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FORMULATION AND DEVELOPMENT OF MICROSPONGE-LOADED ORAL FORMULATION CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY DRUG

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ABSTRACT

Microsponges are porous, polymeric microspheres that are used chiefly for topical and recently, oral administration. Ketoprofen was used as a model drug for systemic drug elivery of microsponges in the study. Ketoprofen microsponges were prepared by the quasi-emulsion solvent diffusion method with Eudragit RS 100, and afterwards, tablets of microsponges were prepared by the direct compression method. Microsponges have shown a better compressibility for tabletting when compared with the other microparticulate systems or the physical mixture of the drug and the polymer. Results indicated that microsponge compressibility was much improved over the physical mixture of the drug and polymer, and owing to the plastic deformation of the sponge-like structure, microsponges produce mechanically strong tablets.

KEYWORDS: Nonsteroidal antiinflammatory drugs, microsponges, oral formulation, Quasi emulsion solvent diffusion method.

INTRODUCTION

Oral drug delivery systems have evolved significantly over the years to enhance therapeutic efficacy and patient compliance. Conventional drug formulations often face limitations such as poor solubility, limited bioavailability, and undesirable side effects due to fluctuations in plasma drug levels. Advanced drug delivery systems like microsponges have gained prominence to overcome these challenges.

Microsponges are porous, polymeric microspheres that can encapsulate active pharmaceutical ingredients (APIs) and provide controlled drug release. These systems offer advantages such as prolonged drug release, reduced side effects, improved stability, and enhanced patient compliance. Ketoprofen, a nonsteroidal anti-inflammatory drug (NSAID), is widely used for the treatment of pain, inflammation, and musculoskeletal disorders. However, its conventional oral formulations suffer from gastrointestinal irritation, short half-life, and erratic absorption. Incorporating ketoprofen into a microsponges-based delivery system can mitigate these challenges by offering controlled release, reduced gastric irritation, and enhanced bioavailability.

The present study focuses on the formulation and characterization of ketoprofen-loaded microsponges and their subsequent incorporation into tablet dosage forms. This research aims to evaluate the physicochemical properties, drug release kinetics, and therapeutic potential of the formulated microsponges to establish an effective oral drug delivery system for ketoprofen.

2. METHODS

I. Preformulation Study of Ketoprofen Drug

Preformulation is the initial phase in dosage form development, involving the study of the drug's physical and chemical properties alone and with excipients. One key parameter assessed is compatibility by FTIR spectroscopy, where pellets were made by mixing 200 mg of potassium bromide with 1 mg of the sample. Using a SHIMADZU FTIR spectrophotometer, spectra were recorded for pure drug, drug with excipients for microsponges, and blank KBr to evaluate compatibility.

II. Method of Preparation

Formulation of Microsponge

Microsponge formulations were prepared using the quasi-emulsion solvent diffusion method, involving an inner organic phase and an outer aqueous phase. The inner phase, containing Eudragit RS 100 dissolved in a suitable organic solvent, was mixed with the drug solution using ultrasonication at 35°C. This was then added to the outer phase containing PVA and stirred at

room temperature for 3 hours. The resulting microsponges were dried in a hot air oven at 40°C for 12 hours. Various polymer ratios (chitosan, sodium alginate, Eudragit RS 100) were used in the formulations.

Table No. 1: Different formulations of microsponges.

Sl.No	Ingredients	F1	F2	F3	F4	F5	F6
1	Ketoprofen	100	100	100	100	100	100
2	Eudragit RS-100	25	50	75	100	125	150
3	Chitosan	75	50	25	125	100	75
4	Sodium Alginate	75	100	125	25	50	75
5	Polyvinyl Alcohol	1%	1%	1%	1%	1%	1%
6	Acetone(ml)	20	20	20	20	20	20
7	Distilled water(ml)	100	100	100	100	100	100

III. Optimization study

Design, development, and optimization of processes and products using DoE. It is a versatile tool that may be applied to a number of scenarios, including robust design, variable screening, transfer function discovery, optimization, and comparative design.

Preparation of Ketoprofen Tablet

Direct compression was used to prepare the Ketoprofen control release matrix tablet. Using Ketoprofen microsponges with excipients at a continuous 100 mg dose. In formulations, hydroxypropyl methylcellulose is the polymer of choice.

Table No. 2: Formulation of Ketoprofen control release matrix tablets.

Composition	F1(mg)
Ketoprofen microsponges	200mg
HPMC K100M	100mg
Avicel PH102	50mg
Talc	8mg
Magnesium Stearate	4mg

Post-Compression Evaluation

a. Physical Appearance: Tablets are visually examined for defects like capping, chipping, lamination, and discoloration.

b. Tablet Thickness: Measured using a Vernier caliper on five tablets. The average thickness should remain within ±5% of the recommended value to avoid packing issues.

c. Hardness: Tested using a Monsanto hardness tester (kg/cm²) on ten randomly selected tablets to ensure mechanical strength.

d. Weight Variation & Friability: Individual tablet weights are recorded to check for variation. Friability is assessed using a Roche Friabilator (25 rpm, 4 minutes, 100 revolutions). Tablets are weighed before and after testing; acceptable friability is <1%.

e. Swelling Behavior: A tablet is placed in phosphate buffer (pH 7.4) and weighed at intervals (up to 12 hours). Swelling Index (S.I.) is calculated using:

$$S.I. = \{(Mt - M0) / M0\} \times 100$$

f. In-Vitro Dissolution Study: Dissolution carried out using USP Type I apparatus in phosphate buffer (pH 7.4) at 37±0.5°C, 100 rpm. Samples (5 ml) collected at multiple intervals and analyzed at 260 nm using UV-visible spectrophotometry.

g. Drug Release Kinetics: Drug release analyzed using the following models:

- **Zero-order:** $C = K_0t$
- **First-order:** $\log Ct = \log C_0 – (K_1t / 2.303)$
- **Higuchi:** $W = K_2t^{\wedge}1/2$
- **Korsmeyer-Peppas:** $Mt/M\infty = K_4t^n$
  - $n = 0.45$: Fickian diffusion
  - $n < 0.89$: Anomalous diffusion
  - $n = 0.89$: Case-II transport

RESULTS AND DISCUSSION

Preformulation Studies

A preformulation study was performed as per the standard procedure. The results of the study are given below.

Table No. 3: Particle size distribution of Ketoprofen.

S. No.	Raw Material	Nature of Sample
1.	Ketoprofen	Moderately fine powder

Result analysis: Not less than 95% of the sample mass passed through the sieve 36#, and not more than 40% powder passed through 100#. Hence, the powder was found to be moderately fine, which will have good flow properties suitable for microsponge formulation.

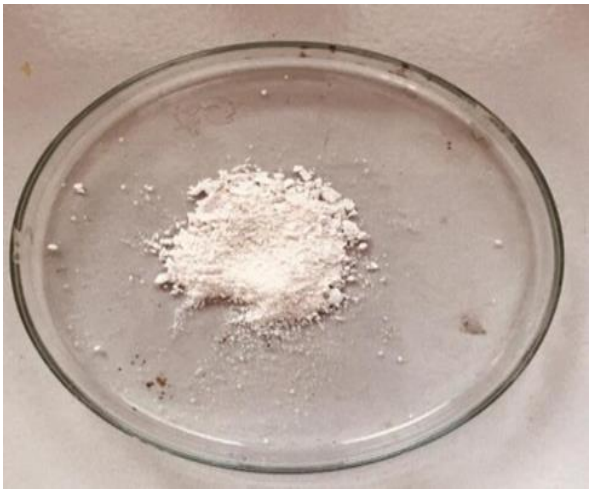


Fig. No 1: Formulated microsponges using drugs and polymers.

FT-IR Compatibility Study

The FT-IR spectrum of the drug was analyzed to assess potential interactions with excipients. Characteristic peaks corresponding to specific functional groups were identified to confirm compatibility.

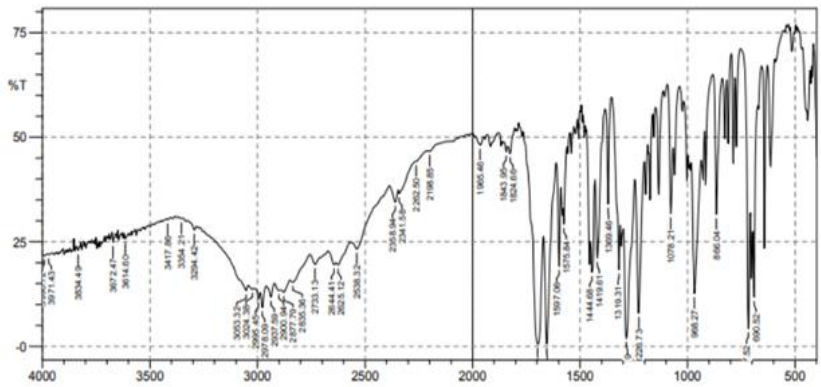


Fig. No. 2: FTIR spectroscopy for Ketoprofen pure.

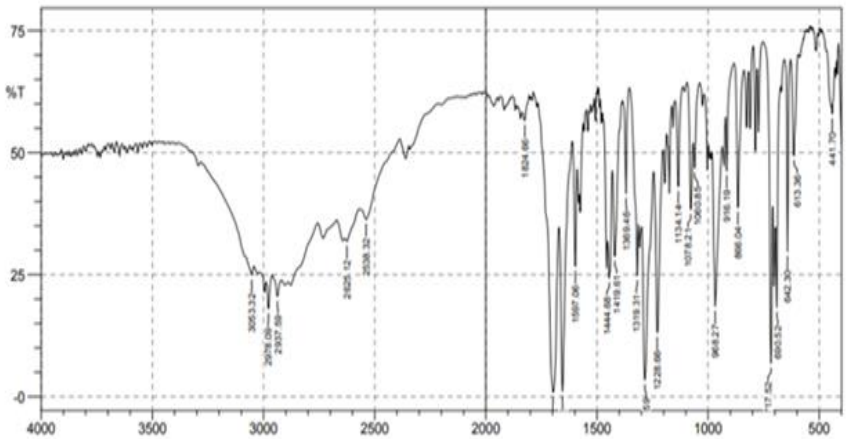


Fig. No.3: FTIR spectroscopy of drug and Excipients for microsponges.

Polyvinyl Alcohol

FTIR analysis revealed that all major peaks of ketoprofen were present in both the pure drug and formulations, indicating no significant interaction between the drug and excipients. This confirms the compatibility of ketoprofen with the excipients used in the microsponge preparation.

Optimization Study

Optimized among the prepared microsponges using DoE experiment.

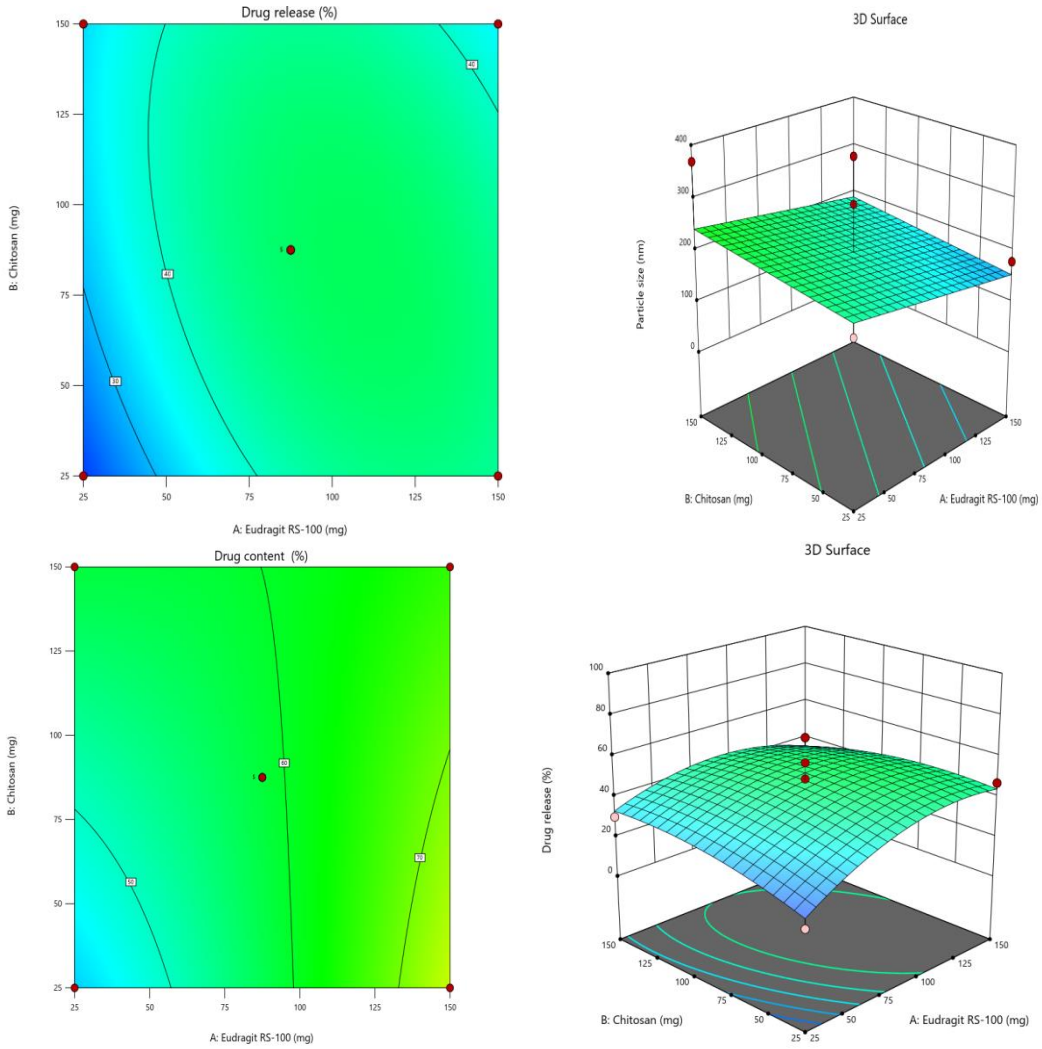


Fig. No. 4: Images for optimization studies using DoE.

Statistical Optimization

A two-factor, three-level full factorial design (3^2 FFD) was used to identify significant and optimal formulation variables. Using Design Expert® software (v13.0.5.0), the effects of gelling agent (X1) and polymer (X2) on particle size, drug content (R1), and in vitro drug release (R2) were evaluated.

Effect of Mixing Speed

Ketoprofen, Eudragit RS 100, and plasticizer were emulsified into a PVA aqueous phase and mixed for 2 hours for microsponge formation.

Post-Mixing

The microsponges were filtered, washed, and dried in a vacuum oven at 40°C for 24 hours.

Formulation of microsponge as tablet

The direct compression method was used to make the Ketoprofen microsponge control release tablet because it is a very time- and cost-effective technology. The microsponges may have a unique compression property due to their matrix or sponge-like structure, which differs from standard microcapsules or physical powder mixtures.

Their plastic qualities enabled microsponges to be compressed more easily by direct compression, resulting in a mechanically stronger tablet than the physically mixing the medication and polymer. This feature is useful for the manufacture of matrix tablets containing polymers for controlled release.

Fig. No. 5: Picture of ketoprofen microsponge tablet.

Post-Compression Tablet Evaluation

Prepared optimized formulation of ketoprofen microsponge compressed in the form of tablet. The tablet undergone the quality control test for solid dosage forms.

Table No. 4: Physical parameters evaluation of Ketoprofen microsponges tablet formulations.

Formulation	Average weight	Diameter(mm)n=10	Thickness(mm) n=10	Hardness(N) n=10	Friability (%)
F	391.82 ± 2.60	10.11 ± 0.02	4.82 ± 0.04	5.49 ± 2.37	0.17

Post-compression Evaluation

The compressed tablets were assessed for appearance, weight variation, diameter, thickness, hardness, and friability. No signs of capping, chipping, or lamination were observed across all formulations. Tablets with mucilage polymers appeared light brown, darkening with increased polymer concentration. Weight, thickness, and diameter remained within ±5% variation, ensuring consistent dosage and repeatability. All formulations showed friability below 1%, indicating good resistance to handling stress. Hardness levels were adequate across the board. Physical parameter values are summarized in the accompanying table.

Swelling Index

The swelling index reflects how much water a tablet absorbs, leading to an increase in its weight and volume due to polymer hydration. Water enters through pores, breaks hydrogen bonds, and binds to polymer molecules, causing the tablet to swell. Hydrophilic natural and synthetic polymers used in the formulation promote this behavior. An increase in polymer concentration enhances swelling, with Eudragit and HPMC showing the highest swelling indices. The swelling behavior directly influences drug release from the matrix.

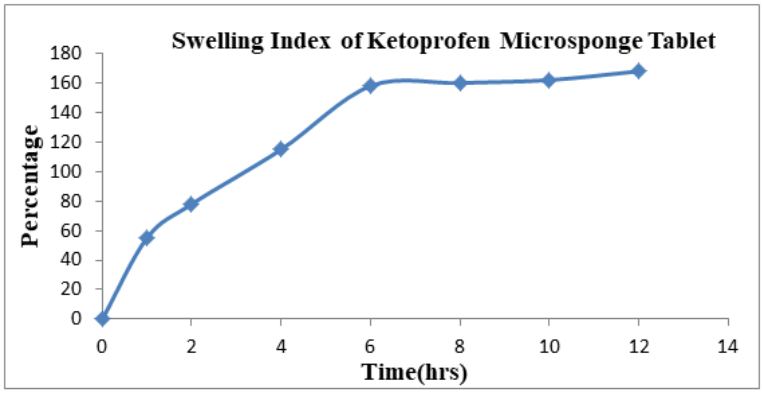
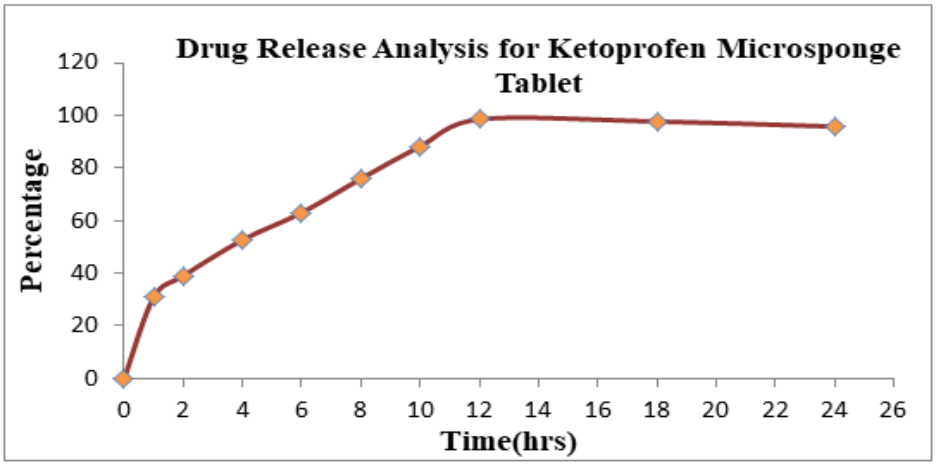


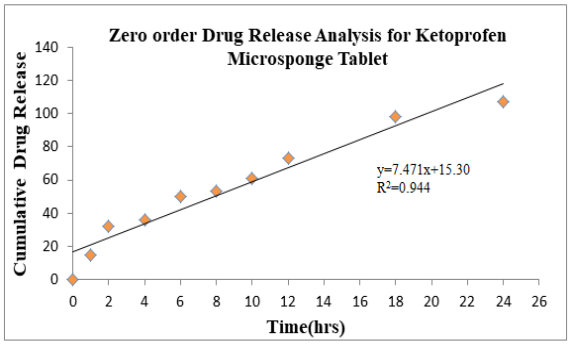
Fig. No. 6: swelling-index of ketoprofen microsponge tablet.

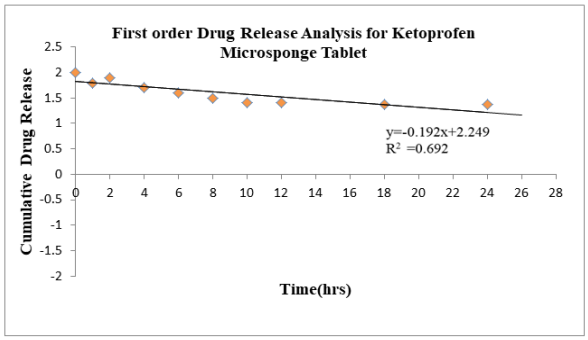
In-vitro Dissolution Study

The dissolution profile analysis showed that over 50% of the drug was released in 0.05M phosphate buffer (pH 7.4) within 24 hours, demonstrating the medium's suitable discriminating power. Although similar conditions are commonly used in ketoprofen studies, this formulation achieved nearly 98% drug release in just 10 hours, despite a maximum expected release of 60% in 24 hours. Figure No. 6: Drug release studies of ketoprofen microsponge tablet.

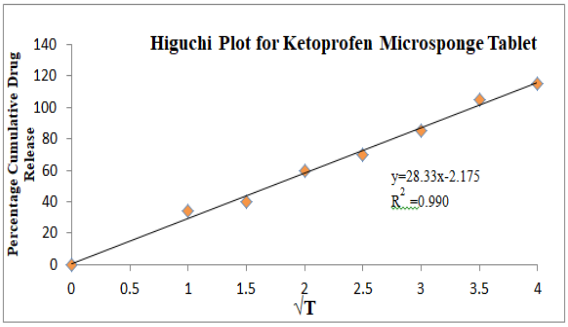


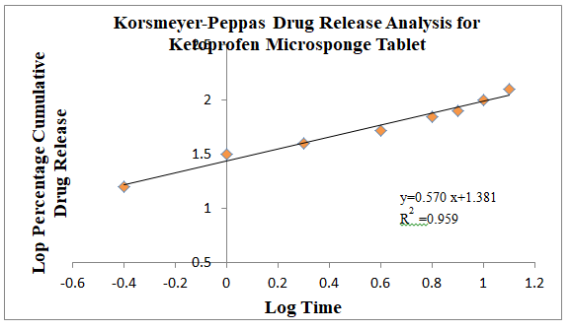
Release kinetics





Higuchi & Korsmeyer Peppas





Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer Peppas	
	R^2	K	R^2	K	R^2	K	R^2	K
F	0.944	2.333	0.951	-0.036	0.990	12.680	0.959	0.599

Various kinetic models, such as zero-order kinetics, first-order kinetics, and the Higuchi model, have been used to characterize drug dissolution from solid dosage forms. Korsmeyer-Peppas can be used to interpret the mechanics of drug release from a matrix. It is clear from fitting dissolving data into first-order and zero-order kinetics equations that the formulation adheres to first-order kinetics, suggesting concentration-dependent drug release from the controlled-release system.

The formulation, on the other hand, releases the drug from the matrix system according to zero-order kinetics, which is concentration-independent. The non-Fickian type of drug release ($0.45 < n < 0.89$) suggested by the Korsmeyer-Peppas equation is present in all formulations, with n values ranging from 0.446 to 0.750, indicating a combination of both diffusion and erosion drug release mechanisms. The dissolving data fitting into Higuchi has provided additional explanation for this.

CONCLUSION

In the present research study, a microsponge-based drug delivery system containing Ketoprofen was successfully developed and optimized with the aim of enhancing therapeutic outcomes by reducing the frequency of drug administration, minimizing drug-related toxicity,

improving patient compliance, and lowering overall treatment costs. The formulation was specifically designed to provide a sustained and controlled release of Ketoprofen when administered via the oral route, thereby ensuring prolonged drug retention at the site of action. The study findings demonstrate that the microsponge delivery system represents a promising and efficient approach for achieving extended drug release profiles.

The optimized microsponge formulation was prepared using Eudragit R S 100 as the polymeric matrix and Polyvinyl Alcohol (PVA) as the stabilizing agent, along with other essential excipients that contributed to the desired physicochemical and release characteristics. Among the various trial formulations, the optimized batch, designated as R4, exhibited satisfactory drug release behavior, making it suitable for a once-daily administration regimen. This dosing frequency can be adjusted based on factors such as the severity of the disease and the age of the patient, thereby offering a flexible and patient-centric treatment option.

Comprehensive evaluation of the formulation parameters, including particle size, encapsulation efficiency, drug release kinetics, and stability studies, confirmed the robustness and efficacy of the developed microsponge system. Furthermore, the reproducibility and scalability of the formulation process suggest that the optimized Ketoprofen-loaded microsponge (R4) is highly suitable for large-scale manufacturing, making it a viable candidate for future pharmaceutical development and commercialization.

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