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Implication of inclusion complexation of glimepiride in cyclodextrin–polymer systems on its dissolution, stability and therapeutic efficacy

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Abstract

The effect of complexation of glimepiride, a poorly water-soluble antidiabetic drug, with β-cyclodextrin and its derivatives (HP-β-CyD and SBE-β-CyD) in presence of different concentrations of water-soluble polymers (HPMC, PVP, PEG 4000 and PEG 6000) on the dissolution rate of the drug has been investigated. The results revealed that the dissolution rate of the drug from these ternary systems is highly dependent on polymer type and concentration. The dissolution rate of the drug from ternary systems containing PEG 4000 or PEG 6000 seems to be generally higher than from systems containing HPMC or PVP. An optimum increase in the dissolution rate of the drug was observed at a polymer concentration of 5% for PEG 4000 or PEG 6000 and at 20% concentration of HPMC or PVP. The dissolution rate of the drug from the ternary system glimepiride–HP-β-CyD–5% PEG 4000 was high compared to the other systems. Tablets containing the drug or its equivalent amount of this ternary system were prepared and subjected to accelerated stability testing at 40 °C/75% R.H. to investigate the effect of storage on the chemical stability as well as therapeutic efficacy of the tablets. The results revealed stability of the tablets and consistent therapeutic efficacy on storage.

Keywords: Glimepiride; Cyclodextrins; Water-soluble polymers; Complexation; Stability

1. Introduction

In a preceding communication (Ammar et al., 2006), the potentiality of complex formation between glimepiride and β-cyclodextrin (β-CyD), hydroxypropyl-β-cyclodextrin (HP-β-CyD) and sulfobutyl-β-cyclodextrin (SBE-β-CyD) was monitored. Inclusion complexes of the drug in these cyclodextrins were prepared and characterized by thermogravimetric analysis, IR spectroscopy and X-ray diffractometry. Ternary systems containing the drug–cyclodextrin–a water-soluble polymer were also prepared. Hyroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol 4000 (PEG 4000) and polyethylene glycol 6000 (PEG 6000) were used in a 5% concentration for monitoring their effect on the dissolution rate of the drug. The rationale of the presented paper was to investigate the effect of polymer concentration in the ternary system on the dissolution behavior of the drug. Evaluation of the effect of storage on the chemical stability as well as therapeutic efficacy of tablets prepared with a selected formulation was not beyond the scope of this communication.

2. Materials and methods

2.1. Materials

Glimepiride was kindly provided by Delta Pharma. Co. (Tenth of Ramadan City, Egypt). β-cyclodextrin, hydroxypropyl-β-cyclodextrin (MW 1380), and hyroxypropyl methylcellulose were purchased from Sigma Chemical Company (St. Louis, USA). Sulfobutylether-β-cyclodextrin sodium salt (MW 2160) was kindly provided by Cydex L.C. (Overland Park, KS, USA). Polyethylene glycol 4000, polyvinylpyrrolidone (K-30) and dimethyl formamide were purchased from Sisco Research Laboratories Pvt. Ltd. (Bombay, India). Polyethylene glycol 6000 was purchased from Fluka (Germany). Sodium dihydrogen

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phosphate was supplied from S.D. Fine Chem. Ltd., Mumbai, India and disodium hydrogen phosphate was purchased from BDH Laboratory Supplies, Poole, England.

2.2. Methods

2.2.1. Preparation of glimepiride–cyclodextrin systems

Inclusion complexes of glimepiride in cyclodextrins were prepared by the kneading method (Uekema et al., 1988). Glimepiride was added to β-CyD or HP-β-CyD in a molar ratio of 1:2 and to SBE-β-CyD in a molar ratio of 1:3 (Ammar et al., 2006). Ternary systems containing the drug, cyclodextrin and a water-soluble polymer (HPMC, PVP, PEG 4000 or PEG 6000) were also prepared.

Microcrystalline complexes of glimepiride with cyclodextrins were monitored by infrared spectroscopy, thermal analysis (TGA) and X-ray diffractometry in a previous study (Ammar et al., 2006). These investigations revealed complex formation between the drug and the studied cyclodextrins.

2.2.2. In vitro dissolution studies

Dissolution of glimepiride was assessed at 37 °C by the USP Dissolution Tester, Apparatus I (Rotating basket), using 900 ml of phosphate buffer (pH 6.8) as the dissolution medium and at a rotation rate of 75 rpm. Aliquots, each of 5 ml, from the dissolution medium were withdrawn at time intervals of 5, 10, 15, 20, 30, 45, 60, 90, 120 and 180 min and replenished by an equal volume of fresh dissolution medium. The samples were withdrawn through sintered glass filter and analyzed for glimepiride content by measuring its absorbance at 226 nm using phosphate buffer (pH 6.8) as a blank. Replicate batches of each binary and ternary complex were used for dissolution studies.

2.2.3. Effect of storage on the stability and therapeutic efficacy of glimepiride and glimepiride–CyD–polymer system

Glimepiride and glimepiride–HP-β-CyD–5%PEG 4000 system were formulated in tablet form containing 3 mg of the drug or its equivalent amount of the ternary system. The tablets were stored at 40 °C and 75% relative humidity (maintained using a saturated solution of NaCl) (Bodmeier and Paeratakul, 1991) for a period of 3 months. The stored tablets were evaluated for chemical stability and therapeutic efficacy.

2.2.3.1. Chemical stability. Stability indicating assay was adopted for quantitative determination of glimepiride in dimethyl formamide (DMF) and the second order derivative spectra were calculated using peak to zero at 265.5 nm (Altinoz and Tekeli, 2001). A standard calibration curve for the drug was established.

Ten glimepiride or glimepiride–CyD–polymer tablets were powdered. An aliquot of this powder corresponding to one tablet was weighed and transferred to a 10 ml volumetric flask. The flask was completed to volume with DMF and its content was then filtered through a 0.45 μm Millipore filter. Appropriate dilutions with DMF were made in the range of the calibration curve. The second order derivative UV spectra of the resulting solutions were recorded against DMF as a reference solution.

2.2.3.2. Therapeutic efficacy. This study was of a single dose and parallel group design using normal rabbits. Male albino rabbits weighing 1–1.25 kg were kept on standard diet and fasted over night. Rabbits were divided into two groups, each of six animals. Blood samples were withdrawn from the marginal ear vein of the animal. Fasting blood glucose level was assessed using FastTake glucometer (SmartScan®) (Gabra and Sirois, 2005). FastTake glucometer provides rapid, accurate and reproducible results in both laboratory and clinical settings (Albertson et al., 1998). Each animal of the first group received one tablet containing 3 mg of the drug and each rabbit of the second group received one tablet containing glimepiride–HP-β-CyD–5%PEG 4000 system in an amount equivalent to 3 mg of the drug. Blood glucose level (BGL) was measured at different time intervals, up to 24 h. Each animal served as its own control and hence, the hypoglycemic response was evaluated as percentage decrease in blood glucose level:

$$\text{Decrease in BGL (\%)} = \frac{\text{BGL at } t = 0 - \text{BGL at } t}{\text{BGL at } t = 0} \times 100$$

The pharmacodynamic parameter of the area under percentage decrease in BGL versus time curve (AUC_{0-24h}) was calculated adopting the trapezoidal rule (Wagner, 1975).

Statistical analysis of the results was performed using one-way analysis of variance (ANOVA), followed by the least-significant difference test (LSD). This statistical analysis was computed with the SPSS® software.

3. Results and discussion

3.1. Effect of polymers on the dissolution rate of glimepiride–cyclodextrin complexes

Figs. 1 and 2 illustrate the effect of inclusion complexation of glimepiride in β-CyD in presence of polymers, at different concentrations, on the dissolution efficiency of glimepiride. Data of dissolution efficiency of the ternary systems revealed

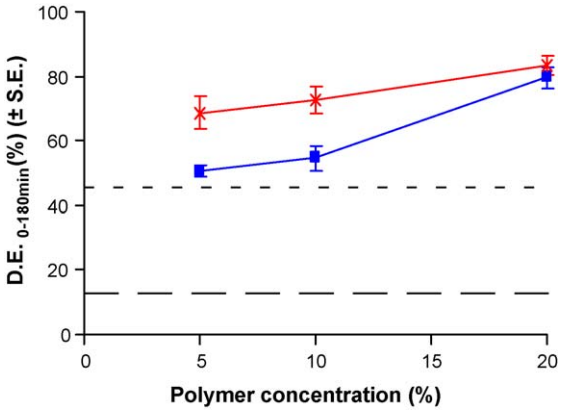

Fig. 1. Effect of HPMC and PVP concentration on the D.E. of glimepiride–β-CyD complex. Glimepiride (– –); glimepiride–β-CyD (- -); glimepiride–β-CyD–HPMC (■); glimepiride–β-CyD–PVP (✳).

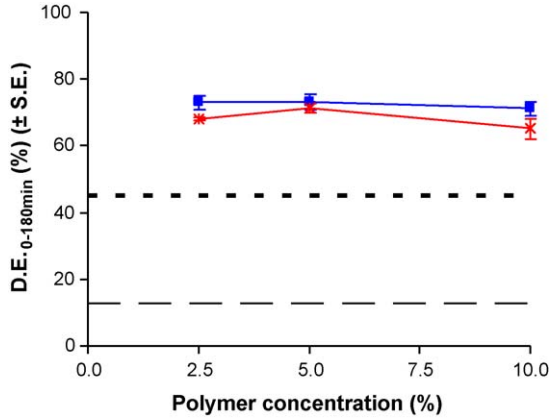

Fig. 2. Effect of PEG 4000 and PEG 6000 concentration on the D.E. of glimepiride–β-CyD complex. Glimepiride (– –); glimepiride–β-CyD (- -); glimepiride–β-CyD–PEG 4000 (■); glimepiride–β-CyD–PEG 6000 (✱).

an enhancement of dissolution of glimepiride compared to the binary systems. In presence of HPMC or PVP, the enhancement of dissolution rate was found to increase with increasing polymer concentration. Previous studies showed that HPMC and PVP increase complexation of hydrocortisone, dexamethasone and naproxone with β-CyD (Loftsson et al., 1993; Loftsson and Sigurdardottir, 1994; Mura et al., 2001; Valero et al., 2003). Valero et al. (2003) stated that at low PVP concentrations, the complexation process is driven entropically, while at higher proportions it is enthalpically favoured. The dissolution of glimepiride from the ternary systems containing PEG 4000 was increased irrespective of polymer concentration (Fig. 2). For PEG 6000, the dissolution rate of the drug showed optimum increase at 5% polymer concentration.

Figs. 3 and 4 illustrate the effect of polymers on the dissolution efficiency of glimepiride–HP-β-CyD complex. An improvement in dissolution of the drug was achieved in presence of these polymers. For HPMC or PVP, the dissolution rate of the drug was dependent on polymer concentration; optimum increase was at 20% polymer concentration (Fig. 3). The increase in the dissolution rate of the drug in presence of these polymers could be interpreted on the basis that in ternary prepa-

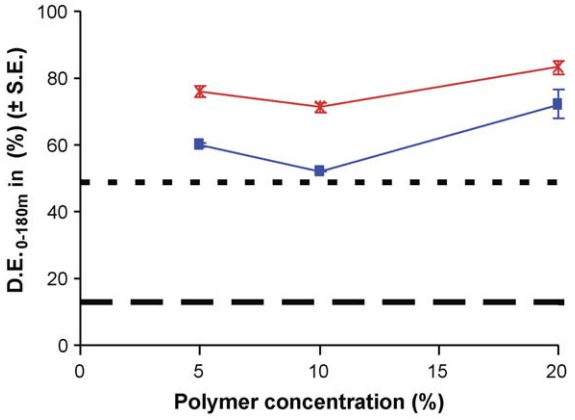

Fig. 3. Effect of HPMC and PVP concentration on the D.E. of glimepiride–HP-β-CyD complex. Glimepiride (– –); glimepiride–HP-β-CyD (- -); glimepiride–HP-β-CyD–HPMC (■); glimepiride–HP-β-CyD–PVP (✱).

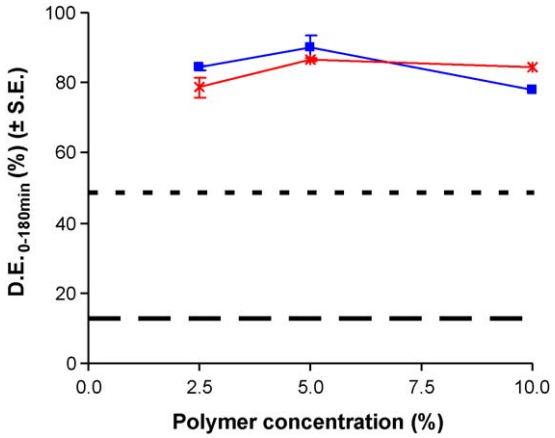

Fig. 4. Effect of PEG 4000 and PEG 6000 concentration on the D.E. of glimepiride–HP-β-CyD complex. Glimepiride (– –); glimepiride–HP-β-CyD (- -); glimepiride–HP-β-CyD–PEG 4000 (■); glimepiride–HP-β-CyD–PEG 6000 (✱).

rations, the molecules of the glimepiride–HP-β-CyD complex are supposed to be present in a more or less intimate dispersed state within the polymer matrix through interactions between exterior of the complex and the polymer (Mura et al., 2001). For PEG 4000 and PEG 6000, Fig. 4 shows an optimum increase in dissolution rate at 5% polymer concentration.

Fig. 5 illustrates the effect of different polymers on the dissolution efficiency of glimepiride–SBE-β-CyD complex. It is evident that low concentrations of HPMC and PVP decreased the dissolution of glimepiride–SBE-β-CyD complex. An increase in dissolution was only evident at 20% PVP concentration. Regarding PEG 4000, an increase in dissolution of glimepiride was evident only at 5% polymer concentration (Fig. 6). However, PEG 6000 showed no effect on the dissolution rate of the drug.

Ribeiro et al. (2003) proved an improvement of the complexation efficiency of the binary systems of vinpocetine and each of β-CyD and SBE-β-CyD in presence of the water-soluble polymers PVP and HPMC. The authors attributed this to establishing different interactions of polymers with CyD and drug molecules

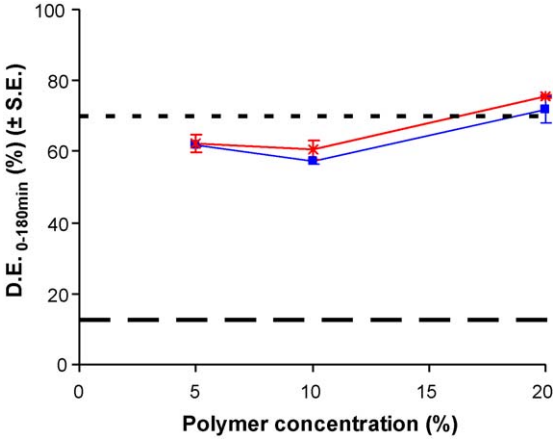

Fig. 5. Effect of HPMC and PVP concentration on the D.E. of glimepiride–SBE-β-CyD complex. Glimepiride (– –); glimepiride–SBE-β-CyD (- -); glimepiride–SBE-β-CyD–HPMC (■); glimepiride–SBE-β-CyD–PVP (✱).

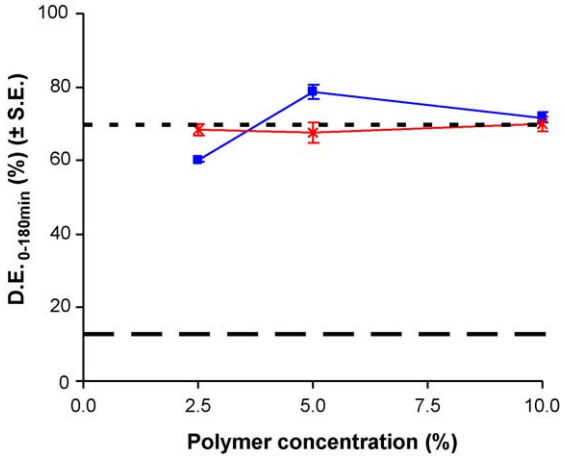

Fig. 6. Effect of PEG 4000 and PEG 6000 concentration on the D.E. of glimepiride–SBE-β-CyD complex. Glimepiride (– –); glimepiride–SBE-β-CyD (- -); glimepiride–SBE-β-CyD–PEG 4000 (■); glimepiride–SBE-β-CyD–PEG 6000 (✳).

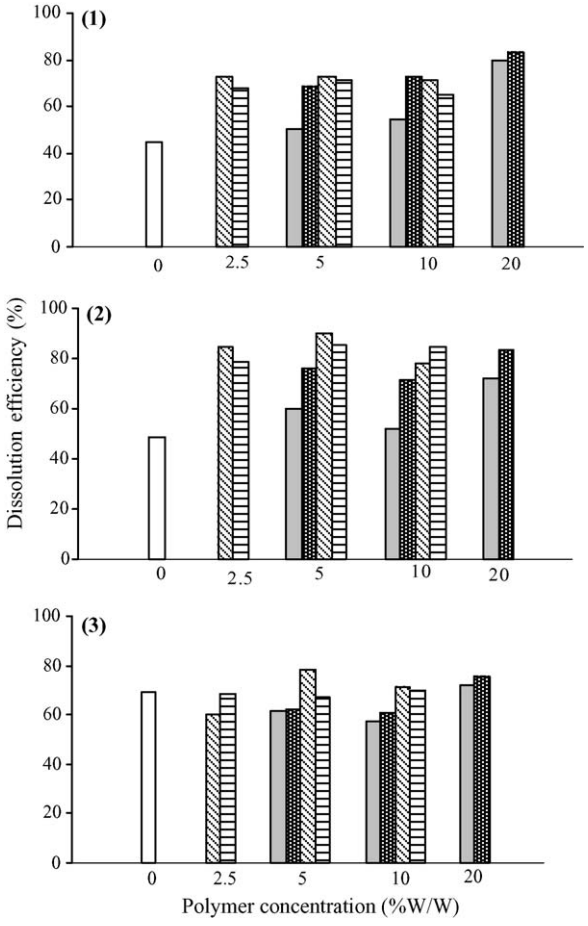

Fig. 7. Effect of polymers on the dissolution rate of: (1) glimepiride–β-CyD complex; (2) glimepiride–HP-β-CyD complex; (3) glimepiride–SBE-β-CyD complex. Complex (□); complex + HPMC (▤); complex + PVP (▦); complex + PEG 4000 (▨); complex + PEG 6000 (▤).

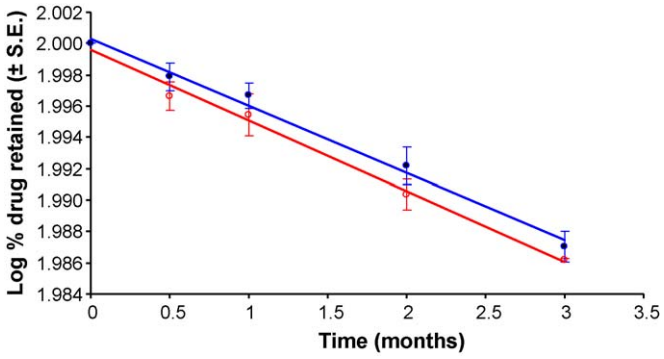

Fig. 8. Effect of storage on the stability of glimepiride and glimepiride–CyD–polymer tablets. Glimepiride tablets (◯); glimepiride–CyD–polymer tablets (●).

such as hydrophobic bonds, van der Waals dispersion forces or hydrogen bonds (Faucci and Mura, 2001).

Comparing the effect of polymers on the dissolution of glimepiride–cyclodextrin complexes (Fig. 7), it is evident that a concentration of 20% PVP exhibited the highest effect in the case of glimepiride–β-CyD complex. With respect to glimepiride complexes with HP-β-CyD and SBE-β-CyD, a 5% concentration of PEG 4000 had the highest effect.

On the basis of the above results, it is evident that the dissolution of glimepiride from complexes with HP-β-CyD–5% PEG 4000 was higher than from other complexes. Exploitation of the cyclodextrin properties in the pharmaceutical area reveals that HP-β-CyD appears to be the most useful as a pharmaceutical complexing agent because of its amorphousness, high water solubility and solubilizing ability, low cost and low toxicity (Ruan et al., 2005). Also, HP-β-cyclodextrin is useful for inhibition of polymorphic transition and crystallization rates of poorly water-soluble drugs during storage, which can, consequently, maintain the high dissolution characteristics and oral bioavailability of drugs (Uekama, 2002). Therefore, the ternary system glimepiride–HP-β-CyD–5% PEG 4000 was selected for testing the effect of storage on the stability and therapeutic efficacy of the drug.

3.2. *Effect of storage on the stability and therapeutic efficacy of glimepiride tablets*

3.2.1. *Chemical stability*

Glimepiride and glimepiride–CyD–polymer tablets showed no marked changes in drug content, complying with the International Conference on Harmonization (ICH) conditions of less than 5% potency change from the initial assay.

Kinetic analysis of stability data revealed that degradation of glimepiride and glimepiride–CyD–polymer tablets followed first order kinetics (Fig. 8) with correlation coefficients of 0.996 and 0.995, respectively. The rate constants were determined from the slope of the kinetic curves and their values were: 10.36 and 9.90×10^{-3} month^{-1}, respectively. On the other hand, the half-life times were 66.9 and 70.0 months, respectively. This denotes that HP-β-CyD and 5% PEG 4000 have no deleterious effect on the chemical stability of the drug.

Table 1
Effect of storage on the therapeutic efficacy of glimepiride and glimepiride–CyD–polymer tablets

	AUC_{0-24h} for			
	Glimepiride tablets		Glimepiride–CyD–polymer tablets	
	Before storage	After storage	Before storage	After storage
Mean	285.0	297.9	422.0	469.4
S.E. (±)	30.2	31.9	52.3	44.2

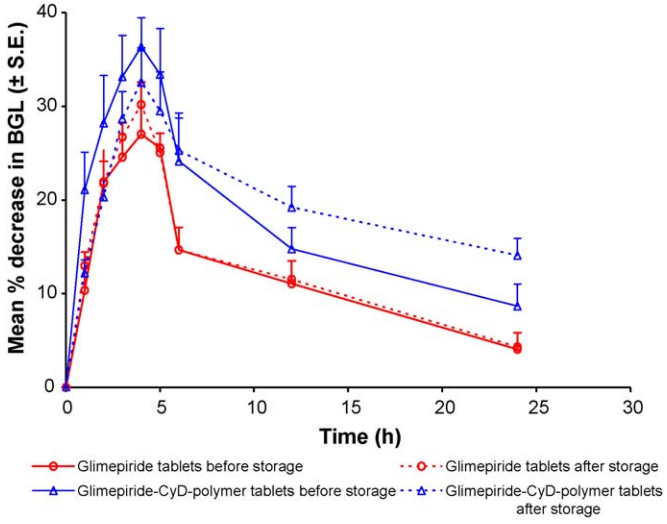

Fig. 9. Effect of storage of glimepiride and glimepiride–HP-β-CyD–PEG 4000 tablets on the mean percentage decrease in blood glucose level on normal rabbits. Glimepiride tablets before storage (–◯–); glimepiride tablets after storage (- -◯- -); glimepiride–CyD–polymer tablets before storage (–△–); glimepiride–CyD–polymer tablets after storage (- -△- -) .

3.2.2. *Therapeutic efficacy*

Fig. 9 shows the mean percentage decrease in blood glucose level (BGL) in normal rabbits after administration of glimepiride and glimepiride–HP-β-CyD–5% PEG 4000 system, in tablet form, before and after storage. It is evident that the AUC-values for tablets containing glimepiride–HP-β-CyD–5% PEG 4000 system were higher than the corresponding values of glimepiride tablets before as well as after storage (Table 1). These differences were found to be significant ($P < 0.05$ and $P < 0.01$, respectively). On the other hand, statistical analysis of the data revealed that there was no significant difference between the biological performance of glimepiride tablets or glimepiride–CyD–polymer tablets before and after storage. This would clearly indicate that storage of these tablets for 3 months at 40 °C/75% R.H. did not affect their biological performance and therapeutic efficacy.

The above-mentioned results reveal that the dissolution rate of glimepiride–cyclodextrin polymer systems is highly dependent on polymer type and concentration. In this respect, incorporation of 5% PEG 4000 in glimepiride–HP-β-CyD complex improves significantly the dissolution behavior of the drug. Tablets formulated with this system are stable and show consistent therapeutic efficacy on storage.

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