ELSEVIER

International Journal of Pharmaceutics 174 (1998) 47–54

international journal of pharmaceutics

Air compartment multiple-unit system for prolonged gastric residence. Part I. Formulation study

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Received 15 April 1998; received in revised form 1 July 1998; accepted 3 July 1998

Abstract

A pre-formulation study was directed to optimize the in vitro floating ability of an air compartment multiple-unit system. Each unit was formed by a coated bead composed of a calcium alginate core separated by an air compartment from a calcium alginate or calcium alginate/polyvinylalcohol (PVA) membrane. The floating ability depended on the presence of the air compartment and on membrane porosity. The porous structure generated by the leaching of PVA, employed as a water-soluble additive in the coating composition, increased the membrane permeability preventing air compartment shrinkage. In this way, units were produced which were able to float immediately upon contact with artificial gastric juice and for a long period of time. The floating ability increased with the increase in PVA concentration and molecular weight and it was found to be excellent when using PVA 100000 at a concentration of at least 5%.

Keywords: Floating dosage form; Multiple-unit dosage form; Calcium alginate; Poly(vinyl alcohol); Floating ability; Porosity

1. Introduction

Oral sustained-drug delivery formulations show some limitations connected with the gastric emptying time. In fact, variable and too rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone (stomach or limited sites in the upper part of the intestine) leading to diminished efficacy of the administered dose.

To overcome these problems and improve the efficacy of oral administration, some recent studies have reported controlled oral drug delivery systems with prolonged gastric residence time, such as floating dosage systems (Kawashima et

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0378-5173/98/$ - see front matter
PII S0378-5173(98)00229-4

al., 1992; Oth et al., 1992; Desai and Bolton, 1993; Deshpande et al., 1996).

A gastrointestinal drug delivery system can be made to float in the stomach by a gelling process of hydrocolloid materials (Chien, 1992) or by incorporating a flotation chamber, vacuum or gas filled (Chien, 1992). In this way a bulk density less than that of the gastric fluid is produced. However, most of the devices generating gas or gelling need time to be floated and this parameter must be checked carefully in order to prevent the dosage form from transiting into the small intestine together with food before floating in the stomach. Otherwise, systems incorporating a flotation chamber causing the dosage form to float immediately are complicated to produce. Among the floating systems, multiple-unit formulations show several advantages over monolithic ones: more predictable drug release kinetics, less chance of localised mucosal damage, insignificant impairing of performance due to failure of a few units, co-administration of units with different release profiles or containing incompatible substances, larger margin of safety against dosage form failure.

Thus, this work aims to design a multiple-unit air compartment system able to float immediately on being placed into the gastric fluid and obtainable by a new simple technological approach.

The designed units are constituted by coated beads each composed of a calcium alginate core separated by an air compartment from a calcium alginate or calcium alginate/polyvinylalcohol (PVA) membrane. The materials selected, calcium alginate and PVA, are known to be atoxic when taken orally. Also, calcium alginate, as the polymer substrate, is stable at the gastric values of pH and it was shown to have sustained-release characteristics (Stockwell et al., 1986; Bodmeier et al., 1989; Kim and Lee, 1992).

In this paper, the effects of preparative parameters on the 'in vitro' floating capacity are investigated in order to design the most suitable drug delivery system for the subsequent 'in vivo' examination.

Table 1
Formulation parameters of the units

Sample	Coating time (min)	PVA molecular weight	PVA (%, w/w)
A1	10	—	—
A2	30	—	—
A3	60	—	—
B1	10	100 000	2
B2	10	100 000	3
B3	10	100 000	4
B4	10	100 000	5
B5	10	100 000	6
C1	10	49 000	2
C2	10	49 000	3
C3	10	49 000	4
C4	10	49 000	5
C5	10	49 000	6
D1	10	15 000	2
D2	10	15 000	3
D3	10	15 000	4
D4	10	15 000	5
D5	10	15 000	6

2. Materials and methods

2.1. Materials

The following chemicals were obtained from commercial suppliers and used without further purification. Sodium alginate [MW about 115000, extracted from Laminaria hyperborea, containing

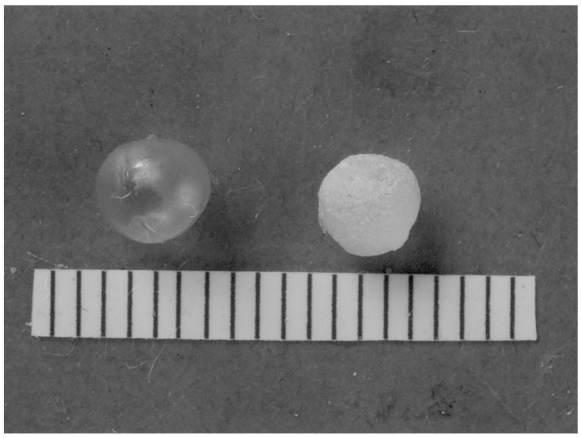


Fig. 1. Photograph of the units with calcium alginate membrane (on the left) or calcium alginate /PVA membrane (on the right). Scale: mm.

Table 2
Physical parameters of the units (S.D. in parenthesis)

Sample	Weight (mg)	Diameter (mm)	Apparent density (mg/mm^3)	Membrane thickness (μm)
Core	8.1 (0.5)	2.4 (0.3)	1.1 (0.1)	—
A1	12.1 (1.1)	3.7 (0.5)	0.5 (0.02)	76 (20)
A2	13.9 (1.5)	3.4 (0.8)	0.7 (0.06)	116 (16)
A3	17.1 (1.3)	3.7 (0.9)	0.6 (0.05)	248 (23)
B1	12.1 (0.7)	3.9 (0.8)	0.4 (0.03)	142 (34)
B2	13.9 (1.3)	3.5 (0.6)	0.6 (0.03)	166 (18)
B3	14.3 (1.2)	4.0 (0.8)	0.4 (0.03)	161 (23)
B4	12.3 (1.7)	3.6 (0.5)	0.5 (0.01)	170 (32)
B5	12.4 (1.8)	3.6 (0.5)	0.5 (0.02)	172 (34)
C1	10.6 (0.5)	3.7 (0.4)	0.4 (0.01)	128 (14)
C2	12.9 (1.3)	3.7 (0.5)	0.5 (0.01)	113 (21)
C3	16.2 (1.9)	4.1 (0.8)	0.4 (0.02)	134 (23)
C4	15.2 (1.6)	3.8 (0.9)	0.5 (0.03)	140 (23)
C5	16.1 (0.9)	3.8 (0.7)	0.6 (0.03)	141 (21)
D1	12.2 (1.0)	3.3 (0.7)	0.6 (0.02)	142 (17)
D2	14.1 (1.1)	3.7 (0.6)	0.5 (0.02)	129 (14)
D3	17.3 (0.7)	3.9 (0.8)	0.6 (0.02)	141 (23)
D4	12.4 (1.0)	3.1 (0.5)	0.7 (0.04)	185 (22)
D5	15.7 (1.1)	3.5 (0.6)	0.7 (0.06)	173 (25)

30% mannuronic acid and 70% guluronic acid], polyvinylalcohol (PVA) having three different molecular weight (100000, 49000 and 15000) and calcium chloride dihydrate were purchased from Fluka Chemie (Buchs, Switzerland). Tween 20 (polyoxyethylen sorbitan monolaurate) was purchased from Atlas Europol (Ternate, Italy). All the solvents (analytical grade) were purchased from Carlo Erba (Milan, Italy).

2.2. Methods

2.2.1. Preparation of the floating units

The floating units were developed by preparing and covering calcium alginate beads through ionotropic gelation of sodium alginate by calcium ions.

(A) Preparation of calcium alginate beads. Sodium alginate water solution (5%, w/w) was

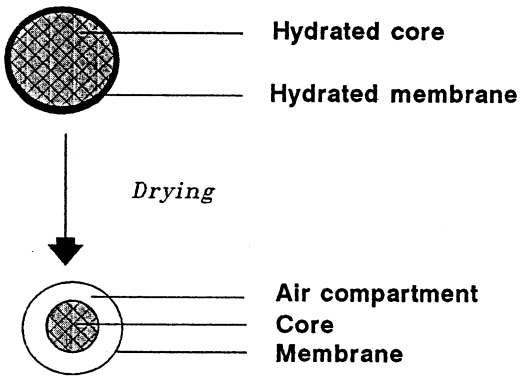


Fig. 2. Schematic drawing of the air compartment unit formation.

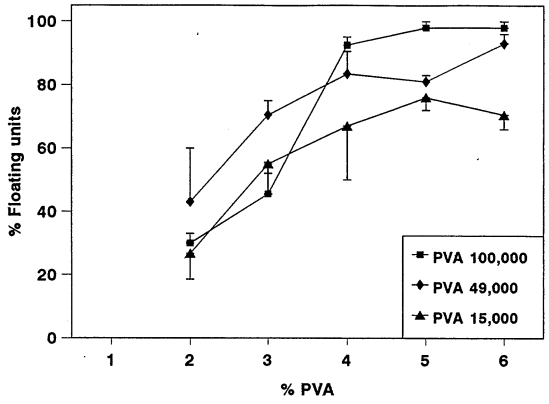


Fig. 3. Effect of the PVA concentration on the floating ability of the units.

Table 3
Floating ability of the units: ++ excellent; + fair/poor; − absent

Sample	Water	Acidic media
A1	++	−
A2	++	−
A3	++	−
B1	++	+
B2	++	+
B3	++	+
B4	++	++
B5	++	++
C1	++	+
C2	++	+
C3	++	+
C4	++	+
C5	++	+
D1	++	+
D2	++	+
D3	++	+
D4	++	+
D5	++	+

used after being degassed under a vacuum. Then, 3 ml of sodium alginate water solution was dropped through a 2 mm nozzle into a medium constituted by 20 ml of n-heptane and 10 ml of calcium chloride (10%, w/v), Tween 20 (1%, w/v) water solution. The medium was stirred (1000 rpm) for 5 min at room temperature. The formed particles were separated from the medium, washed quickly with water and, then, with diethyl ether.

(B) Coating procedure. Calcium alginate membrane formation was carried out by soaking undried, i.e. just prepared, calcium alginate beads in water solutions of 5% (w/w) sodium alginate alone or containing various amounts of PVA. The formulation parameters (concentration and molecular weight of PVA and coating times) are listed in Table 1. The coated beads were quickly rinsed with water and dietyl ether and, then, vacuum dried.

The resultant dried coated beads, named units throughout the text, consisted of a core separated from a membrane by an air compartment.

2.2.2. Morphological and dimensional analysis

The analysis of the morphology and of the size of both units and their separate components (cores and membranes) was carried out.

The morphological structure was examined with a Scanning Electron Microscope (SEM) (XL-40, Philips, Eindhoven, The Netherlands).

The units and the cores were measured for size using an optical microscope (Carl Zeiss, Jena, Germany). The membrane thickness was calculated by measuring the cross-section of the membrane in at least four areas on SEM micrographs. Apparent density values of the units and the cores were determined from the mass volume of samples having known weights. All the data are averaged on ten samples from three different batches.

2.2.3. In vitro evaluation of floating ability

The floating ability of the units and of their separate components (cores and membranes) was determined by using the USP paddle method at 50 rpm and 37 ± 0.2°C in 900 ml of water or simulated gastric fluid (pH 1.2; USP XXIII, without pepsin) or HCl solutions at two different pH values (3.0 and 5.0). Then, 20 units or their separate components were placed in the medium and the percentage of floating samples and the floating times were measured by visual observation. All the data are averaged on three determinations.

2.2.4. Artificial gastric juice uptake

The rate of entry of the acidic media (pH 1.2, 3.0 and 5.0) into the floating units was determined by means of the Enslin apparatus (Bornemann et al., 1983). One unit of each sample was placed into contact with the medium and the amount absorbed was measured at determined intervals of time at 25 ± 0.2°C. All the data are averaged on three determinations.

3. Results and discussion

The units forming the system were composed of a calcium alginate core separated by an air compartment from a membrane of calcium alginate (Table 1, samples A) or of calcium alginate/PVA (Table 1, samples B, C and D). The units showed a nearly spherical shape and a size of about 3.7 mm. The calcium alginate membrane appeared translucent, and the calcium alginate/PVA membrane opaque (Fig. 1). The physical characteristics of the

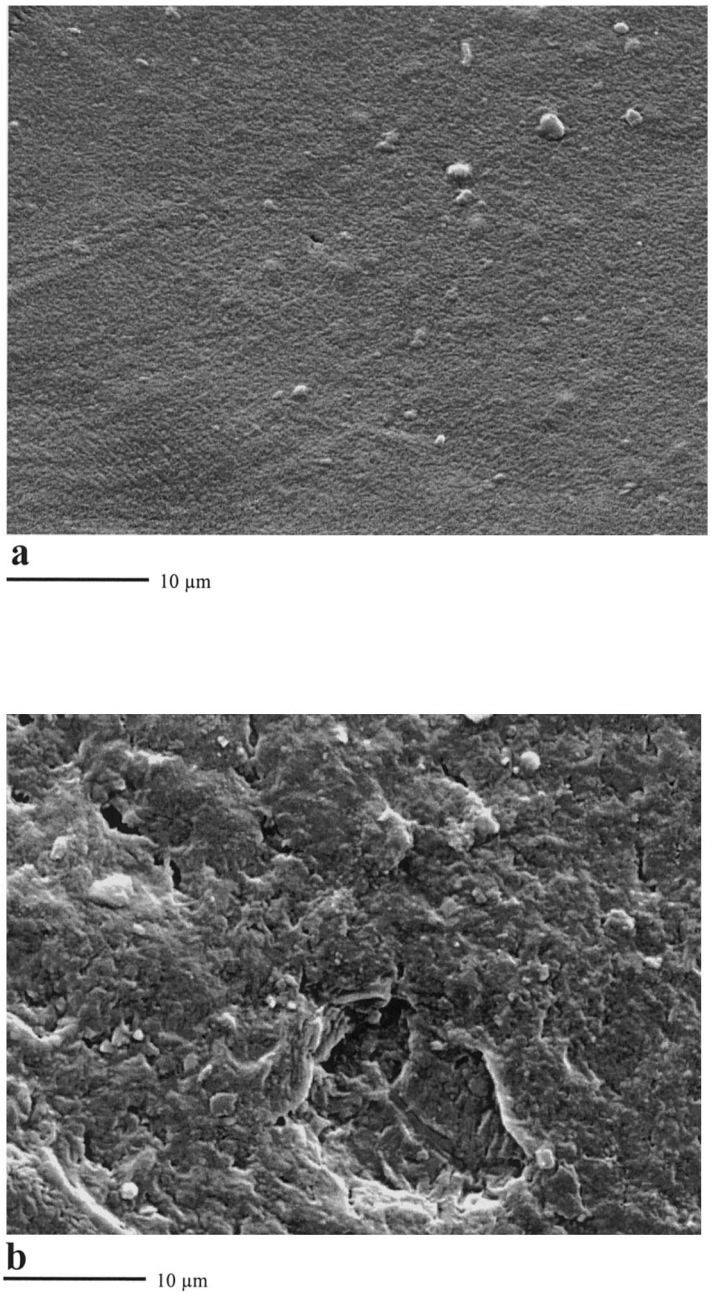
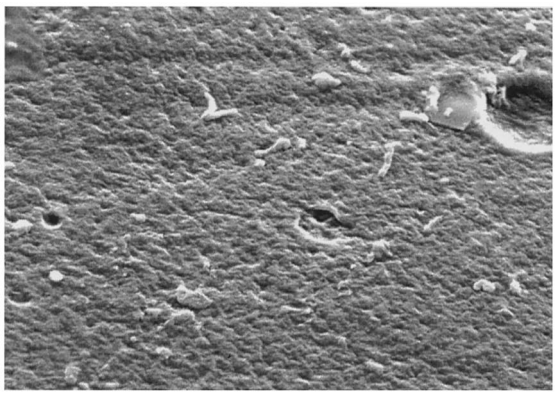
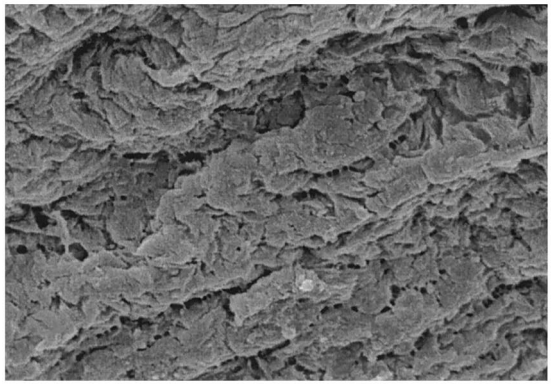


Fig. 4. SEM micrographs of the surface of calcium alginate (a) or calcium alginate/5% PVA membranes (b).

various samples are listed in Table 2.

Calcium alginate resulted from the complexation of the polyguluronic sequences by calcium ions (Grant et al., 1973). The gelation of the polymer occurs in water solution and forms an insoluble material which is mechanically strong, easy to handle and resistant to acidic media so remaining unchanged in the gastric region.





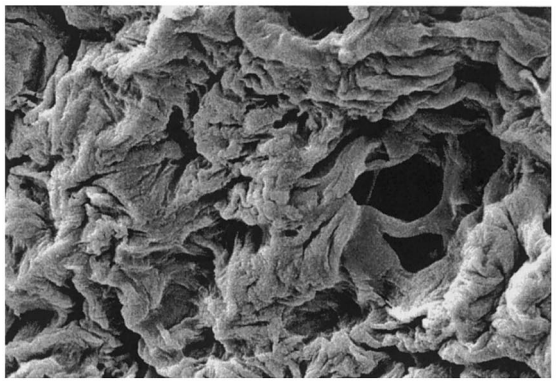


Fig. 5. SEM micrographs of the surface of calcium alginate/PVA membranes after immersion in artificial gastric juices: (a) PVA 15000; (b) PVA 49000; (c) PVA 100000.

Among the cations forming gels with alginates, calcium ions are preferred for their biocompatibility and high selectivity coefficient for alginates (Haug, 1959; Haug and Smidsrød, 1965). Since the high selectivity depends on the guluronic residues in the alginate molecules, an alginate having a high guluronic acid content was used to provide a polymer with greater crosslinking density and stability in acidic media (Bhagat et al., 1994).

Since the polymer crosslinking reaction forming the beads occurred in a medium containing an excess of $CaCl_2$ (Iannuccelli et al., 1995), unreacted calcium ions, i.e. not associated with the polymer, remained inside the crosslinked alginate matrix. As the beads were immersed in a water solution of sodium alginate, a calcium alginate membrane was formed on the surface as the consequence of the interfacial crosslinking reaction of sodium alginate in the solution with the free $CaCl_2$ diffusing from the beads.

After drying, the resultant units showed an air compartment between the core and the membrane. The air compartment was produced when hydrated, i.e. just formed, beads were used in the coating procedure, whereas it could not be produced by covering dried beads. Therefore, the air compartment formation is thought to be the consequence of core shrinkage occurring during the drying process of the resultant units, as schematized in Fig. 2.

The presence of the air compartment provided units with apparent density values less than unity (Table 2) and able to float immediately on immersion in water. In contrast, the components of the units (membranes and cores) assayed separately did not show any floatability. Upon contact with water the units showed lasting (more than 24 h) and excellent (100% floating ability) buoyancy. The water penetrated into the compartment but did not fill it completely thus not impairing floating ability. However, in the acidic media (pH 1.2, 3.0 and 5.0), the units prepared without PVA (A1) did not float. In these media the alginate film collapsed immediately (<1 min) causing the shrinkage of the air compartment. This phenomenon could result from the capillary forces, generated by water-air interfacial tension along the narrow channels of the membrane at the

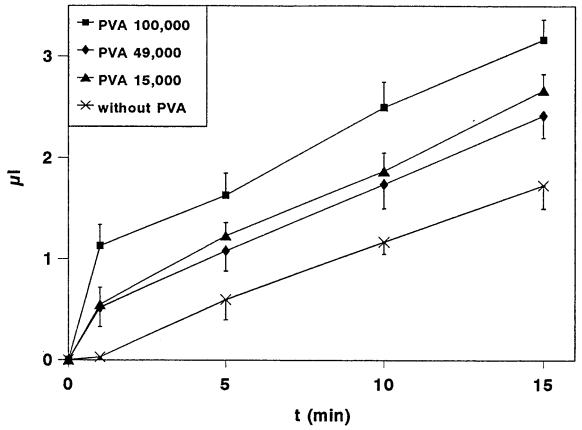


Fig. 6. Artificial gastric juice uptake of the units prepared by using 5% PVA with different molecular weight compared with those prepared without PVA.

boundary of the units (Richardson, 1961). The resulting pressure exerted by the medium on the membrane would determine, in acidic media, the collapse of the membrane probably weakened by a partial displacement process of the Ca linkages by non-crosslinking ions in the medium.

To overcome this drawback, two different approaches were adopted.

The first one aimed to make a stronger membrane, which resisted deformations, by increasing its thickness. This was achieved by prolonging the coating time (Table 1, samples A) for as long as an increase in membrane thickness could be produced (Table 2, samples A). However, the buoyancy of the units in artificial gastric juices could not be provided.

The second approach tried to diminish the effect of the capillary forces by producing a more permeable membrane. This was achieved by adding to the membrane-forming solution different amounts of a water-soluble polymeric substance, PVA with various molecular weights (Table 1, samples B, C and D). The addition of water-soluble ingredients to a water-insoluble film-coating can modify the permeability characteristics of the final coating membrane owing to the formation of discrete pores following additive leaching. This can occur also when macromolecular water-soluble additives dispersed on the molecular scale are used (Porter and Ghebre-Sellassie, 1994).

The units so prepared showed floating ability immediately upon contact with artificial gastric fluids, irrespective of pH, and for a long time (more than 24 h).

The floating ability increased along with the molecular weight and the concentration of the water-soluble macromolecule, reaching a maximum value of 100% by using PVA with the highest molecular weight (100000) at a concentration of at least 5% (Fig. 3). Samples, prepared with PVA having molecular weight less than 100000, showed a similar trend according to the PVA concentration, without, however, achieving floating abilities higher than 80%. The comparison between the floating abilities of the samples is shown in Table 3.

The presence of PVA in the calcium alginate membrane did not significantly modify physical parameters such as weight, diameter or density, but it determined the increase of the membrane thickness in comparison with sample A1 prepared with the same coating time (Table 2). Since the effect of the membrane thickness on the floating ability has been excluded (samples A2 and A3 which presented membranes thicker than A1 did not float, as reported above), the buoyancy could be reasonably attributed to modifications in membrane structure.

SEM analysis revealed a change in the membrane structure in function of the concentration and molecular weight of PVA. In fact, the membranes prepared without or with PVA concentrations $<4\%$ appeared quite compact and smooth both before and after contact with the artificial gastric juices (Fig. 4 a). Otherwise, the alginate/PVA membranes obtained by using a PVA concentration of at least 4% exhibited a rough and porous structure (Fig. 4 b). Upon contact with acidic media, a progressively more porous membrane structure, increasing with the PVA molecular weight, was observed (Fig. 5). This suggested that the water-soluble macromolecule in a concentration of at least 4% created pores both because it affected the calcium alginate network formation during the unit preparation and because it was leached from the membrane into the medium during the floatability evaluation.

To verify the role of the porosity on the membrane permeability, the uptake of the artificial gastric juices by the units was investigated. The resultant patterns were not affected by the pH of the gastric medium. No significant differences in permeability were noticed between the units with alginate membranes and units with membranes containing PVA concentrations less than 5%. In contrast, concentrations of the hydrophilic macromolecule of at least 5% led to detection of increased absorption rates in the early stage of the process (Fig. 6). The highest permeation rate was observed when using PVA 100000. Thus, the accelerated flow rate through the porous membrane obtained by using 5% PVA 100000, indicative of a diminished capillary pressure, prevented membrane deformation in all the units and determined the best floating ability.

4. Conclusions

A floating air compartment multiple unit system was developed by a rather simple procedure. It showed an excellent immediate and lasting buoyancy in artificial gastric juices. The formulation study revealed that the degree of membrane porosity, necessary to provide and maintain the buoyancy of the units for a prolonged period of time, could be achieved by using PVA 100000 at the minimum concentration of 5% (sample B4), as the porogeneous compound. The units so obtained can be considered as the optimum dosage formulation.

In order to investigate the actual buoyancy of the system on the gastric content and its usefulness in extending gastric residence time, such a formulation will be selected for an 'in vivo' examination.

Acknowledgements

This work was supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST), Rome, Italy.

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