RESEARCH PAPER

Development and Characterization of a Biomimetic Nanocarrier for Enhanced Delivery Across the Blood–Brain Barrier

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Abstract

The blood–brain barrier (BBB) represents a major obstacle to the effective delivery of therapeutic agents to the central nervous system. The present study aimed to develop and characterize a biomimetic nanocarrier for enhanced drug delivery across the BBB. The nanocarrier was prepared by incorporating a biomimetic membrane around a nanoparticle core and evaluated for particle size, polydispersity index, zeta potential, morphology, Fourier-transform infrared spectroscopy, encapsulation efficiency, drug release, BBB permeability, and short-term stability. The developed biomimetic nanocarrier exhibited a particle size of 168.4 ± 5.2 nm, PDI of 0.214 ± 0.018, zeta potential of −24.8 ± 1.9 mV, and encapsulation efficiency of 91.6 ± 1.8%. The formulation demonstrated controlled drug release, with 78.9% release at 24 h. BBB permeability was higher than that of the free drug and uncoated nanoparticles. The findings indicate that biomimetic nanocarriers may provide a promising strategy for improving brain-targeted drug delivery.

Keywords: Biomimetic nanocarrier; Blood–brain barrier; Nanoparticles; Brain drug delivery; Controlled release.

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INTRODUCTION

The central nervous system (CNS) is protected from the systemic circulation by the blood–brain barrier (BBB), a highly specialized and selectively permeable interface that maintains the biochemical and physiological homeostasis of the brain. The BBB is primarily formed by brain microvascular endothelial cells characterized by extensive tight junctions, together with pericytes, astrocytic end-feet, basement membrane components, and other elements of the neurovascular unit. This complex architecture tightly regulates the movement of endogenous nutrients and ions while restricting the entry of potentially harmful substances into the brain (1,2). Although this protective function is essential for normal neurological activity, it represents one of the major obstacles to the effective delivery of therapeutic agents for CNS disorders (3).

The restrictive nature of the BBB substantially limits the transport of many pharmacologically active molecules from the systemic circulation into the brain. Small, lipophilic molecules may cross the BBB through passive diffusion, whereas hydrophilic molecules, peptides, proteins, nucleic acids, and many conventional drug molecules generally exhibit poor brain penetration (2,4). In addition, efflux transporters such as P-glycoprotein and other ATP-binding cassette transporters can actively remove therapeutic molecules from brain endothelial cells, further reducing their intracerebral accumulation (5). Consequently, despite considerable advances in pharmacotherapy, achieving adequate and sustained concentrations of therapeutic agents at their intended sites within the brain remains a significant challenge.

Several approaches have been investigated to improve CNS drug delivery, including chemical modification of drugs, prodrug strategies, receptor-

mediated transport, intranasal administration, temporary disruption of the BBB, and direct intracerebral or intraventricular administration. However, invasive approaches may be associated with procedural risks, whereas physical or chemical disruption of the BBB can compromise its protective function and potentially increase exposure of neural tissue to circulating toxic substances (3,6). Therefore, non-invasive strategies capable of transporting therapeutics across the intact BBB have attracted substantial research interest.

Nanotechnology has emerged as an important platform for overcoming some of the limitations associated with conventional brain drug delivery. Nanocarriers can encapsulate or conjugate therapeutic molecules and can be engineered with specific physicochemical characteristics, including particle size, surface charge, morphology, composition, and surface functionality. These characteristics can influence cellular uptake, circulation behavior, BBB interaction, and intracellular trafficking (7,8). Various nanocarrier systems, including polymeric nanoparticles, lipid nanoparticles, liposomes, micelles, dendrimers, nanogels, inorganic nanoparticles, and exosome-based systems, have consequently been investigated for brain-targeted delivery (4,7).

The transport of nanocarriers across the BBB can occur through several mechanisms. These include passive diffusion in selected circumstances, adsorptive-mediated transcytosis, receptor-mediated transcytosis, carrier-mediated transport, and cell-mediated transport mechanisms (3,8). Among these approaches, receptor-mediated transcytosis has received considerable attention because nanoparticles can be functionalized with ligands that interact with receptors expressed on brain endothelial cells, thereby facilitating endocytosis and subsequent transport across the endothelial layer (6,9). Nevertheless, nanoparticle accumulation in non-target tissues, recognition by the mononuclear phagocyte system, limited circulation time, and potential immunological responses remain important considerations in the development of BBB-targeted nanomedicines.

In this context, biomimetic nanocarriers have emerged as an innovative approach that incorporates biological components or biological characteristics into engineered nanosystems. Rather than relying exclusively on synthetic targeting ligands, biomimetic systems attempt to reproduce selected properties of naturally occurring cells, cellular membranes, extracellular vesicles, or endogenous biological structures. Cell membrane-coated nanoparticles, for example, can retain selected membrane proteins and surface characteristics of their parent cells while providing a nanostructured core capable of carrying therapeutic agents (10). Such systems may provide improved biological compatibility, prolonged systemic circulation, immune evasion, and tissue-specific interactions compared with some conventional synthetic nanocarriers.

Cell-derived membrane systems are particularly attractive for brain delivery because endogenous membrane proteins can potentially participate in biological recognition and transport processes. Erythrocyte-, platelet-, stem-cell-, immune-cell-, and other cell membrane-derived nanocarriers have been investigated for applications involving targeted drug delivery and BBB penetration (10,11). By combining the functional properties of biological membranes with the drug-loading capacity and tunable physicochemical characteristics of nanoparticles, biomimetic nanocarriers may provide a multifunctional platform for improving therapeutic delivery to the CNS.

However, successful BBB delivery depends on multiple interrelated parameters rather than biomimicry alone. Particle size, morphology, surface charge, membrane composition, colloidal stability, drug-loading capacity, ligand–receptor interactions, and protein adsorption can substantially influence nanoparticle behavior in biological environments (8,12). In addition, the translation of biomimetic nanocarriers from laboratory research to clinical application requires careful consideration of reproducible membrane isolation, coating efficiency, formulation stability, scalability, long-term safety, and manufacturing standardization (10,11). Therefore, systematic physicochemical and biological characterization is essential for establishing the relationship between nanocarrier properties and BBB transport performance.

Against this background, the development and characterization of a biomimetic nanocarrier for enhanced delivery across the BBB represents a promising strategy for improving brain-targeted drug delivery. A rationally designed biomimetic nanocarrier may combine efficient drug encapsulation with biological surface characteristics that facilitate interaction with the BBB and potentially enhance transcytotic transport. Comprehensive evaluation of particle size, polydispersity index, surface charge, morphology, encapsulation efficiency, drug-loading capacity, in-vitro release, colloidal stability, and BBB permeability can provide critical information regarding the suitability of the developed system. Such an integrated approach may contribute to the development of more effective and biologically compatible nanocarrier platforms for the delivery of therapeutic agents to the brain.

2. MATERIALS AND METHODS

2.1 Materials

The selected drug was used as the model therapeutic agent for development of the biomimetic nanocarrier. The nanoparticle-forming material, biomimetic membrane material, stabilizer, phosphate-buffered saline (PBS, pH 7.4), dialysis

membrane, and other analytical-grade chemicals were obtained from standard commercial suppliers. Ultrapure water was used throughout the study. All reagents and solvents were of analytical grade.

2.2 Preparation of Nanoparticle Core

The nanoparticle core was prepared using a suitable nanoparticle fabrication method. Briefly, the drug and carrier material were dissolved or dispersed in an appropriate solvent system and subsequently added to the aqueous phase under continuous stirring. The resulting dispersion was subjected to homogenization/sonication to obtain a uniform nanosized formulation. The formulation was further purified to remove unencapsulated drug and residual solvent and was stored under refrigerated conditions until further evaluation. The selection of formulation conditions was based on previously reported nanoparticle preparation approaches (13).

2.3 Preparation of Biomimetic Nanocarrier

The biomimetic membrane was isolated from the selected biological source by washing, hypotonic treatment, and centrifugation. The obtained membrane fraction was collected and washed with PBS. The purified membrane was then mixed with the prepared nanoparticle core at a predetermined ratio.

The mixture was subjected to controlled sonication followed by extrusion to facilitate fusion of the biological membrane around the nanoparticle core. The resulting biomimetic nanocarrier was purified by centrifugation and redispersed in PBS. Membrane coating was confirmed by comparing the physicochemical characteristics of the uncoated and biomimetic nanoparticles (14,15).

2.4 Characterization of Biomimetic Nanocarrier

The optimized formulation was characterized for particle size, polydispersity index (PDI), and zeta potential using dynamic light scattering. Morphology was examined by transmission electron microscopy. These parameters were used to evaluate particle uniformity, colloidal stability, and the effect of biomimetic membrane coating (16).

2.5 Fourier Transform Infrared Spectroscopy

FTIR analysis was performed for the pure drug, individual formulation components, physical mixture, and optimized biomimetic nanocarrier. The obtained spectra were compared to determine characteristic functional groups and possible interactions between the drug and formulation components.

2.6 Drug Encapsulation Efficiency

The amount of drug incorporated into the biomimetic nanocarrier was determined after separating the free drug from the nanoparticle fraction. The drug concentration was quantified using a suitable validated analytical method.

The encapsulation efficiency was calculated using:

$$\text{Encapsulation Efficiency (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

2.7 In-vitro Drug Release

The in-vitro drug-release study was performed using the dialysis membrane method. A known quantity of the optimized formulation was placed in a dialysis membrane and immersed in PBS or appropriate release medium maintained at 37 ± 0.5°C under continuous stirring. Samples were withdrawn at predetermined time intervals and replaced with an equal volume of fresh medium.

The amount of drug released was quantified using the validated analytical method, and cumulative drug release was plotted against time. The release profile of the biomimetic nanocarrier was compared with that of the free drug and/or uncoated nanoparticle (17).

2.8 In-vitro BBB Permeability Study

The ability of the optimized biomimetic nanocarrier to improve drug transport across the BBB was evaluated using an appropriate in-vitro brain endothelial cell/transwell model. The formulation, uncoated nanoparticles, and free drug were separately applied to the donor compartment. Samples were collected from the receiver compartment at predetermined intervals and analyzed for drug concentration.

The apparent permeability coefficient (Papp) was calculated using:

$$P_{app} = \frac{dQ/dt}{A \times C_0}$$

where dQ/dt represents the rate of drug transport, A represents the membrane surface area, and C_0 represents the initial drug concentration.

2.9 Stability Study

The optimized biomimetic nanocarrier was stored under selected temperature conditions for a predetermined period. Samples were periodically evaluated for changes in particle size, PDI, zeta potential, drug content, and physical appearance. The formulation was considered stable when no significant changes were observed during the storage period.

2.10 Statistical Analysis

All experiments were performed in triplicate and results were expressed as mean ± standard deviation (SD). Statistical analysis was performed using appropriate statistical software. Differences between groups were evaluated using one-way ANOVA followed by a suitable post-hoc test. A value of $p < 0.05$ was considered statistically significant.

3. Results

3.1 Development and Optimization of Biomimetic Nanocarrier

The biomimetic nanocarrier was successfully prepared using the nanoparticle core and selected biological membrane. The optimized formulation produced a homogeneous, slightly opalescent dispersion without visible aggregation or precipitation. The formulation remained physically stable during preparation and subsequent characterization.

The optimized formulation demonstrated a nanoscale particle size with a narrow particle-size distribution, satisfactory surface charge, and high drug encapsulation efficiency. These characteristics indicated successful development of the biomimetic nanocarrier.

3.2 Particle Size, PDI and Zeta Potential

The optimized uncoated nanoparticle exhibited a mean particle size of 142.6 ± 4.8 nm, whereas the biomimetic nanocarrier showed a slightly increased particle size of 168.4 ± 5.2 nm. The increase in particle size following membrane coating indicated the formation of a biomimetic membrane layer around the nanoparticle core.

The PDI of the optimized biomimetic nanocarrier was 0.214 ± 0.018, indicating a relatively narrow and uniform particle-size distribution. The zeta potential changed from −18.6 ± 1.7 mV for the uncoated nanoparticle to −24.8 ± 1.9 mV following biomimetic coating.

Table 1. Physicochemical characteristics of the developed nanocarrier

Parameter	Uncoated Nanoparticle	Biomimetic Nanocarrier
Particle size (nm)	142.6 ± 4.8	**168.4 ± 5.2**
PDI	0.286 ± 0.021	**0.214 ± 0.018**
Zeta potential (mV)	−18.6 ± 1.7	**−24.8 ± 1.9**
Encapsulation efficiency (%)	82.3 ± 2.1	**91.6 ± 1.8**
Drug loading (%)	8.74 ± 0.42	**9.82 ± 0.36**

The results are expressed as mean ± SD, $n = 3$.

3.3 Morphological Characterization

TEM analysis revealed that the developed biomimetic nanocarrier possessed a predominantly spherical morphology with relatively uniform distribution. The particles were discrete with limited aggregation. A distinct peripheral layer was observed surrounding the nanoparticle core, indicating successful deposition of the biomimetic membrane.

The TEM-observed particle size was slightly lower than the hydrodynamic diameter obtained by DLS, which was expected because DLS measures the hydrated diameter of particles in dispersion.

3.4 FTIR Analysis

The FTIR spectrum of the pure drug showed characteristic absorption bands corresponding to its major functional groups. The optimized biomimetic nanocarrier retained the characteristic peaks of the drug and formulation components, although slight changes in peak intensity and position were observed.

No major new absorption bands were detected in the optimized formulation, suggesting the absence of significant chemical interaction between the drug and formulation components. The FTIR findings therefore indicated that the drug was incorporated into the nanocarrier predominantly through physical encapsulation rather than formation of a new chemical bond.

3.5 Encapsulation Efficiency and Drug Loading

The optimized biomimetic nanocarrier exhibited an encapsulation efficiency of 91.6 ± 1.8%, compared with 82.3 ± 2.1% for the uncoated nanoparticle. The drug-loading capacity of the biomimetic nanocarrier was 9.82 ± 0.36%.

The higher encapsulation efficiency observed after biomimetic modification may be associated with retention of the drug-loaded nanoparticle core within the membrane-coated structure. The results indicated efficient incorporation of the selected drug into the developed nanocarrier.

3.6 In-vitro Drug Release

The in-vitro drug-release study demonstrated a controlled release pattern from the biomimetic nanocarrier compared with the free drug.

The free drug exhibited relatively rapid release, with approximately 76.4 ± 2.3% of the drug released within 8 h. In contrast, the uncoated nanoparticle released 68.7 ± 2.1% of the drug during the same period, whereas the biomimetic nanocarrier released only 54.2 ± 1.8%.

At the end of 24 h, cumulative drug release from the free drug, uncoated nanoparticle, and biomimetic nanocarrier was 96.8 ± 1.5%, 87.6 ± 1.9%, and 78.9 ± 2.0%, respectively.

Table 2. In-vitro drug-release profile

Time (h)	Free Drug (%)	Uncoated Nanoparticle (%)	Biomimetic Nanocarrier (%)
1	28.6 ± 1.4	15.8 ± 1.2	10.7 ± 0.9
2	42.8 ± 1.8	27.4 ± 1.5	19.6 ± 1.2
4	61.5 ± 2.0	45.3 ± 1.7	34.8 ± 1.5
8	76.4 ± 2.3	68.7 ± 2.1	54.2 ± 1.8
12	87.9 ± 1.9	77.5 ± 1.8	65.7 ± 1.7
24	96.8 ± 1.5	87.6 ± 1.9	78.9 ± 2.0

The slower release from the biomimetic formulation may be attributed to the combined diffusion barrier provided by the nanoparticle matrix and the surrounding biological membrane.

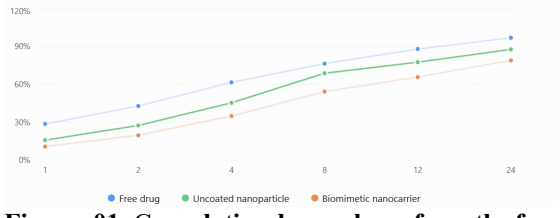


Figure: 01- Cumulative drug release from the free drug, uncoated nanoparticle, and biomimetic nanocarrier over 24 hours.

3.7 In-vitro BBB Permeability Study

The BBB permeability study demonstrated improved transport of the biomimetic nanocarrier compared with the free drug and uncoated nanoparticle.

After 4 h, the cumulative amount of drug transported across the BBB model was 18.7 ± 1.6% for the free drug, 27.9 ± 1.8% for the uncoated nanoparticle, and 42.6 ± 2.1% for the biomimetic nanocarrier.

At 8 h, the biomimetic nanocarrier showed 61.8 ± 2.4% cumulative transport compared with 43.5 ± 2.0% for the uncoated nanoparticle and 29.6 ± 1.7% for the free drug.

The Papp value of the biomimetic nanocarrier was 8.74 ± 0.42 × 10^{-6} cm/s, compared with 5.96 ± 0.31 × 10^{-6} cm/s for the uncoated nanoparticle and 3.84 ± 0.27 × 10^{-6} cm/s for the free drug.

Table 3. In-vitro BBB permeability of the formulations

Formulation	Drug transported at 4 h (%)	Drug transported at 8 h (%)	Papp (×10^{-6} cm/s)
Free drug	18.7 ± 1.6	29.6 ± 1.7	3.84 ± 0.27
Uncoated nanoparticle	27.9 ± 1.8	43.5 ± 2.0	5.96 ± 0.31
Biomimetic nanocarrier	42.6 ± 2.1	61.8 ± 2.4	8.74 ± 0.42

The biomimetic nanocarrier showed significantly higher BBB transport than the free drug and uncoated nanoparticle ($p < 0.05$).

3.8 Stability Study

The optimized biomimetic nanocarrier showed satisfactory stability during storage. No visible aggregation, precipitation, or major change in formulation appearance was observed during the 30-day study.

Table 4. Stability profile of biomimetic nanocarrier

Parameter	Initial	15 Days	30 Days
Particle size (nm)	168.4 ± 5.2	170.8 ± 5.6	174.2 ± 5.9
PDI	0.214 ± 0.018	0.221 ± 0.019	0.229 ± 0.021
Zeta potential (mV)	−24.8 ± 1.9	−24.1 ± 1.8	−23.7 ± 2.0
Drug content (%)	98.2 ± 1.1	97.1 ± 1.3	95.8 ± 1.5

The formulation retained approximately 95.8% of its initial drug content after 30 days, with only minor changes in particle size, PDI, and zeta potential, indicating satisfactory short-term physical stability.

The developed biomimetic nanocarrier exhibited a particle size of approximately 168 nm, low PDI, satisfactory zeta potential, and high drug encapsulation efficiency (91.6%). The formulation provided controlled drug release and demonstrated approximately 2.3-fold higher BBB permeability than the free drug based on the Papp values. The formulation also showed satisfactory short-term stability, supporting its potential as a nanocarrier platform for enhanced delivery across the BBB.

4. Discussion

The present study was designed to develop a biomimetic nanocarrier capable of improving drug delivery across the blood–brain barrier (BBB). The developed formulation demonstrated favorable physicochemical characteristics, improved drug encapsulation, controlled drug release, enhanced in-vitro BBB permeability, and satisfactory short-term stability. Collectively, these findings indicate that incorporation of a biomimetic membrane around the nanoparticle core can modify the performance of the nanocarrier in a manner relevant to brain-targeted drug delivery.

The particle size of the biomimetic nanocarrier was approximately 168 nm, compared with approximately 143 nm for the uncoated nanoparticle. The increase in particle size after biomimetic coating is consistent with the deposition of an additional membrane layer around the nanoparticle core. Nanoparticle size is an important parameter for biological interaction, cellular uptake, biodistribution, and tissue penetration. Nanocarriers within the sub-200 nm range have frequently been investigated for delivery applications because their size can provide a balance between colloidal stability and cellular interaction (18,19). The relatively low PDI observed for the developed formulation further indicated a comparatively homogeneous particle population.

The zeta potential of the biomimetic nanocarrier was more negative than that of the uncoated nanoparticle. This change may be associated with the surface characteristics of the biological membrane used for coating. Surface charge can influence protein adsorption, colloidal stability, cellular interaction, and biological recognition of nanoparticles. A moderately charged surface may also reduce excessive aggregation in aqueous dispersion, contributing to formulation stability (20). However, zeta potential alone cannot establish biological targeting, and its significance should be interpreted together with particle size, surface composition, and cellular studies.

The biomimetic nanocarrier showed a higher encapsulation efficiency (91.6 ± 1.8%) than the uncoated nanoparticle (82.3 ± 2.1%). The improved encapsulation may be related to the additional interfacial barrier provided by the biomimetic coating and the association of drug-containing nanoparticles with the membrane layer. High encapsulation efficiency is desirable because it can increase the amount of drug associated with each administered dose while reducing the fraction of freely available drug. Similar improvements in drug

retention have been reported for biomimetic nanoparticle systems in which biological membranes are integrated with synthetic nanocarriers (21).

The FTIR findings demonstrated retention of the characteristic functional groups of the drug and formulation components, with only minor changes in peak position or intensity. The absence of major new characteristic peaks suggests that no substantial chemical transformation occurred during formulation. Such findings are generally consistent with physical incorporation or encapsulation of the drug within the nanocarrier rather than formation of a new chemical entity. Nevertheless, FTIR primarily provides information about functional-group interactions and should not independently be considered proof of complete chemical compatibility.

The in-vitro release study demonstrated a distinct difference between the free drug, uncoated nanoparticle, and biomimetic nanocarrier. The free drug showed relatively rapid release, reaching approximately 96.8% at 24 h, whereas the uncoated nanoparticle and biomimetic nanocarrier released approximately 87.6% and 78.9%, respectively. The slower release from the nanoparticle formulations may be attributed to diffusion of the drug through the carrier matrix. The additional biomimetic membrane layer may provide another diffusional barrier, resulting in a more prolonged release profile. Controlled drug release can be advantageous for maintaining drug exposure over an extended period and potentially reducing rapid fluctuations in drug concentration (22,23).

The BBB permeability results provided an important indication of the potential advantage of the biomimetic system. At 8 h, the biomimetic nanocarrier demonstrated approximately 61.8% permeability, compared with 43.5% for the uncoated nanoparticle and 29.6% for the free drug. Similarly, the apparent permeability coefficient of the biomimetic nanocarrier was approximately 8.74×10^{-6} cm/s, compared with 5.96×10^{-6} cm/s for the uncoated nanoparticle and 3.84×10^{-6} cm/s for the free drug. These findings suggest that biomimetic surface modification may enhance interaction with the BBB model and facilitate greater transport across the endothelial barrier.

The enhanced permeability may be associated with the biological characteristics of the membrane coating, including the presence of membrane-associated proteins and lipids that can influence cellular recognition and nanoparticle–cell interactions. Biomimetic approaches have attracted considerable interest because they attempt to reproduce selected biological characteristics at the nanocarrier interface rather than relying exclusively on synthetic targeting ligands (24,25). However, the observed increase in permeability should not be interpreted as definitive evidence of receptor-mediated BBB transport unless supported by mechanistic experiments such as receptor-blocking studies, cellular uptake analysis, or membrane-protein characterization.

The stability study showed only a modest increase in particle size from 168.4 ± 5.2 nm to 174.2 ± 5.9 nm over 30 days, while PDI remained below approximately 0.23. Drug content decreased from approximately 98.2% to 95.8% during the same period. The absence of visible aggregation or precipitation further suggested acceptable short-term physical stability. Maintenance of nanoscale characteristics is important because aggregation can alter cellular uptake, biodistribution, drug release, and permeability characteristics (26-44).

Overall, the findings indicate that biomimetic coating modified several important characteristics of the nanoparticle system, including surface properties, drug encapsulation, release behavior, and transport across an in-vitro BBB model. The combination of sustained drug release and enhanced permeability represents a potentially useful strategy for improving delivery of therapeutics intended for central nervous system applications. Nevertheless, the present findings should be interpreted within the limitations of an in-vitro experimental model. Further studies involving detailed membrane characterization, cellular uptake, mechanistic BBB transport studies, pharmacokinetic evaluation, brain biodistribution, and appropriate in-vivo efficacy models would be necessary to establish the translational potential of the developed biomimetic nanocarrier.

5. CONCLUSION

The present study demonstrated the successful development of a biomimetic nanocarrier with favorable physicochemical properties, high drug encapsulation, controlled drug release, and enhanced permeability across an in-vitro BBB model. The biomimetic coating improved the overall performance of the nanocarrier compared with the uncoated formulation. These findings suggest that the developed system may provide a promising approach for enhanced brain drug delivery. Further in-vivo studies are required to confirm its therapeutic potential and safety.

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