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The Influence of Release Modifier Differences in Formulations on the Pharmacokinetic Profile of Ketoprofen in Rats: A Scoping Review

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Abstract
The pharmacokinetic profile of drugs can be changed by genetic, environmental, and physiological variables such as age, sex, pregnancy, and different preparations and formulations. Ketoprofen is widely used in many different preparations and formulations. The various formulations can made by adding solubilizing and extending release agents. This study aimed to determine the influence of formulation differences on the pharmacokinetic profile of ketoprofen in rats. This research was a Literature Review. Articles were retrieved from the ScienceDirect and PubMed databases from 2011 to 2020. The inclusion criteria were the research article, the presence of ketoprofen was formulated with the addition of a solubilizing or extended-release agent, given orally and available in open access. The study resulted in differences in formulation, notably the addition of various dissolving agents or extended-release agents, which caused changes in the pharmacokinetic profile of ketoprofen. The highest increase in the pharmacokinetic parameters C_{max} and AUC of ketoprofen was observed with poloxamer-188 as a release modifier agent. Therefore, the use of release modifier agents could have a significant effect on the drug's pharmacokinetic profile.

Keywords: Ketoprofen; Pharmacokinetics Profile; Systematic Review; Formulation

1. INTRODUCTION

Ketoprofen is a non-steroidal anti-inflammatory inhibition drug (NSAID) derived from propionic acid derivatives, which have anti-inflammatory, analgesic, and antipyretic properties in acute and chronic rheumatoid arthritis therapy and for the treatment of osteoarthritis (Kuczynska and Nieradko-Iwanicka, 2022; Mariniello et al., 2022; Sarzi-Puttini et al., 2010). Ketoprofen is classified as a BCS class II (Biopharmaceutical Classification System) drug with low solubility and high permeability. Oral ketoprofen is very effective because of its relatively short onset, about 30 minutes, with a duration of action of 6 hours. However, ketoprofen has several side effects across various systems: cardiovascular reactions (peripheral edema), central nervous system effects (headache, drowsiness), dermatological issues (skin sensitization and

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photosensitization after topical use), hematological effects (edema, platelet dysfunction), hepatic effects (increased liver enzymes), ocular effects, renal issues, respiratory effects (asthma), systemic reactions (sweating, itching), and gastrointestinal problems (vomiting, diarrhea, ulcers, and stomach bleeding) (Carbone et al., 2013; Thibault et al., 2019). Additionally, when administered orally, ketoprofen undergoes first-pass metabolism, which affects its bioavailability in the human body (Pandey et al., 2023; Zhang et al., 2021).

Ketoprofen works by inhibiting the cyclooxygenase (COX) enzyme, thus inhibiting the formation of prostaglandins, and it can have anti-inflammatory, analgesic, and antipyretic effects (Fox et al., 2016). Ketoprofen is more effective in managing pain than paracetamol (Gazal and Al-Samadani, 2017; Velásquez et al., 2014). Ketoprofen is widely used as a postoperative analgesic and is effective for moderate to severe pain (Gaskell et al., 2017). In a previous study, ketoprofen demonstrated superior efficacy to diclofenac in alleviating post-surgical pain, as evidenced by a longer duration of analgesia and a lower incidence of patients requiring initial rescue analgesia following surgery (Velásquez et al., 2014). Furthermore, it reported that administering dexketoprofen trometamol 30 minutes before the conclusion of surgery resulted in adequate analgesia, diminished opioid consumption, and a reduced necessity for rescue analgesics compared to diclofenac sodium in patients undergoing laparoscopic cholecystectomy (Anil et al., 2016).

Ketoprofen is widely chosen to treat moderate to severe pain because it can reduce the risk of bleeding, nausea, and vomiting. It indicates ketoprofen has many advantages as a postoperative analgesic. Another advantage of ketoprofen is having a short onset, and it can quickly deal with pain in patients, especially in postoperative patients (Gaskell et al., 2017). Ketoprofen is widely used in different preparations and formulations and can change the drug's pharmacokinetic profile.

Drug pharmacokinetics describes changes in drug concentration per unit of time after administration of a particular drug dose (Fan and De Lannoy, 2014). It is used to determine the dosage setting of a drug, and it is necessary to know its pharmacokinetic profile. The pharmacokinetic profile has three parameters: primary, secondary, and derivative. Primary pharmacokinetic parameters include absorption rate, volume distribution (Vd), and clearance (Cl). Secondary pharmacokinetic parameters include elimination half-time (t½ elimination) and elimination rate constant (Ke). Meanwhile, the derived pharmacokinetic parameters include peak levels (C_{max}), peak time ($_{Tmax}$), and Area Under Curve (AUC).

The pharmacokinetic profile of a drug can change. It can happen because of the many factors that play a role, including genetic, environmental, and physiological variables such as age, sex, and pregnancy, as well as using different preparations and formulations. Other

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formulations can be made by adding a new active compound or excipient, such as solubilizing and extending release agents.

The impact of changing the pharmacokinetic profile of a drug is the achievement of the pharmacokinetic target of the drug (Adepu and Ramakrishna, 2021; Van der Merwe et al., 2020). This study aimed to determine the effect of solubilizing addition and extended-release agents on the pharmacokinetic parameters of ketoprofen through a literature review of existing research.

2. MATERIALS AND METHODS

2.1. Materials and tools

The search strategy for identifying papers in this study was to make questions by formulating them in the form of PICO (Population, Intervention, Comparison, and Outcome), then matching the keywords obtained and limiting the paper according to inclusion and exclusion criteria (see 2.3). The articles were searched using MeSH (Medical Subject Headings) terms, a controlled vocabulary of biomedical and health-related terms used to describe the subject of a journal article, making searches more specific. The data sources used were published papers from PubMed and ScienceDirect with the following terms and keywords: "Ketoprofen" and "Pharmacokinetics," adjusted according to the search instructions of each respective database. The databases and search engines used focused on medical and herbal medicine research.

2.2. Search strategy and selection of articles

The selection of articles was based on the formulation of research questions. The formulation of these questions focused on predetermined research topics. Determination of the formulation of the problem in this study referred to the PICO instrument, which aimed to make the search method more selective and sensitive so that the literature obtained was genuinely related to the research topic (Methley et al., 2014). The PICO instrument consists of four elements, namely: Population (P): Rats, Intervention (I): Formulated ketoprofen without the addition of solubilizing and extended-release agents, Comparison (C): Formulated ketoprofen with the addition of release modifier agents, Outcome (O): Pharmacokinetics parameter

2.3. Inclusion and exclusion criteria

All candidate articles were considered eligible for the literature review to inclusion criteria: 1) original research paper; 2) published from 2011−2020; 3) available through open access; 4) utilized rat test animals as research subjects; 5) involved ketoprofen formulated with the addition of release modifier agents and administered orally; 6) available study of the pharmacokinetic profile of ketoprofen. All articles, non-original papers (e.g., review articles or

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editorial texts), and multiple publications (duplicate entries within the database used) were excluded.

2.4. Quality assessment

Quality assessments were evaluated using instruments from the Center for Laboratory Animal Experimentation SYRCLE's Risk of Bias Tool for Animal Studies (Hooijmans et al., 2014). This instrument was one of the recommended instruments for evaluating papers in research with animals (Zeng et al., 2015). This analysis with the RoB SYRCLE instrument had ten critical points related to the bias of a study. Points 1 to 3 explained selection bias, points 4 and 5 explained performance bias, points 6 and 7 explained detection bias, point 8 explained attrition bias, point 9 explained reporting bias, and point 10 explained other biases.

2.5. Data extraction

Data extraction in this research discussed data on this study that have significant changes on the pharmacokinetics profile of ketoprofen and have the same parameters as other selected studies.

2.6. Data Analysis

In synthesizing data, a qualitative approach in systematic review was used to synthesize (summarize) the results of descriptive qualitative research. This method of synthesizing the results of research is called "meta-synthesis." Data analysis processing was carried out descriptively by summarizing and extracting the data obtained to determine the influence of formulation differences on the pharmacokinetic profile of ketoprofen in rats.

3. RESULTS AND DISCUSSION

3.1. Article selection

The article was selected by reading the articles regarding ketoprofen's pharmacokinetic profile and their addition with or without solubilizing and extended-release agents. This study sample selection was based on the PRISMA Guidelines (Moher et al., 2009). The PRISMA guidelines consist of a flow chart with four phases describing the criteria: identification, screening, eligibility, and inclusion of paper reports included in the scope of review (Liberati et al., 2009). Outlines of the procedure for including or excluding potential studies in a flowchart based on PRISMA guidelines are depicted in Figure 1.

The search results using the appropriate keywords in the PubMed and ScienceDirect databases found 695 identified reference articles (128 from PubMed and 567 from ScienceDirect). Articles related to the category of duplicate papers were eliminated, so the total number of articles that could be screened in the full text was 685. Observations based on titles and abstracts found 87 articles with criteria and relationships to the scope of the review. An assessment of these 87 articles was conducted based on the predetermined inclusion and

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exclusion criteria. A total of 69 articles were excluded for not studying the pharmacokinetic profile of ketoprofen (reason 1), 1 article was excluded for not being original research (reason 2), 19 articles were excluded for not using rat test animals or ketoprofen formulations with the addition of release modifier agents (reason 3), and two articles were excluded because the full text was not accessible (reason 4).

Rats were chosen as subjects because, in formulation development research, most pharmacokinetic profile studies use rats before progressing to other test subjects. This approach facilitates easier comparison of pharmacokinetic parameters based solely on the effects of formulation differences. The papers excluded are in the form of article reviews and articles irrelevant to the related topic based on the criteria applied. Three articles met the inclusion criteria after screening, identification, and eligibility processes.

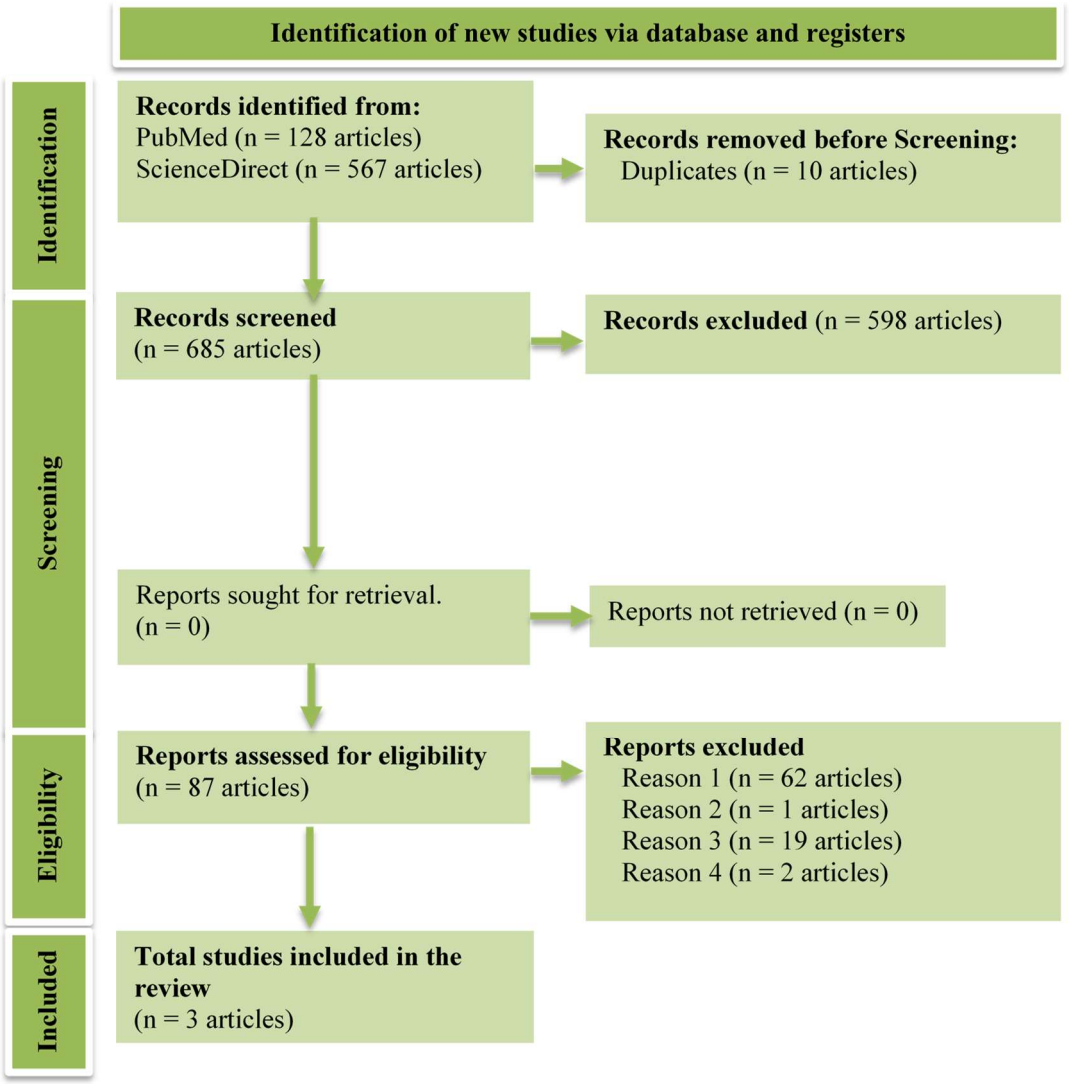

Figure 1. Flow PRISMA diagram of the article selection process.

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3.2. Quality assessment of the article

A reporting study on paper quality and risk of bias from papers is carried out using the SYRCLE risk of bias tool where there are ten items related to 6 types of bias (selection, performance, detection, attrition, reporting, and other preferences) (Hooijmans et al., 2014).

The results of the evaluation based on these instruments each point present information that researchers can assess as positive if they choose "Yes," which indicates a low risk of bias; negative when selecting "No," which indicates a high risk of bias; and is not clear when selecting "Unclear" which means if the detail is not sufficient at that point. The included studies reported an average low risk of bias of 9 out of 10 points. The lowest score was 6 out of 10 points, and the highest-scoring study reported 10 points out of 10. The percentage of bias risk assessment on the paper is presented in Table 1.

From the existing domains, it can be determined which one most influences the study results. In this case, the baseline characteristics (selection bias) are the most important because the pharmacokinetic profile's value significantly affects the type and test animal used in presenting the drug profile. The bias assessment for this domain is stated to have a low-risk bias with the result "✓" for each paper used. Furthermore, this paper can be used as data in this study.

Table 1. The study quality assessment includes the percentage of risk bias from the paper. Abbreviations: n.a.: not available.

Assessment parameter	Article		
	Pai *et al.*, 2011	**Fischer *et al.*, 2012**	**Mazzoni *et al.*, 2017**
Sequence generation	✓	✓	✓
Baseline characteristic	✓	✓	✓
Allocation concealment	✓	✓	✓
Random housing	✓	✓	✓
Blinding (performance bias caregiver)	n.a.	n.a.	n.a.
Random outcome assessment	n.a.	n.a.	n.a.
Blinding (detection bias assessors)	✓	✓	✓
Incomplete outcome data	✓	✓	✓
Selective outcome reporting	✓	✓	✓
Other sources of bias	✓	✓	✓

3.3. Data synthesis and discussion

The research results on the pharmacokinetic profile of ketoprofen in rats are summarized in Table 2. Three articles describe the pharmacokinetic profile values of ketoprofen with different results for each pharmacokinetic profile parameter.

Poloxamer is a nonionic polyoxyethylene-polypropylene copolymer used in the preparation of pharmaceuticals as emulsifiers or solubilizers and is used in drug delivery systems. Polyoxyethylene is hydrophilic, increasing ketoprofen's solubility (Chiappisi, 2017). The bioavailability of the drug can be affected by the solubility of the drug (Diaz-Reval et al.,

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2001). Increased solubility of ketoprofen with poloxamer-188 will increase the amount of ketoprofen absorbed and absorption of maximum ketoprofen. Poloxamer-188 is also used to increase the dissolution rate of ketoprofen by reducing surface or interfacial tension. Besides, Poloxamer-188 is capable of aggregating to form micelle structures. Forming this structure is one of the advantages of solubilizing drugs that are difficult to dissolve in water, such as ketoprofen (Newa et al., 2007). This mechanism contributes to the increased AUC and C_{max} values. The increase in the Cmax value in ketoprofen suspension with 5 mg/mL poloxamer-188 was 18.252 µg/mL (613.5%).

Table 2. Summary of pharmacokinetic parameters from selected articles. Abbreviations: mg/kg BW (milligram per kilogram of body weight); C_{max} (maximum concentration); t_{max} (maximum time to peak); AUC (area under the curve); µg/mL (micrograms per milliliter); µg h/mL (micrograms hours per milliliter); $scCO_2$ (Supercritical fluid CO_2).

Dosage form and dose (mg/kg BW)	Addition solubilizing or extended-release agent	Pharmacokinetic parameter			Article
		C_{max} (µg/mL)	T_{max} (h)	AUC (µg h/mL)	
Tablet (4)	-	0.0063	1.50	0.0137	(Pai et al., 2011)
SR tablet (4)	Etil selulosa and *Shellac*	0.0045	5.00	0.0402	
Suspension (5)	-	2.975 ± 0.288	-	185 ± 43	(Fischer et al., 2012)
	Poloxamer-188	21.227 ± 2.146	-	796 ± 272	
Solution (1.27)	-	5.171 ± 1.210	-	665 ± 104	
	Poloxamer-188	6.816 ± 0.652	-	720 ± 145	
Capsule (14.2)	-	0.488 ± 0.105	3.53 ± 1.00	19.2 ± 2.94	(Mazzoni et al., 2017)
	$scCO_2$	0.657 ± 0.078	1.55 ± 0.28	24.3 ± 2.4	

Meanwhile, the increase in the AUC value with adding 5 mg/mL poloxamer-188 was 611 µg·h/mL (330.2%). This improvement in the pharmacokinetic profile was caused by the presence of Poloxamer-188 in the formulation, which increased the solubility of ketoprofen by approximately 2.5 times (Fischer et al., 2012). This result was consistent with other research, which showed that Poloxamer 188 could enhance the solubility of drugs and the speed of their release from the dosage form, thereby increasing their bioavailability (De Stefani et al., 2022; Munir et al., 2022).

The Ethyl Cellulose-Shellac Coating (ECS) utilizes ethyl cellulose and shellac as binders and polymers to modulate drug release for sustained release (SR) applications. Shellac restricts drug release in the gastric environment, while ethyl cellulose governs drug release within the intestinal region (Pearnchob et al., 2003; Wakamatsu et al., 2021). The increase in ECS t_{max} values compared to immediate release (IR) was 3.5 hours, representing a percentage increase of 233.3%. This significant increase in t_{max} value is due to the slow release of the drug, causing

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a more prolonged absorption period for the released ketoprofen to reach maximum levels (Pai et al., 2011).

On the other hand, there was a decrease in the C_{max} value for ECS compared to IR by 28.5%. The C_{max} value decreases because ECS releases the drug slowly and gradually in small quantities, resulting in a smaller amount of drug being absorbed and a lower maximum level in plasma. The use of an inert ethyl cellulose matrix, which is insoluble in water, slightly inhibits the dissolution of ketoprofen, causing limited drug absorption and a decrease in maximum plasma concentration (van der Merwe et al., 2020; Vueba et al., 2013). Furthermore, the AUC parameter for ECS is three times greater than the AUC for IR. This difference is caused by the ECS extended-release mechanism, which results in the drug remaining in the body longer, thus increasing the AUC value compared to IR (Pai et al., 2011).

Supercritical fluid CO_2 ($scCO_2$) is used as a polymer impregnation to increase the solubility of ketoprofen, resulting in more excellent absorption of the drug. Consequently, the C_{max} value is significantly higher than the control (Sabegh et al., 2012; Verano Naranjo et al., 2021). During the impregnation process using $scCO_2$, ketoprofen is obtained from the form the crystals become amorphous. Ketoprofen is a BCS drug class II, which means it has poor solubility in water; therefore, its solubility can be increased by taking advantage of the amorphous form. Increased solubility of ketoprofen causes the drug to be easily absorbed so that the maximal value is much higher than controls (Abou-Taleb et al., 2023; Das et al., 2021). The difference is an increase in the C_{max} value of 0.169 µg/mL with a percentage of 34.6%, and the difference in the decrease in the t_{max} value is 1.98 h with a rate of 127.7%. The results of the analysis of the literature study from the three papers used above used a significance level of 5% or p-value <0.05. Level significance indicates the probability of error of a quantity statistic to be used to estimate parameters or apply to its population. It shows that the three papers above have a tolerable likelihood of error in the study by 5%. Based on the percentage change, the highest increase and lowest values of C_{max} were found in poloxamer-188 (613.5%) and $scCO_2$ (34.6%), respectively. The highest percentage increase and lowest AUC values were found in poloxamer-188 (330.2%) and ethyl cellulose + shellac (193.4%).

The highest percentage increase in C_{max} was in poloxamer-188 (613.5%), while the lowest was in $scCO_2$ (34.6%). It is significant because Poloxamer 188 utilizes a dosage form suspension integrated with a solid dispersion system, whereas ScCO2 is administered as a capsule containing a powder with a low dissolution rate. The reliable dispersion technique has the following advantages: particle size reduction, barriers to crystallization occurring in medicinal ingredients, and solubility enhancement (Malkawi et al., 2022; Patel et al., 2022). Poloxamer-188 can increase lipid packing density through direct incorporation into phospholipid bilayers, modulated by lipid membrane surface tension, as demonstrated by in vitro lipid monolayer experiments. Additionally, Poloxamer 188 can repair damaged cell membranes and was approved by the FDA over 50 years ago as a copolymer for pharmaceutical and cosmetic applications (Moloughney and Weisleder, 2012).

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Mixing hydrophobic drugs with hydrophilic carriers like poloxamer-188 can increase the drug release surface area and decrease the interfacial tension between hydrophobic drugs and the dissolution medium, leading to enhanced drug release (Munir et al., 2022). This mechanism enables medicines difficult to dissolve in water, such as ketoprofen, to be absorbed more effectively than when using ScCO2 in capsule form (Newa et al., 2007).

The highest percentage increase in AUC was found with Poloxamer 188 (330.2%), while the lowest was with ECS (193.4%). This result is because ethyl cellulose, used in ECS, is a matrix with inert and water-insoluble properties, inhibiting the drug dissolution rate (Wasilewska & Winnicka, 2019). Using ECS (2 – 7% w/w) in tablet preparations can slow down the dissolution rate of ketoprofen, resulting in the drug being released in small amounts and a smaller amount being absorbed. The study indicates that higher ECS concentrations correlate with ketoprofen's lower in vitro release profile. In contrast, poloxamer-188 at a concentration of 5 mg/mL can increase the solubility and formation of micelle structures, thereby enhancing the dissolution rate of ketoprofen. The higher the concentration of poloxamer-188, the better the drug solubility, leading to an improved drug release profile (Newa et al., 2007). Therefore, in the formulation of drug preparations, it is necessary to consider the additional ingredients used according to the desired drug release profile. Using poloxamer-188 can enhance the dissolution profile and bioavailability of the drug. At the same time, ECS can slow down the dissolution rate, making it suitable for preparations with slow-release purposes. Additionally, attention must be paid to the concentration of the release modifier agent used, as it will affect the resulting dissolution profile and bioavailability.

4. CONCLUSION

The study concluded that poloxamer-188, as a release modifier agent, causes a significant increase in the C_{max} and AUC of ketoprofen. Meanwhile, the use of ethyl cellulose-shellac caused a rise in t_{max} and AUC but resulted in a decrease in C_{max}. Additionally, the use of $ScCO_2$ significantly increased both C_{max} and t_{max}. Overall, the most significant changes in C_{max} and AUC were observed with the addition of poloxamer-188.

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CONFLICT OF INTEREST

All authors declared that there was no conflict of interest.

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