHPC. Judging from this α–τ plot, tablets containing only $CaCO_3$, i.e., control, showed the worst disintegration behavior. The effectiveness of $CaCO_3$ as a gas-evolving disintegrant depends on (*a*) the rate of production of carbon dioxide, and (*b*) the efficiency of the disintegrant to create capillaries within the compact and the granules upon reaction with the acid from the medium. Both processes depend on the extent of hydration of the particles and the accompanying rate of solvent penetration. Apparently, the hydrophobic nature of terfenadine and its strong capacity to adsorb on surfaces (8) limited the accessibility of the solvent components to the surfaces and hence, the effectiveness of the $CaCO_3$ disintegrant. The fast disintegrants used in the investigation were characterized by good hydration capacities (10). Therefore, judging from the obtained results, addition of the fast disintegrants to the formulation compensated for the hydrophobicity of

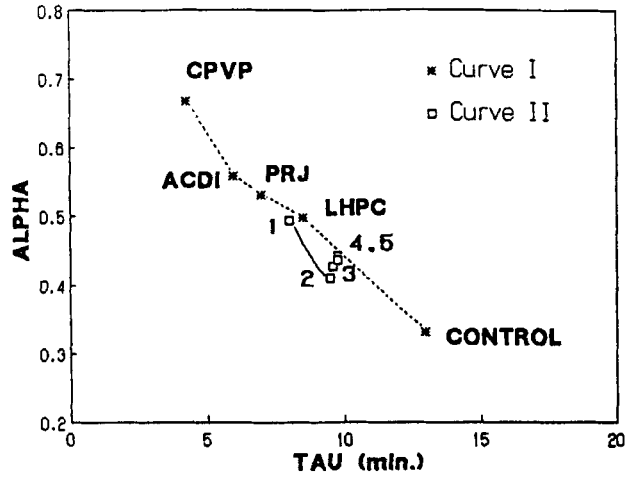

Figure 5. Changes in α–τ dissolution parameters of terfenadine tablet containing 30 mg of different fast disintegrants; curve I: tablets containing no starch; curve II: tablets containing 95 mg starch; key: (1) CPVP; (2) control; (3) LPHC; (4) ACDI; (5) PRJ.

terfenadine and provided the needed extent of hydration for the $CaCO_3$ to function effectively.

CPVP is known for its strong hydration capacity compared to the other tested fast disintegrants (10–12). Primojel and to a lesser extent ACDI, on the other hand, are known to form a viscous environment upon hydration (13). Therefore, keeping in mind that tablet hardness was 17–19 kN, the superiority of CPVP over other disintegrants could also be attributed to its ability to perform better at high compression pressures.

It is customary to use starch as an excipient in pharmaceutical formulations. Effects of combinations of starch and the fast disintegrant on the dissolution behavior of the terfenadine formulation was thus investigated. Tablets containing 30 mg CPVP and increasing amounts of starch (replacing corresponding amounts of extragranule lactose) were used in the study. Table 2 shows the α and τ values as a function of the added amount of starch. From Table 2, it is obvious that the disintegration behavior of the tablets was advertently influenced by starch. The increase in the τ values and the concomitant decrease in the α values suggest loss of disintegration combination efficiency. The previous dramatic increase in dissolution, which was achieved by adding 30 mg CPVP to the original formulation, was almost halved by replacing 95 mg of the extragranular lactose with starch. Apparently, starch interfered with the mechanism of action of the CPVP–$CaCO_3$ disintegrant combination. This dissolution-retarding effect of starch was shown with all tested fast disintegrants (Fig. 5, curve II). From curve II, it is apparent that even though starch alone improved the original formulation (control), its presence in combination with the fast disintegrants practically negated the dissolution enhancement effects of the latter.

Table 2

Dissolution Parameter α and τ of Terfenadine Tablets Containing 30 mg CPVP and Increasing Amounts of Starch

Percent of Starch Replacing Extragranular Lactose	α	τ (min)
0	0.585	4.7
12.5	0.582	5.0
25.0	0.531	6.5
37.5	0.497	7.3
50.0	0.488	7.8
75.0	0.451	8.8
100.0	0.451	9.0

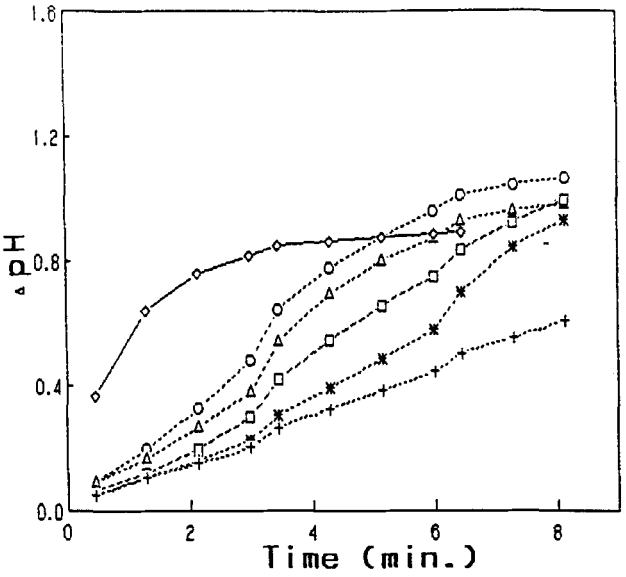

Figure 6. Effect of increasing amounts of starch on rates of acid consumption of terfenadine tablets containing 30 mg CPVP dissolving in a 0.1 N HCl solution. ○, 0 mg; Δ, 23.8 mg; □, 47.5 mg; *, 71.3 mg; +, 95 mg of starch; ◇, uncompressed granules.

As indicated, SEM photomicrographs showed varied degrees of coverage of particle surfaces with starch grains. The starch grains, especially after taking up water from the surroundings and undergoing swelling, probably acted as a barrier hindering the passage of molecules to and from the disintegrant particle surfaces. It is conceivable that components of the dissolution medium would reach those surfaces through channels between the swelled grains. Of special significance is the diffusion of the hydronium ions from the dissolution medium to the granules to effect the interaction with the gas-evolving disintegrant. Therefore, it is reasonable to expect that under these constraining conditions, the overall acid–disintegrant interaction would not be simple, but probably would be controlled by the slow step of bringing the interacting molecules together. Plots in Fig. 6 show changes in pH of the dissolution medium accompanying dissolution of tablets as a function of time. Also included are data corresponding to the uncompressed granules. Keeping in mind that the dissolution runs were carried out in a limited volume of 0.1 N HCl, the changes in pH with time could be correlated with the rates of acid consumption, while the tablet was dissolving. As shown in Fig. 6, presence of increasing amounts of starch in the formulation resulted in a gradual decrease in the overall rate of acid consumption.

It is of interest to examine the profiles of the tablets in relation to that of the uncompressed granules. Even though that of the latter showed an apparent exponential behavior, tablet profiles were, more or less, biphasic; particularly, at lower starch levels, suggesting a change in the kinetics of acid–disintegrant interaction. The progressive decrease in the rates of acid consumption with the increase in the amount of starch could be explained in light of the SEM findings. The barrier generated around the particles by the swelled grains impaired the functions of the fast disintegrant, thus lowering the efficiency of the disintegrant combination.

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