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DEVELOPMENT AND *IN-VITRO* EVALUATION OF IN SITU GELS OF HYDROCORTISONE FROM TEMPERATURE INDUCED GELLING SYSTEM.

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Abstract:
Aphthous ulcers are painful sores that may occur in the mouth's mucous membrane and are the most common type of oral lesions. The present work was aimed to develop a in-situ gels and films of hydrocortisone for the treatment of aphthous ulcer. The in-situ gels and film was developed by using methylcellulose, based on the concept of temperature dependent gelling system. The sol-to-gel transformation occurred during the reduction of temperature. The in-situ gels were evaluated for gelling capacity, drug content, viscosity & in-vitro release were as in the film its evaluated for tensile strength, folding endurance, thickness etc. The experimental part shows that viscosity of the sol was increased by increasing the concentration of polymer. All the results were found to be satisfactory, when compared between the in-situ gels and films. The has shown the best formulation because of their therapeutic efficacy and provided sustained release of the drug over a period of time. These results demonstrate that the developed system is an alternative to conventional drug delivery system, patient compliance, industrially oriented and economical.

Key words: In situ, Film, Methylcellulose, Gellation temperature & gellation time.

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1. INTRODUCTION:

In situ gel forming drug delivery is a type of mucoadhesive drug delivery system. The development of in situ gel systems has received considerable attention over the past few years. Capable of releasing drug in a sustained manner maintaining relatively constant plasma profiles. These hydrogels are liquid at room temperature but undergo gelation when in contact with body fluids or change in pH. These have a characteristic property of temperature dependent, pH dependent and cation induced gelation. Compared to conventional controlled release formulations, in situ forming drug delivery systems possess potential advantages like simple manufacturing process, ease of administration, reduced frequency of administration, improved patient compliance and comfort8. In situ gel can be easily applied in liquid form to the site of drug absorption. At the site of drug absorption, they swell to form a strong gel that is capable of prolonging the residence time of the active substance, In situ gels are administered by oral, ocular, rectal, vaginal, injectable and intra-peritoneal routes.

IMPORTANCE OF IN SITU GELLING SYSTEM:

- The major importance is the possibilities of administrating accurate and reproducible quantities compared to already formed gel.
- In-situ forming polymeric delivery system having advantages like ease of administration and reduced frequency of administration improved patient compliance and comfort.
- Poor bioavailability and therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye and undergoes a sol-gel transition from instilled dose.
- Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
- Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.

2. OBJECTIVES

Nowadays aphthous ulcer is very common type of disease irrespective of the age. presently available delivery systems (tablet, mouth wash) have minimum effect on the aphthous ulcer and about 90% of the drug are wasted during these delivery systems to avoid wastage of the drug, the alternative ways like in-situ gels and films are used. These methods can increase the bioavailability, therapeutic effect and increasing the residency time of the drug by reducing the inflammation of the aphtholmic cells.

The present work is intended to formulate and evaluate the in-situ gels and films of hydrocortisone(corticosteroid), in view of increasing residence time and bioavailability of drug.

1. Aphthous ulcer are round or oval with grayish yellow of inflamed mucosa.
   The ulcer usually occurs on the nonkeratinized oral mucosa, including the lips, the buccal mucosa, floor of the mouth, soft palate and the ventral surface of the tongue.
2. Glucocorticoids (Hydrocortisone) have potent anti-inflammatory actions.
3. Selection of drug and excipient using FTIR.
4. To formulate the in- situ gels and films of hydrocortisone.
5. To achieve sustained and prolonged release of drug from in-situ gels and films.
6. To evaluate the developed gels and films for various characterizations.
7. To carry out the in-vitro release studies, kinetic studies.
8. To carryout short term stability studies.

DRUG PROFILE
Hydrocortisone
Chemical Name:
11β,17,21,-trihydroxy pregn-4-ene-3,20-dione.

Structural formula:

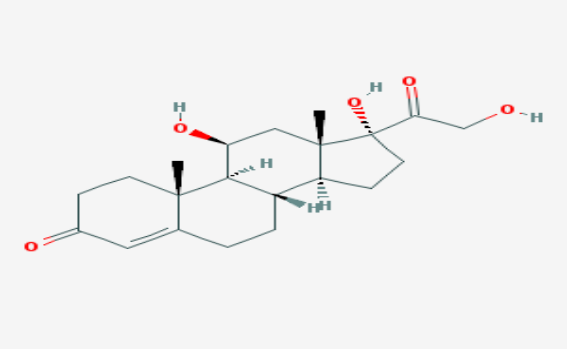

Fig 6 structure of Hydrocortisone

Empirical formula: $C_{21}H_{30}O_5$ **Molecular weight:** 362.47g/mol

3. Preparation of *in situ* gelling system:

For the preparation of methyl cellulose containing in situ gel formulations, sodium citrate was added to distilled water with continuous stirring until clear solution was obtained. Methyl cellulose was added to above solution with continuous stirring and allowed to hydrate overnight. Calculated amount of Hydrocartisone (1% w/v) drops triethanolamine was added separately and then added to polymer solution under constant stirring. The formulation design Of Hydrocartisone in situ gel was tabulated. The optimization concentration of methyl cellulose was selected on the basis of gelation temperature and gelation time. Further, the prepared formulations were evaluated for various characterization studies.

Table 1: Formulation design of *in situ* gel

Batch Code	Hydrocar tisone (%w/v)	Methyl cellulose (%w/v)	Sodium citrate (%w/v)	Triethan olamine	Distilled Water
F1	1	0.25	0.25	Q.S	Q.S
F2	1	0.50	0.25	Q.S	Q.S
F3	1	0.75	0.25	Q.S	Q.S
F4	1	1.00	0.25	Q.S	Q.S
F5	1	1.25	0.25	Q.S	Q.S
F6	1	1.50	0.25	Q.S	Q.S
F7	1	1.75	0.25	Q.S	Q.S
F8	1	2.00	0.25	Q.S	Q.S

RESULTS AND DISCUSSION:

Determination of λ_{max}

The λ_{max} of Hydrocortisone was found to be 242 nm in methanol.

Drug solubility studies

Drug solubility studies have done by using various solvents. Solubility of Hydrocortisone was found to be in methanol. Results have showed that Hydrocortisone is highly soluble in methanol. It has high solubility in methanol than other solvents and poorly soluble in water compared to acetone.

Calibration curve of Hydrocortisone

The absorbance was measured in a UV spectrophotometer (Shimadzu UV"1800) at 242 nm in methanol. The absorbance so obtained was tabulated as in Table 7. Calibration curve was plotted as shown in the figure 1.

Table 2: Calibration data of Hydrocortisone

SL .no	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	0.5	0.132
3	1	0.256
4	1.5	0.412
5	2	0.591
6	2.5	0.772
7	3	0.883

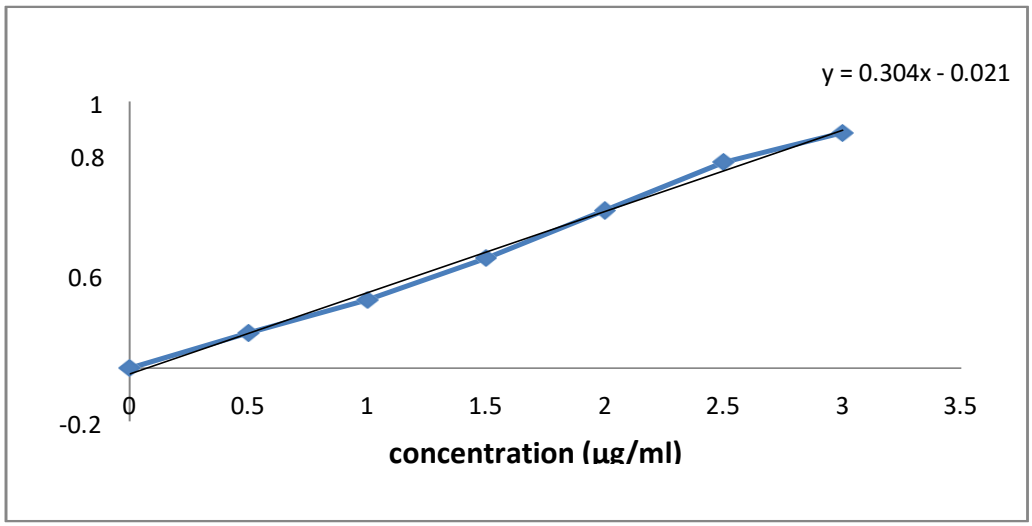

Figure 1: Calibration curve of Hydrocortisone

FT-IR spectrum

Infra-red spectra of pure drug Hydrocortisone and combination of drug with polymers (Methyl cellulose) were obtained ad shown in figures 2 .

All the characteristic peaks of Hydrocortisone were present in spectrum of drug and polymer mixture, indicating compatibility between drug and polymers. The spectrum confirmed that there is no significant change in chemical integrity of the drug.

The functional group peaks of Hydrocortisone were found in all the IR-spectra and was tabulated in Table.

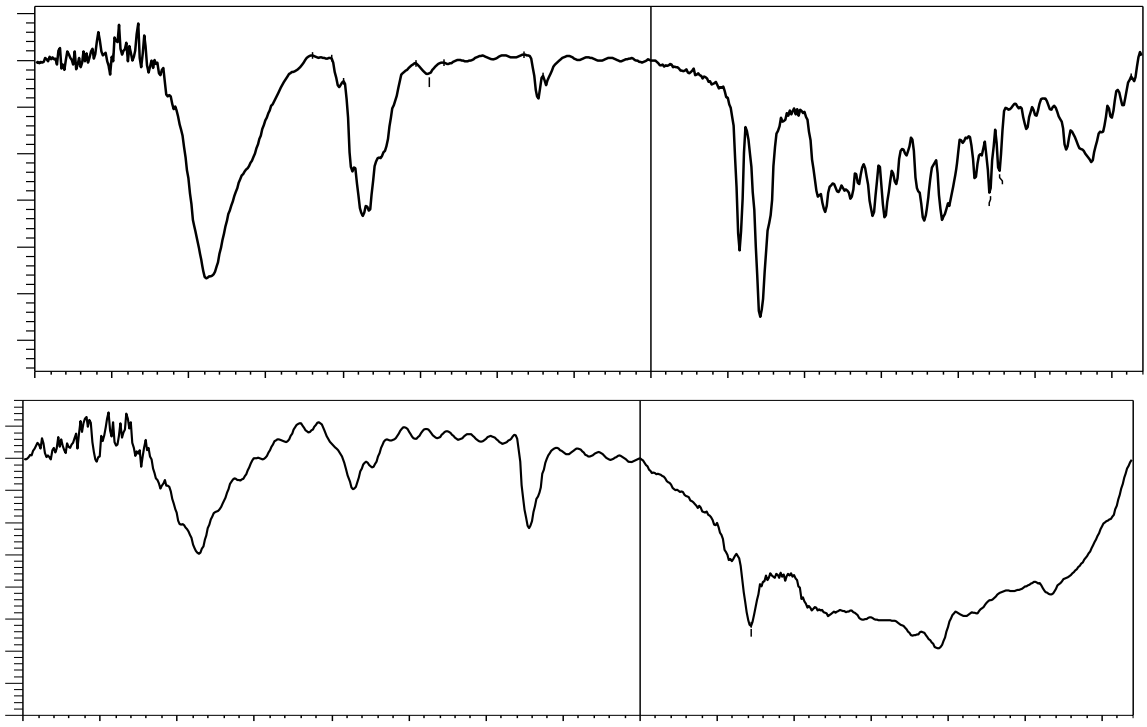

Figure 2: FT-IR spectrum for pure drug

4. Evaluation of hydrocortisone *in situ* gels

Clarity test

Clarity test for the prepared formulations has done by visual inspection under black and white background. There was no evidence of contamination, the entire formulations pass clarity test.

Table 3: Clarity test for the *in-situ* gels

Formulation code	Clarity test
F1	Passes
F2	Passes
F3	Passes
F4	Passes
F5	Passes
F6	Passes
F7	Passes
F8	Passes

Determination of pH

The pH of *in situ* gels was determined using a calibrated pH meter. The readings were taken for average of 3 samples. Methylcellulose exhibited pH values in the range of 5.8 to 6.9 at 25°C which is tabulated in Table 4.

Table 4: Determination of pH for *in situ* gels

Formulation code	pH
F1	5.8±0.008
F2	5.9±0.057
F3	6.2±0.044
F4	6.4±0.072
F5	6.9±0.090
F6	6.5±0.051
F7	6.8±0.018
F8	6.8±0.005

***In vitro* gelling capacity**

It was found that the gel intensity was increased when the concentration of polymers was increased. Experimental parts (Table.5) have showed that the formulation F7 and F8 were satisfactory to cause gelation.

Table 5: *In vitro* gelling capacity of the *in situ* gels

Formulation code	Gelling capacity
F1	+
F2	+
F3	+
F4	+
F5	++
F6	++
F7	+++
F8	+++

+ - Gels after few mints disappear rapidly

++ - Immediately gelling re-disappeared after hour

+++ - Immediately gelling staying for hours

Viscosity and Rheology of the *in situ* sols

The viscosity of *in situ* solutions was determined by Brookfield viscometer (Table.6). Among all formulations, F1 (0.25%) showed least viscosity and F8 (2%) showed more viscosity. This says increase in polymer concentration causes increasein viscosity of the solution.

Table 6: Viscosity of the *in situ* sols

Shear rate (RPM)	Viscosity of the formulation (cps)	
	F1	F8
10	550	1000
20	490	940
30	440	870
40	350	750
50	290	630

The rheological studies of the optimum formulations were studied by plotting a graph of shear rate vs. viscosity (fig 14). This showed that the viscosity of the formulations decreased with increase in shear rate, which indicates the character of pseudoplastic fluids.

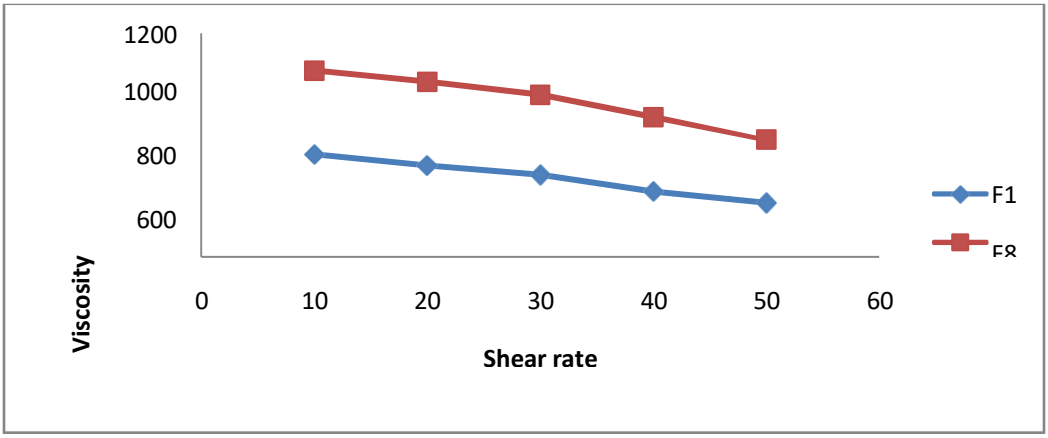

Fig 3: Rheological profile of the *In situ* gelling systems

Syringe ability of in situ gel

Formulations F1 to F3 expelled quite easily from the syringe equipped with 20 gauge needle and passes the syringeability test. Formulation F4 and F8 fail the syringeability test may be because they contain higher concentration of methyl cellulose.

Table 7: Syringeability test

Formulation code	Syringeability
F1	Passes
F2	Passes
F3	Passes
F4	Fail
F5	Fail
F6	Fail
F7	Fail
F8	Fail

Spreadability Test.

With increase in the concentration of the polymeric component, viscosity ofthe solution was increased. At the same time Spreadability of the formulation was reduced. This can be observed from the evaluation tests data compiled in Table 8. F1formulation showed a higher Spreadability compared to F8 formulation because gel strength and viscosity of F8 formulation were higher. Consequently, its Spreadability was less.

Table 8: Spreadability Test

Formulation code	Spreadability
F1	12 ± 0.03
F2	13.6 ±0.15
F3	14.2 ±0.11
F4	16 ±0.09
F5	18.3±0.05
F6	22.5 ±0.18
F7	26.8 ±0.06
F8	30± 0.011

Drug content:

The drug content estimation was done and the absorbance were measured byUV spectrophotometer (Shimadzu UV"1800), drug content was calculated (Table 9).Drug content of all formulations was found between 76.4±0.051 to 97.6±0.093 w/v.

Table 9: Drug content of *in situ* gel

FormulationCode	Absorbance(nm)	Conc. of drugµg/ml	% ofDrug
F1	0.206	0.700	80.3±0.012
F2	0.196	0.66	76.4±0.051
F3	0.208	0.707	81.1±0.076
F4	0.217	0.738	84.7±0.082
F5	0.250	0.850	97.6±0.093
F6	0.218	0.741	85.1±0.091
F7	0.247	0.840	96.4±0.097
F8	0.243	0.826	94.8±0.066

***In vitro* release studies**

The *in vitro* diffusion profile of Hydrocartisone from the gels containing different concentration of methylcellulose is shown in fig 15. Formulation F1 (0.25%)showed least drug release (84.86%) and formulation F5 (1.25%) showed maximum drug release (96.819±0.022%). For the first 6 hours of study, initial burst release was higher in *in-situ* gel formulations. From the *in-vitro* release studies we came to know that release rate was maximum for the formulation F5, but when the concentration of gel was further increased the release rate of the drug was decreased. From the experimental results we can say that release pattern was depends up on the concentration of polymer used.

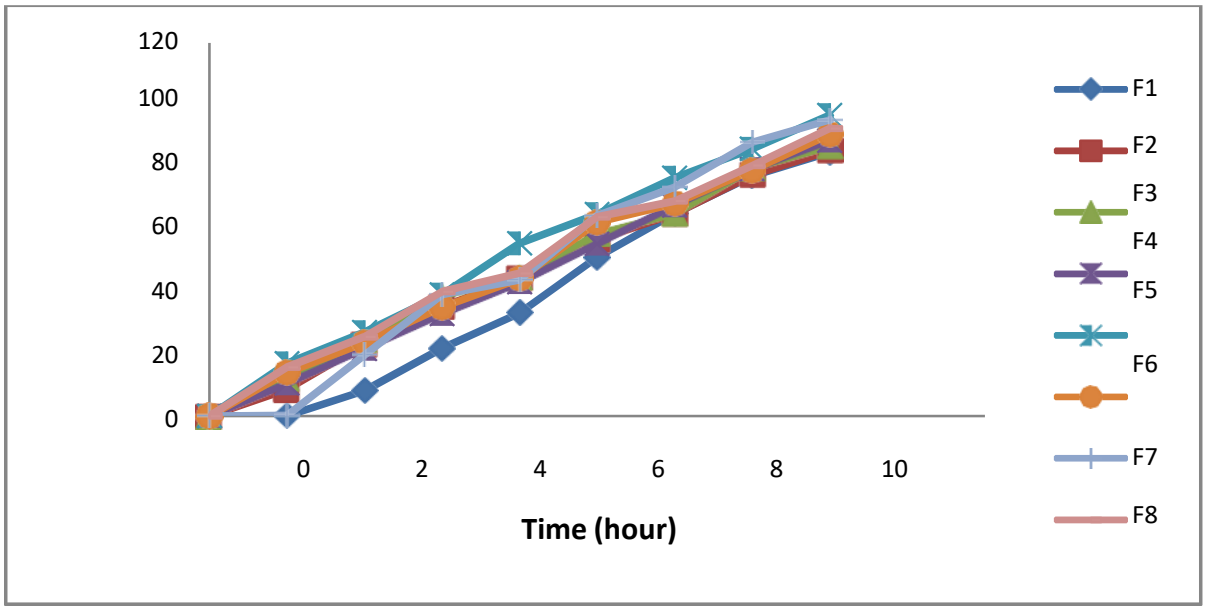

Fig 4: Comparative drug release profile of the *in situ* gel formulation

Release kinetics:

The regression values of zero order kinetics of *in-situ* gel for all the formulations ranges from 0.916 to 0.993 respectively whereas first order kinetics 0.155 to 0.553 respectively. When subjected to Higuchi's model, R^2 value ranges from 0.730 to 0.898 respectively. Korsemeyer-peppas model showed R^2 value of 0.501 to 0.611 respectively for all the 'n' value ranges from 1.592 to 1.6011 indicating that the drug release was by Super case II release mechanism.

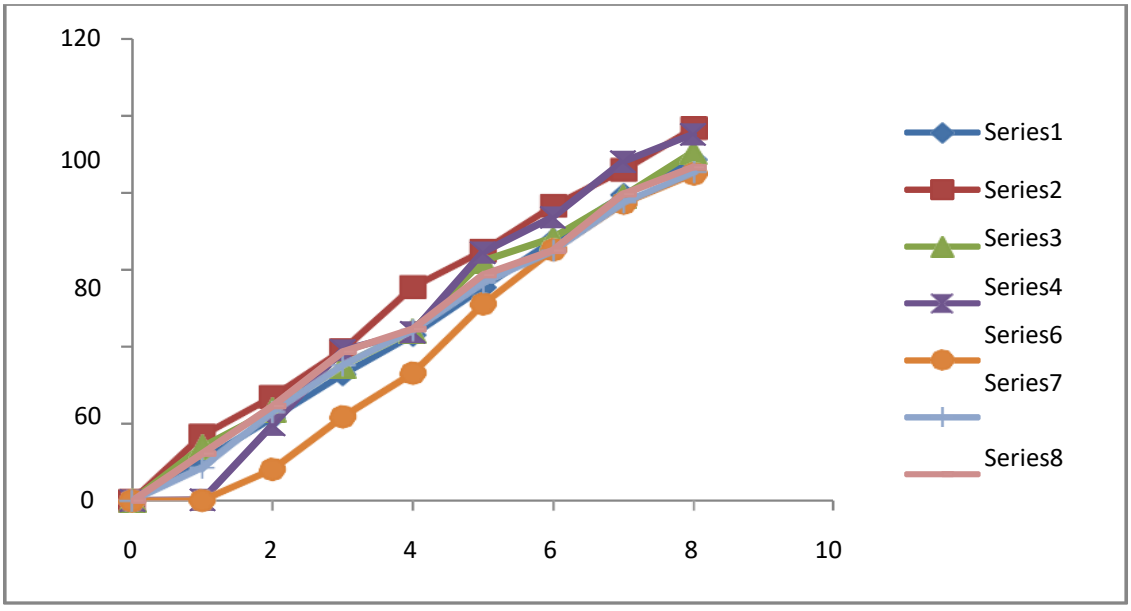

Fig 5: Comparative Zero Order release profile of formulations

CONCLUSION:

The present work is an attempt to develop a *in situ* gels and films of Hydrocortisone from temperature induced gelling system. The study has demonstrated various aspects and from the results obtained, it was concluded that

- ✓ *In situ* gel formulation of Hydrocortisone with mucoadhesive properties is useful to prolonging residence time in mouth.
- ✓ The developed formulation can release the drug at controlled rate for prolonged duration.
- ✓ Local drug delivery may be an advantageous in treatment, since it would probably eliminate side effects, which occur with systemic dosing.
- ✓ Effective and prolonged release of drug could be achieved without much systemic load with comparatively less frequency of administration.
- ✓ This type of drug delivery system can serve as a novel approach for treating mouth infections with better patient compliance.
- ✓ The optimized formulations F5 (Methylcellulose 1.25%), F6 (Methylcellulose 1.50%), F7 (Methylcellulose 1.75%) were liquid before instillation into mouth and underwent rapid gelation upon instillation into mouth.
- ✓ The formulations were found to be clear, having good *in situ* gelling capacity and a drug content 84-96%.
- ✓ Optimised formulations were sterile and showed sustained drug release over8 hrs.

Hence from the above results we can conclude that it is possible to formulate *in situ* gels and films of Hydrocortisone using Methylcellulose for treating aphthous ulcer. In that the (F5) film formulation has shown the best release studies when compared to other formulation, and when compared between the *in-situ* gels and films formulation the films is having sustained and prolonged release of the drug compared to the *in-situ* gel.

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