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Formation and Evaluation of Valganciclovir Hydrochloride Immediate Release Tablets

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A B S T R A C T

Valganciclovir HCl (VGH) is the widely used drug for the treatment of cytomegalovirus (CMV) retinitis infection with an induction dose of 900 mg per oral (p.o.) twice a day and a maintenance dose of 900 mg (p.o.). This required dose of the drug also leads to multiple side effects due to repeated administration. The research was highlighted to formulate and evaluate tablets of VGH with the dose of 455 mg to reduce dosing frequency and associated side effects. The formulation methods are done in two methods i.e., Dry and Wet granulation. The decrease in dose also minimizes the hepatic and nephrotic load. The optimized batch of the formulation was subjected to comparative in vitro and in vivo evaluation. The tablet core composition is the primary influencer of the drug delivery fraction in a first order, whereas the membrane characteristics control the drug release rate. In vivo pharmacokinetic studies revealed that the newly developed formulation has first-order release for 24 h with a single dose of 455 mg while the marketed formulation requires twice administration within 24 h to maintain the plasma concentration in the therapeutic window.

Keywords: Valganciclovir hydrochloride, anti-viral, Therapeutic window, Immediate release tablets.

A R T I C L E I N F O

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C O N T E N T S

1. Introduction

Valganciclovir, a prodrug of ganciclovir, is well absorbed from the gastrointestinaltract and rapidly metabolized in the intestinal wall and liver to ganciclovir. The absolute bioavailability of ganciclovir from VALCYTE tablets following food was approximately 60% (3studies, n=18; n=16; n=28). Valganciclovir hydrochloride is a polar hydrophilic compound with a solubility of 70 mg/mL in water at 25 ºC at a pH of 7.0.

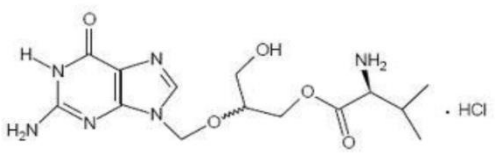

Figure.1. Valganciclovir Hydrochloride

Name : Valganciclovir Hydrochloride
Chemical name : L-valine,2-[(2-amino-1,6-dihydro-6-oxo-9Hpurin-9-yl)methoxy]-3-hydroxypropylester, monohydrochloride
pH : : 4.2
pKa: 7.5
Molecular Wt. 390.83
Molecular formula $C_{14}H_{22}N_6O_5$ HCl
Solubility: Freely soluble in water, sparingly soluble in methanol.

Excepients Profile: Micro crystalline cellulose

Synonyms: Avicel, cellulose gel, crystalline cellulose, E460. Chemical Name: Cellulose Empirical Formula and Molecular Weight: (C6H10O5)n ≈36 000 where n ≈ 220.

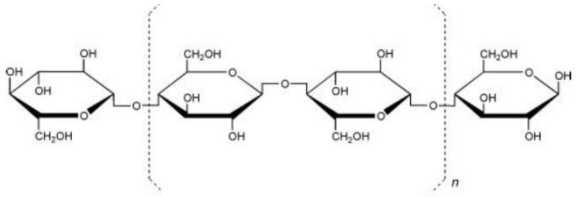

Figure.2

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Melting point: 260–270°C

Moisture content: Typically, less than 5% w/w. However, different grades may contain varying amounts of water. Microcrystalline cellulose is hygroscopic.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution, practically insoluble in water, dilute acids, and most organic solvents.

Specific surface area: 1.06–1.12 m2/g

Applications in Pharmaceutical Formulation or Technology: Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct- compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products.

Croscarmellose Sodium:

Synonyms: Ac-Di-Sol, crosslinked carboxymethylcellulose sodium, Explocel, modified cellulose gum, Nymcel ZSX, Pharmacel XL, Primellose, Solutab, Vivasol.

Chemical Name: Cellulose, carboxymethyl ether, sodium salt, crosslinked Empirical Formula and Molecular Weight: Croscarmellose sodium is a crosslinked polymer of carboxymethylcellulose sodium. Typical molecular weight is 90000–700000.

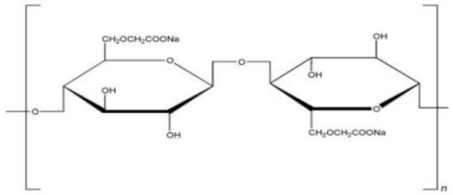

Figure.3

Colloidal Silicon Dioxide

Chemical Name: Silica Empirical Formula and Molecular Weight: SiO2 and 60.08Structural Formula: [CH3(CH2) 16COO]2Mg Functional Category: Adsorbent, anticaking agent, emulsion stabilizer, glidant, suspending agent, tablet disintegrant, thermal stabilizer, viscosity-increasing agent.

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products. Its small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling.

Colloidal silicon dioxide is also used as an adsorbent during the preparation of wax microspheres, as a thickening agent for topical preparations, and has been used to aid the freeze-drying of nano capsules and nanosphere suspensions.

Stability and Storage Conditions: Colloidal silicon dioxide is hygroscopic but adsorbs large quantities of water without liquefying. When used in aqueous systems at a pH 0–7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system. However, at a pH greater than 7.5 the viscosity increasing properties of colloidal silicon dioxide are reduced, and at a pH greater than 10.7 this ability is lost entirely since the silicon dioxide dissolves to form silicates. Colloidal silicon dioxide powder should be stored in a well-closed container.

2. Materials and methods

Drug Delivery System Used in Current Study:

Immediate release drug delivery system:

Methods for the Preparation and Characterization of immediate release valganciclovir hydrochloride tablets. Direct Compression Procedure for the Preparation of immediate release tablets Processing steps are Raw material → Weighing → Screening → Mixing → Compression Definition: The term “direct compression” is defined as the process by which tablets are compressed directly from a powder mixture of API and suitable excipients. No pretreatment of the powder blend by wet or dry granulation procedure is required.

Direct compression consists of compressing tablets directly from powdered materials without modifying the physical nature of the materials. This method is applicable for crystalline chemicals having good compressible characteristics and flow properties. If necessary, direct compression vehicles can be used which have good flow and compressible characteristics. Commonly used direct compression diluents are: MCC (Microcrystalline cellulose (Avicel), Spray dried lactose, Starch - (Sta Rx 1500, Embdex, Celutab), Sugar (Sugartab, Nutab), Dicalcium phosphate dihydrate (Di-Tab), Mannitol for chewable tablets.

Solubility Determination of Drugs:

The solubility study of the active drug was investigated in four different
media viz.,

- Purified water
- 0.1 N hydrochloric Acid (HCl) of pH 1.1 4 - USP
- Acetate buffer of pH 4.5 -USP
- Phosphate buffer of pH 6.8 -USP

The required quantity of respective media was taken to a volumetric flask and heated to 37oC by a magnetic stirrer with a hot plate. Priorly weighed active drug was added to the contents in a volumetric flask up to the saturation stage and the total amount of drug added was noted. Stirring was continued to the next 4 hours at 37 ±0.5 C. The entire samples were filtered through a 0.45 µm Millipore

membrane filter. A measured quantity of filtered sample was transferred to another volumetric flask and made further aliquotes. The absorbance was measured using double beam UV visible spectrophotometer (Cyberlab, UV-1700 E 23) at respectiveλmax values.

Construction of standard Calibration Curves:

The required quantity of active drug was weighed accurately and transferred to the volumetric flask. A specified amount of media was added to the contents of the volumetric flask. The volumetric flask was shaken until the complete solubility of the drug was achieved and made up the required volume with the remaining quantity of respective media. Likewise stock solutions were prepared in all the media. Standard calibration curves in different media were constructed using above stock solutions. The samples were scanned for λmax at the UV range of 180-380 nm. After a day again the samples were scanned for λmax. The λmax at initial and of next day were compared for the assessment of stable nature of pure drug in the above media. From the above stock solutions, different concentrations of the solutions were prepared and standard calibration curves were calibrated.

Drug excipient compatibility studies:

The compatibility of drug and formulation components is an important prerequisite before formulation. It is therefore necessary to confirm that the drug does not react with the polymers and excipients under experimental conditions and affect the shelf life of the product or any other unwanted effects on the formulation. As a part of the product development, the compatibility of various excipients with active was evaluated. According to the functional category these excipients were mixed in different ratios with the drug.

Sample preparation:

- Materials were weighed uniformly, and individual excipients were mixed with Valganciclovir Hydrochloride.
- 4 Samples were prepared from each individual excipient and transferred into dried glass vials. (Total number of samples 76).
- 4 samples of Valganciclovir Hydrochloride were prepared by transferring 2 grams each to dried glass vials. (Total number of samples 4).
- 4 samples of each excipient-drug mixture of approx. 2 grams were prepared and transferred into dried glass vials. (Total number of samples 76).
- Glass vials were closed with the stoppers and crimped with aluminum seals. A small opening was pierced on the stoppers for 2 vials which were placed in accelerated conditions, to expose the sample to the external environment in the chamber. One vial was placed at Room temperature and the remaining vial was submitted to ARD for initial analysis.
- The vials were labeled with adequate identification like Product name, composition, condition/ duration, date of initiation, and protocol number.
- Samples were loaded into an accelerated stability study chamber at 40°C+2°C, 75±5% RH, and Room temperature.

Study Lubricated blend parameters:

Bulk Density:

Bulk Density 20gms of formulation material was taken to a dry 100 ml cylinder, granules were leveled carefully without any compaction, and the unsettled apparent volume, Vo, was read. The bulk density in gm/ml was calculated using the formula.

$$B.D = (M) / (Vo)$$

Where, M = Total mass of the material

Tapped Density

After carrying out the procedure of measuring bulk density, the cylinder containing the sample was tapped manually 100 times initially followed by an additional tapping of 100 times until 124 difference between succeeding measurements was less than 2% and then tapped volume Vf, was measured to the nearest graduated units in ml, using as per the formula:

$$T.D = (M) / (Vf)$$

Assessment of Powder Compressibility:

The Compressibility Index and Hausner Ratio are the indices of the propensity of a powder to be compressed. They are measures of the relative importance of interparticulate interactions. In free-flowing materials, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index and the Hausner Ratio, which are calculated using the following formulae:

Compressibility Index:

The Compressibility Index is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. The compressibility of a material can be estimated from the tap and bulk density measurements.

Particle size determination(P.S.D):

PSD was done by electromagnetic sieve shaker, the sieve was arranged sequencely with respective e of aperture size or mesh20,30,40,60 and 80. Lastly, we keep the base plate then the required amount blend keep in top mesh thenthe sieve shaker runs for 5 min.

Hardness, Weight Variation, and Friability Determination: The weight variation was determined according to the official compendial procedures by taking 20 tablets using an electronic balance. Tablet hardness was determined for 10tablets using a Monsanto tablet hardness tester. Friability was determined by testing 10 tablets in a friability tester (Campbell Electronics) for 300 revolutions at 25 rpm.

In-vitro Drug Release Studies:

The in-vitro dissolution studies were performed for up to 1hoursusing dissolution apparatus (ELECTROLAB, Mumbai, India) The dissolution medium consisted of 900 ml of 0.1 N HCl of pH 1.2 maintained at 37 ±0.5 °C 50 rpm and apddle type. An aliquot sample of 5 ml was withdrawn

at specific time intervals and filtered through a Millipore 0.45 µ filter. Subject to necessary dilutions the samples were analyzed and the cumulative percentage of the drug released was calculated. The mean of 6 tablets from different batches was used for the analysis of the data.

In-*vitro* drug Review Studies Multiple media:The in vitro dissolution studies were performed up to 1hoursusing dissolution apparatus (ELECTROLAB, Mumbai, India) The dissolution medium consisted of 900 ml of 0.1NHCl of pH-1,4.5pH acetate buffer & 6.8pH phosphate buffers maintained at 37±0.5°C, 50 rpm. An aliquot sample of 5 ml was withdrawn at specific time intervals and filtered through a Millipore 0.45µ filter. Subjection to necessary dilution samples were analyzed and the cumulative percentage of the drug released was calculated. The mean of 6 tablets from different batches was used for the analysis.

Table.1: The following are the list of equipments used for the formulation development.

S.no	Equipment	Manufacturer
1	Friability tester USP	Electrolab
2	Tablet hardness tester	Pharmatron tablet tester 8m
3	Electronic LOD measurement apparatus (Halogen Moisture Analyzer)	Sartorius MA 100
4	Electromagnetic sieve shaker	Electrolab
5	Tap Density Apparatus USP	Electrolab
6	Electronic weighing balance	Sartorius precision balance
7	17-station rotatory tableting machine	Cadmach
8	Coating machine	Neocota
9	Rapid dryer	Retsch
10	Lab stirrer	Remi
11	Moisture Content (KF Titrino)	Metrohm
12	UV – Spectrometer	Shimadzu
13	High-pressure liquid chromatographic apparatus	Azilent
14	pH meter	Thermo
15	Mini Roll Compactor, Model: CPMMRC – 100/25	Chamunda Pharma Machinery
16	Fluid bed processor	Pharma glatt
17	Rapid mixer granulator	Anchor mark
18	Blender	Anchor mark
19	FT-IR	Electrolab

Table.2: Chemicals Used in the Current Study

Name of the Excipient/chemical	source
Microcrystalline cellulose	FMC biopolymer
Cross povidone	FMC biopolymer
Cross carmellose sodium	FMC biopolymer
Colloidal silicon dioxide	Evonic industries
Stearic acid	ISP

Table.3: Samples were drawn as per the sampling intervals specified below

S.No.	Storage condition / Packing	Sampling intervals
1	40 ± 2 °C / 75 ± 5% RH Clear Glass vials with holes on the top.	15days&30 days
2	Room Temperature Clear Glass vials without holes	(initial) & 30 days

Table.4: The compressibility of a material can be estimated from the tap and bulk density measurements

S.NO	% Compressibility Index Flow ability	Flow ability
1.	1 5-15	Excellent
2.	12-16	Good
3.	18-21	Fair-passable
4.	23-35	Poor
5.	33-38	Very poor
6.	<40	Very Very Poor

The compressibility index were calculated using the formula: Compressibility index=T.D-B.D/T.D ×100

3. Results and Discussion

Valganciclovir Solubility Determination:

In pre-formulation studies, drug solubility assessment at different pH conditions is the prime most consideration, as it directly simulates the drug absorption throughout the GI tract106-108. Valganciclovir has shown highest solubility in 0.1 N HCl and in pH 6.8 Phosphate buffer. The solubility of Valganciclovir in water is 124.81 mg/ml where as in case of acetate buffer pH 6.8 the solubility is 189.37 mg/ml.

Table.5: 26 Solubility test

Media	Solubility (mg/ml)
Water	124.81
0.1 N HCl	216.06
pH 4.5 Acetate buffer	76.48
pH 6.8 phosphate buffer	189.37

Construction of standard calibration curves for Valganciclovir: Standard calibration curve was constructed by scanning the Valganciclovir in 0.1N HCl. The standard graph of Valganciclovir in 0.1N HCl has shown a good linearity with R^2 of 0.997 in the concentration range at 492 nm range.

Compression parameters:

Punch Description:

Size: : 16.60 X7.75mm

Shape : Oval

Upper punch Embossing :VLG

Lower punch Embossing : 450

Standard aqueous film coating process parameters have been followed for coating of the tablets. The parameters are as follows.

Table.6: Core tablets Parameters:

S.No	Compression parameters	Results F6 450 mg
1	Punch Dimensions (mm)	16.60 x 7.75
2	Average weight (mg)	652.7
3	Hardness (kp)	5.5 ± 0.5
4	Thickness (mm)	3.96 ± 0.008
5	Weight variation (%)	1.4± 0.32
6	Friability %	0.45 ± 0.024

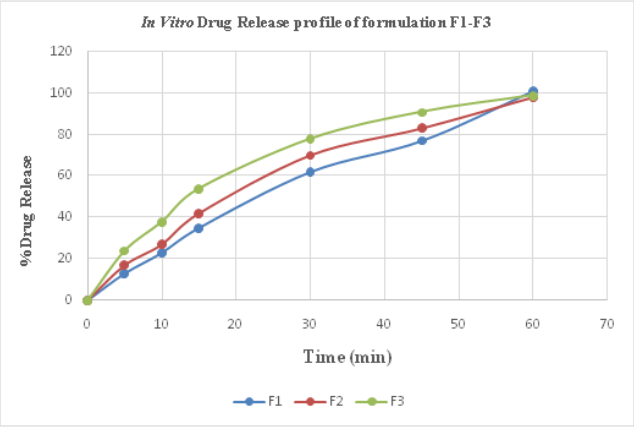

Figure.4

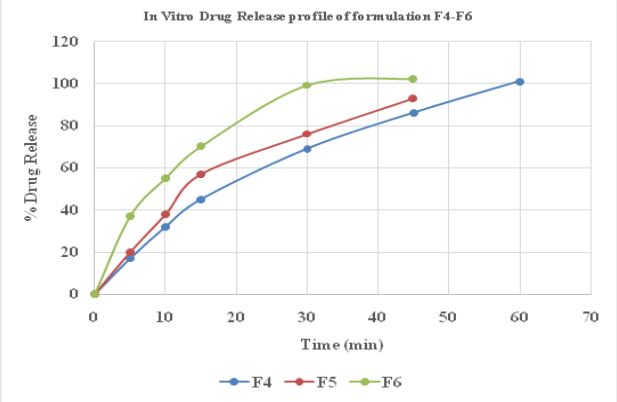

Figure.5

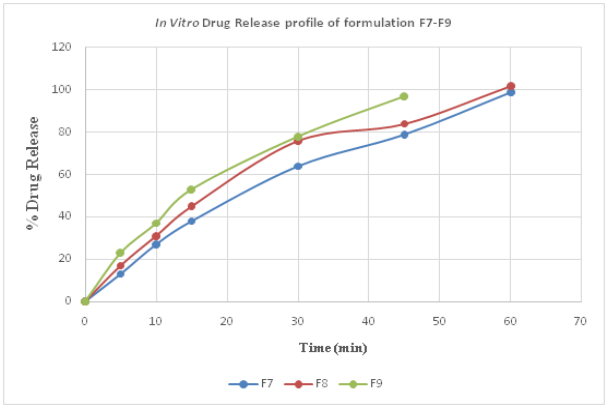

Figure.6

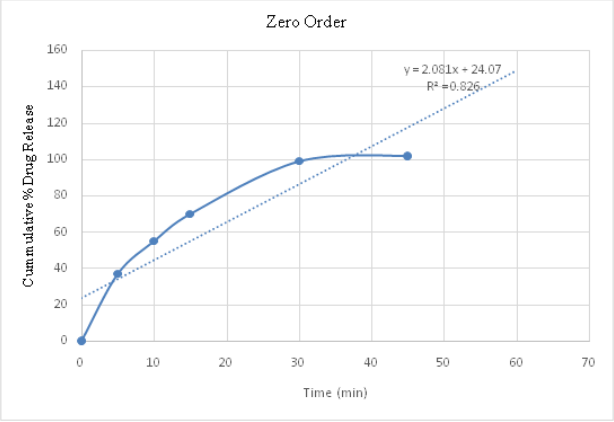

Figure.7

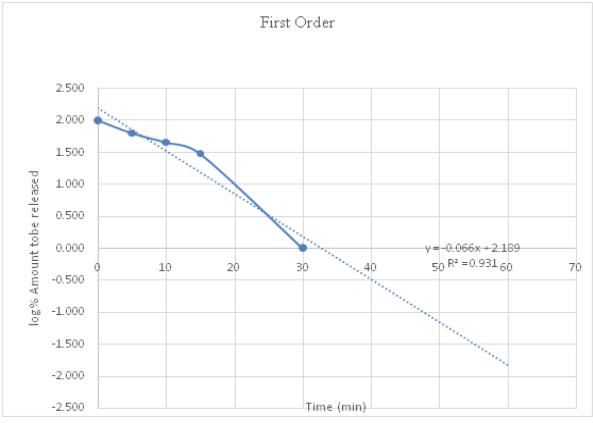

Figure.8

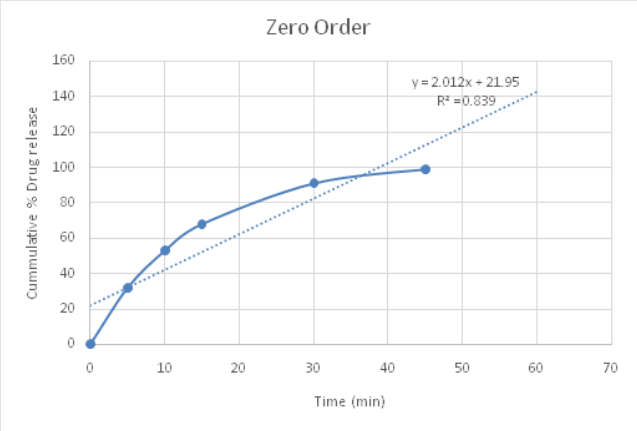

Figure.8

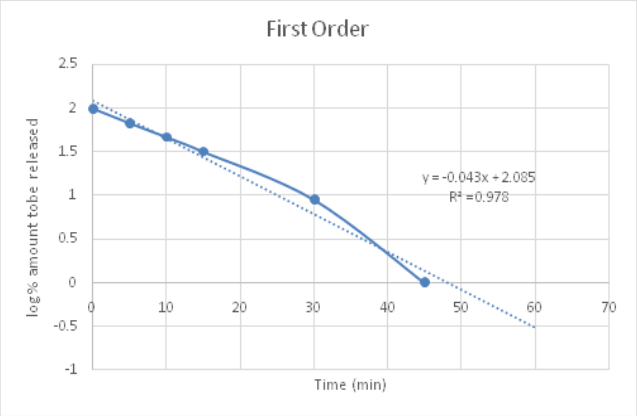

Figure.9

Table.7: Pharmacokinetic parameters of F6

Time (min)	Formulation (F6)				
	Cumulative % Drug release	Log Cumulative % Drug release	log% remaining to be release	sqrt time	log time
0	0		2.000	0.000	
5	37±0.011	1.568	1.799	2.236	0.699
10	55±0.017	1.740	1.653	3.162	1.000
15	70±0.021	1.845	1.477	3.873	1.176
30	99±0.023	1.996	0.000	5.477	1.477
45	102±0.027	2.009		6.708	1.653
60				7.746	1.778

Table.8: Comparative Dissolution Profile F1-F6 With Referance

Order	R^2- value	
	Formulation F6	Reference
Zero order	0.8265	0.8398
First Order	0.9315	0.978

4. Conclusion

The current study was to develop the valganciclovir hydrochloride immediate release tablets and comparing with marketed product. Valganciclovir hydrochloride comes under the category of treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). In this study Valganciclovir hydrochloride were prepared by wet granulation method with top spray, and subjected to physicochemical and in vitro dissolution studies by comparing with marketed product.

- The tablets prepared were found to be within the official limits with respect to hardness, weight variation, drug content, thickness etc.
- Among all the seven formulations of the release profile of trial F6 was found to be similar to the Marketed Product release profiles.
- Formulation-F6 containing Valganciclovir hydrochloride equivalent to Valganciclovir 455mg per tablet and developed, to similar and equal to the innovator product in respect of all tablets properties and dissolution profile.
- Hence the study resulted in the development of Valganciclovir hydrochloride Immediate Release tablets comparable to the innovator product for Valganciclovir hydrochloride which is stable.

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