UNIVERSITI PUTRA MALAYSIA

SYNTHESIS, PHYSICOCHEMICAL CHARACTERIZATION AND EVALUATION OF EFFICACY AND TOXICITY OF LIPOSOMES ENCAPSULATED MEFENAMIC ACID

QAIS BASHIR MAHMOUD JARRAR

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By

QAIS BASHIR MAHMOUD JARRAR

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

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By

QAIS BASHIR MAHMOUD JARRAR

June 2018

Chairman : Professor Muhammad Nazrul Hakim, PhD
Faculty : Medicine and Health Sciences

Mefenamic acid (MFA) is a member of non-steroidal anti-inflammatory drugs (NSAIDs) with anti-inflammatory, anti-nociceptive and febrifugal properties. The poor aqueous solubility of this drug constitutes a major challenge in developing stable and effective formulations for the children in the pharmaceutical market. In light of this, this study was conducted to enhance the solubility and the therapeutic index of MFA using liposomes encapsulation technology. Various formulations of MFA-loaded liposomes including MFA-liposomes, MFA-Tween 80 liposomes and MFA-soduim diethyldithiocarbamate (DDC) liposomes were prepared using the proliposomes method and were subjected to various *in-vitro* characterizations. The *in vivo* toxicity and therapeutic efficacy of these liposomes was evaluated in experimental rats using the oral and intraperitoneal routes at selected doses (0, 20, 40 and 80 mg/kg). The animals were observed for toxicity signs and were used in a number of selected biochemical, histological and ultrastructural investigations. The anti-inflammatory, anti-nociceptive and febrifugal efficacies were determined using carrageenan-induced paw edema model, carrageenan-induced thermal hyperalgesia test, yeast-induced pyrexia test and lipopolysaccharides-induced systemic inflammation model. The finding of the present study demonstrated that MFA-loaded liposomes showed different physicochemical properties, storage stability and reproducibility. In particular, MFA-DDC liposomes were homogeneous (polydispersity index was around 0.2) vesicles with smaller particles size (ranging from 157.50 to 177.14 nm) and higher entrapment efficiency (up to 94.08 %) compared to other formulations used in the present study. Also, MFA-DDC liposomes were physically stable when stored at the room temperature (18-22 ^{o}C) and refrigerator (2-8 ^{o}C) for a period of at least 28 days. In addition, these liposomes were reproducible with a relatively low coefficient of variation (not more than 7.2 %) between different prepared batches at all tested parameters. The maximum tolerated dose of the

intraperitoneally administered MFA-loaded liposomes was 20 mg MFA/kg, whereas for those oral administration was up to 80 mg MFA/kg. The repeated administration of MFA-DDC liposomes caused significant elevation of serum alanine aminotransferase and aspartate transaminase at high oral dose (80 mg MFA/kg). on the other hand, blood levels of total bilirubin, alkaline phosphatase, triglycerides, cholesterol, total proteins, glucose, uric acid, blood urea nitrogen and creatinine, and uric acid as well as urine physicochemical parameters were not statistically affected. In contrast to MFA-DDC liposomes, the repeated administration of free MFA and MFA-Tween 80 liposomes resulted in hepatorenal histological and ultra-structural alterations in dose-dependent manner. Administration of MFA-DDC liposomes caused significantly higher inhibition in paw edema, pain sensation and fever than those of free MFA and MFA-Tween 80 liposomes administration. Results obtained from lipopolysaccharides-induced systemic inflammation revealed that MFA-DDC liposomes exhibited a significantly stronger suppression of serum proinflammatory mediators (PGE2, NO, IL-1beta, IL-6 and L-selectin) than that of free MFA and MFA-Tween 80 liposomes dosage (80 mg MFA/kg). The findings of the present study showed that MFA-DDC liposomes have higher entrapment efficiency, smaller particles size, more reproducible and stable during storage than those of MFA liposomes and MFA-Tween 80 liposomes. MFA-DDC liposomes are also much safer and more suitable than MFA-Tween 80 liposomes for delivering of MFA *in vivo*.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

SINTESIS, PENGKELASAN FIZIKOKIMIA DAN PENILAIAN TERHADAP EFIKASI DAN KETOKSIKAN LIPOSOM-BERKANDUNGKAN MEFENAMIC ACID

Oleh

QAIS BASHIR MAHMOUD JARRAR

Jun 2018

Pengerusi : Profesor Muhammad Nazrul Hakim, PhD
Faculti : Perubatan dan Sains Kesihatan

Mefenamic acid (MFA) tergolong dalam kumpulan 'non-steroidal anti-inflammatory drugs (NSAIDs)' dengan sifat anti-inflammasi, anti-nosiseptif dan 'febrifugal'. Kadar kelarutan yang rendah di dalam larutan akueus pada kompaun ini menghasilkan cabaran yang besar dalam menghasilkan formulasi yang stabil dan efektif untuk kanak-kanak di dalam pasaran farmaseutikal. Oleh itu, kajian ini dijalankan untuk meningkatkan kadar kelarutan dan indeks terapeutik MFA dengan menggunakan teknologi liposom-berkandungkan MFA. Beberapa formulasi melalui teknologi 'liposomes encapsulation' termasuk MFA-liposom, MFA-Tween 80 liposom dan MFA-soduim diethyldithiocarbamate (DDC) liposom telah dihasilkan dengan kaedah proliposom dan dikaji dengan pelbagai pencirian karakter melalui *in vitro*. Kadar ketoksikan dalam kajian *in vivo* dan kadar keberkesanan terapeutik liposom ini ditentukan dengan menggunakan tikus di dalam pemberian oral dan intraperitoneal dengan menggunakan dosej (0, 20, 40 and 80 mg/kg). Gejala ketoksikan yang terhasil terhadap tikus kemudiannya dikaji dan digunakan di dalam kajian biokimia, histologi dan ultrastruktur terpilih. Keberkesanan ubat terhadap tindakan anti-inflammasi, anti-nosiseptif dan anti-piretik dikaji melalui ujian edema kaki aruhan carrageenan, ujian hyperalgesia termal aruhan carrageenan, ujian pireksia aruhan brewer yis dan model inflammasi sistemik aruhan lipopolisakarida. Kajian ini mendapati komposisi kimia liposom-berkandungkan MFA menunjukkan sifat yang berbeza dari segi fizikokimia, kestabilan penyimpanan dan kebolehan penghasilan semula. Lebih terperinci, ia didapati homogenus (iaitu poli-sebaran indeks berada dalam lingkungan 0.2), dengan vesikel yang mempunyai partikel yang lebih kecil (bermula dari aras 157.50 sehingga 177.14nm) dengan efisiensi pemerangkapan yang lebih tinggi (sehingga 94.08%) berbanding formulasi lain yang digunakan di dalam kajian ini. MFA-DDC liposom juga mempunyai ciri-ciri fizikal yang stabil apabila disimpan pada suhu bilik (18-22°) dan disejukkan pada suhu (2-8°C) dalam jangka masa selama 28 hari. Selain itu, ia

didapati mempunyai sifat boleh dihasilkan semula dengan kadar pekali variasi yang rendah (tidak lebih daripada 7.2 %) di antara kesemua parameter yang telah diuji. Dos toleransi maksimum liposom-berkandungkan MFA melalui kaedah intraperitoneal ialah 20 mg MFA/kg BW, manakala melalui kaedah oral, dos yang diberi adalah sehingga mencapai 80 mg MFA/kg. Terdapat peningkatan signifikan amaun serum alanine aminotransferase dan aspartate transaminase melalui kaedah oral secara berkala pada dos yang tinggi (80 mg MFA/kg). Sementara itu, tiada perubahan statistik terhadap bacaan darah bagi keseluruhan bilirubin, alkaline phosphatase, trigeliserida, kolesterol, keseluruhan protein, glukos, *blood urea nitrogen (BUN)*, kreatinin dan asid urik serta parameter fizikokimia terhadap urin. Berbanding MFA-DDC liposom, pemberian berulang kumpulan tanpa MFA dan MFA-Tween 80 liposom menghasilkan perbezaan histologi hepatorenal dan kepelbagaian ultrastruktur dengan mengikuti aras dos. Pemberian MFA-DDC liposom terhadap tikus kajian menunjukkan peningkatan yang signifikan terhadap perencatan edema kaki, sensasi rasa sakit dan demam berbanding kumpulan tanpa MFA dan MFA-Tween 80 liposom. Hasil kajian daripada inflammasi sistemik aruhan lipopolisakarida menunjukkan kumpulan MFA-DDC liposom menghasilkan kadar penghalangan yang tinggi terhadap mediator pro-inflammasi (PGE2, NO, IL-1beta, IL-6 dan L-selectin) berbanding kumpulan ketiadaan MFA dan MFA-Tween 80 liposom dengan dosej (80 mg MFA/kg). Hasil kajian mendapati MFA-DDC liposom mempunyai kadar efisiensi pemerangkapan yang lebih tinggi, saiz partikel yang lebih kecil, lebih tinggi kadar penghasilan semula dan stabil semasa penyimpanan berbanding kumpulan MFA-liposom dan MFA-Tween 80 liposom. MFA-DDC liposom juga lebih selamat dan lebih sesuai digunakan di dalam penggunaan MFA *in vivo* berbanding MFA-Tween 80 liposom.

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I certify that a Thesis Examination Committee has met on 7 June 2018 to conduct the final examination of Qais Bashir Mahmoud Jarrar on his thesis entitled "Synthesis, Physicochemical Characterization and Evaluation of Efficacy and Toxicity of Liposomes Encapsulated Mefenamic Acid" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Doctor of Philosophy.

Members of the Thesis Examination Committee were as follows:

Mohd Nasir bin Mohd Desa, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Datin Sharida binti Fakurazi, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Rusliza binti Basir, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Internal Examiner)

Chandradhar Dwivedi, PhD
Professor
South Dakota State University
United States
(External Examiner)

RUSLI HAJI ABDULLAH, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 30 July 2018

This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

Muhammad Nazrul Hakim bin Abdullah, PhD
Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Chairman)

Zainul Amiruddin bin Zakaria, PhD
Associate Professor
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

Manraj Singh Cheema, PhD
Senior Lecturer
Faculty of Medicine and Health Sciences
Universiti Putra Malaysia
(Member)

ROBIAH BINTI YUNUS, PhD
Professor and Dean
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Signature: _____
Name of Member of Supervisory Committee: Associate Professor Dr. Zainul Amiruddin bin Zakaria

Signature: _____
Name of Member of Supervisory Committee: Dr. Manraj Singh Cheema

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

ACUC	Animal care and use committee
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
COX	Cyclooxygenase
CV	Coefficient of variation
DDC	Sodium diethyldithiocarbamate
DMSO	Dimethyl sulfoxide
ELISA	Enzyme-linked immunosorbent assay
et al.	*Et alii* (and others)
e.g.	*Exempli gratia* (for example)
FDA	Food and drug adminstration
FMHS	Faculty of Medicine and Health Sciences
GIT	Gastrointestinal tract
H & E	Hematoxylin and eosin
IL	Interleukin
I.P.	Intraperitoneal
LOD	Limit of detection
LOQ	Limit of quantification
LPS	Lipopolysaccharides
LUV	Large unilamellar vesicle

MFA	Mefenamic acid
MTD	Maximum tolerated dose
MVLs	Multivesicular liposomes
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
N/A	Not applicable
OECD	Organization of Economic Cooperation and Development
OLV	Oligolamellar vesicle
PDI	Polydispersity index
PG	Prostaglandin
P.O.	*Per os* (oral administration)
ROS	Reactive oxygen species
rpm	Rotation per minute
S.E.M	Standard error mean
SUV	Small unilamellar vesicle
TEM	Transmission electron microscopy
v/v	Volume to volume
w/w	Weight to weight

CHAPTER 1

INTRODUCTION AND OBJECTIVES OF THE STUDY

1.1 Introduction

Therapeutic agents should be formulated in pharmaceutical preparations that generate good patient compliance with safe and reproducible plasma concentrations (Hareendran et al., 2012). Manipulation of drug delivery system is a felicitous approach to enhance pharmaceutical and therapeutic properties of the drugs. The capability of such manipulation to alter drug performance *in vitro* and *in vivo* helps to identify novel molecular mechanisms and build new animal models for further pharmacological studies (Bhattachar et al., 2015).

The insufficient water solubility of the drugs is one of the most intricate issues in drugs development that demand a deep understanding in the pharmaceutical chemistry of the drugs. In addition, the poor solubility is implicated directly in a number of clinical limitations such as poor absorption and bioavailability, insufficient solubility for parental dosing and demands frequent and high dose of administration (Savjani et al., 2012).

According to pharmaceutical classification, drugs can categorized into the following classes: high soluble-high permeable drugs (class I); low soluble-high permeable drugs (class II); high soluble -low permeable drugs (class III) and low soluble -low permeable drugs (class IV). Because most of the drugs belong to class II, enhancing their poor water solubility constitute a critical element to improve their bioavailability and enhance their curative efficacy (Hamaguchi et al., 1986; Nurhikmah et al., 2016; Shinkuma et al., 1984).

NSAIDs is a large group of drugs which take a great attention in the clinical community owing to their wide applications in the treatment of inflammation, pain and fever (Cashman, 1996). In general, NSAIDs are inexpensive and widely available over the counter and with a doctor's prescription. The overall annual sales of NSAIDs is estimated at $18 billion worldwide (Petkova et al., 2014). These drugs produce their anti-inflammatory effect by blocking prostaglandins biosynthesis through inhibition the activity of cyclooxygenase isoforms (Cashman, 1996).

The therapeutic development of NSAIDs is an ongoing process since the 1950s and thereafter (Altman et al., 2015). Most of NSAIDs exhibit poor bioavailability as a result of their poor dissolution and low solubility in water. The researchers have made a lot of efforts to improve the solubility of NSAIDs as a key factor for improving their therapeutic responses.

Among NSAIDs, mefenamic acid (MFA) has widely been used in a number of countries including Philippine, Pakistan, Malaysia, Indonesia and China (McGettigan & Henry, 2013). Mefenamic acid is was introduced to the market by Parke-Davis in the 1960s and nowadays is available in the pharmacy as a single treatment or combined with other drugs (Asif, 2014). This drug was proved to exhibit potent anti-inflammatory activities and unique pharmacodynamics properties in various *in vitro* models (Cimolai, 2013). However, MFA has low aqueous solubility and poor bioavailability that result in suboptimal *in vivo* performance. Previous studies indicated that elevating the clinical doses of MFA may result in serious adverse reactions such as gastrointestinal ulceration and bleeding, hepatic and renal toxicity, pancreatitis and extrapyramidal symptoms (Cremona-Barbaro, 1983; Somchit et al., 2004; Wolfe et al., 1976). Considering these may suggest the necessity of improving the bioavailability of MFA using the approaches that have no or less potential to increase MFA toxicity.

During the last decades, scientists have developed various insoluble drug delivery technologies which involve several physical and chemical modifications and miscellaneous methods (Kalepu & Nekkanti, 2015; Savjani et al., 2012). Among these, encapsulation of the therapeutic agents in nanocarriers (NCs) such as liposomes, micelles, carbon nanotubes, dendrimers, and magnetic NCs has gained great attention in various research applications (Kumari et al., 2014).

Liposomes are tiny spherical vesicles consisting of at least one-phospholipid bilayers and studied extensively in the field of drug delivery. These particles have unique particle sizes (25-25000 nm) which render them selective carries for targeting inflamed and tumor tissues (Akbarzadeh et al., 2013). In addition, the amphiphilic structure of liposomes helps to entrap both of hydrophobic and hydrophilic drugs and to protect them from the surrounding environment (Bozzuto & Molinari, 2015). In the pharmacological point of view, liposomes improve the bioavailability, avoiding enzymatic degradation, provide sustain drug release and prolong the half-life of the drugs (Akbarzadeh et al., 2013; Bozzuto & Molinari, 2015).

In a comparison with solid-based nanoparticles, liposomes exert superior advantages in term of safety owing to their biocompatibility and biodegradability. Also, liposomes are capable to reduce gastrointestinal tract (GIT) and systemic toxicity of drugs by providing sustained drug release profiles (O'brien et al., 2004; Soehngen et al., 1988). Thus, the fact that liposomes can carry multiple drugs and reduce their toxicity concomitantly may strongly suggest using of these particles as an ideal platform for developing talented combination therapies (Fukuta et al., 2017; Meng et al., 2016). In addition, liposomes are highly flexible in nature and can be decorated by biologically targeting ligands or attached by stabilizing agents (Lin et al., 2017).

Liposomes *in vivo* performance depends highly on their physicochemical properties including the chemical constituent of phospholipids as well as liposomes size, surface charge, pH sensitivity and drug release profile (Gatoo et al., 2014). Therefore, determining the *in vitro* characteristics of liposomes is important for detection the suitable route of administration and prediction the *in vivo* performance of liposomes.

Numerous methods are used to prepare liposomes of variable characteristic. However, the pro-liposome method has been recently appreciated for developing various liposomal formulations using a rapid, simple and applicable procedure. Proliposomes are optimized mixtures of phospholipids that can spontaneously produce liposome upon controlled hydration condition. One of the major limitations of liposomes used in the pharmaceutical community is their low thermodynamic stability. It is, therefore, highly recommended to identify proper storage condition of the liposomes as a basic requirement in the liposomal researches (Toh & Chiu, 2013).

1.2 Problem statement

The poor aqueous solubility of MFA constitutes a major challenge in developing stable and homogenous formulations for the children in the pharmaceutical market. In addition, the insufficient solubility is a common limiting factor in the oral bioavailability of the hydrophobic drugs that reduces their therapeutic efficacy.

1.3 Research hypothesis

Liposome encapsulation can enhance the solubility, reduce the toxicity as well as improve the anti-inflammatory, anti-nociceptive and anti-pyretic efficacy of MFA.

1.4 Objectives

1.4.1 General objectives

The primary goals of the present study are to prepare various formulations of MFA-loaded liposomes, determine their physicochemical properties and investigate their *in-vivo* toxicity and efficacy in comparison to the ones of free (nonencapsulated) MFA.

1.4.2 Specific objectives

1. To prepare homogenous, stable and reproducible aqueous formulation of MFA using liposomes encapsulation technology.
2. To study the physicochemical properties of MFA-loaded liposomes using various *in-vitro* experiments.

3. To investigate the *in-vivo* toxicity of MFA-loaded liposomes in rats via oral and intraperitoneal administrations.
4. To evaluate the anti-inflammatory, anti-nociceptive and anti-pyretic efficacy of MFA-loaded liposomes in rats via oral and intraperitoneal administrations.

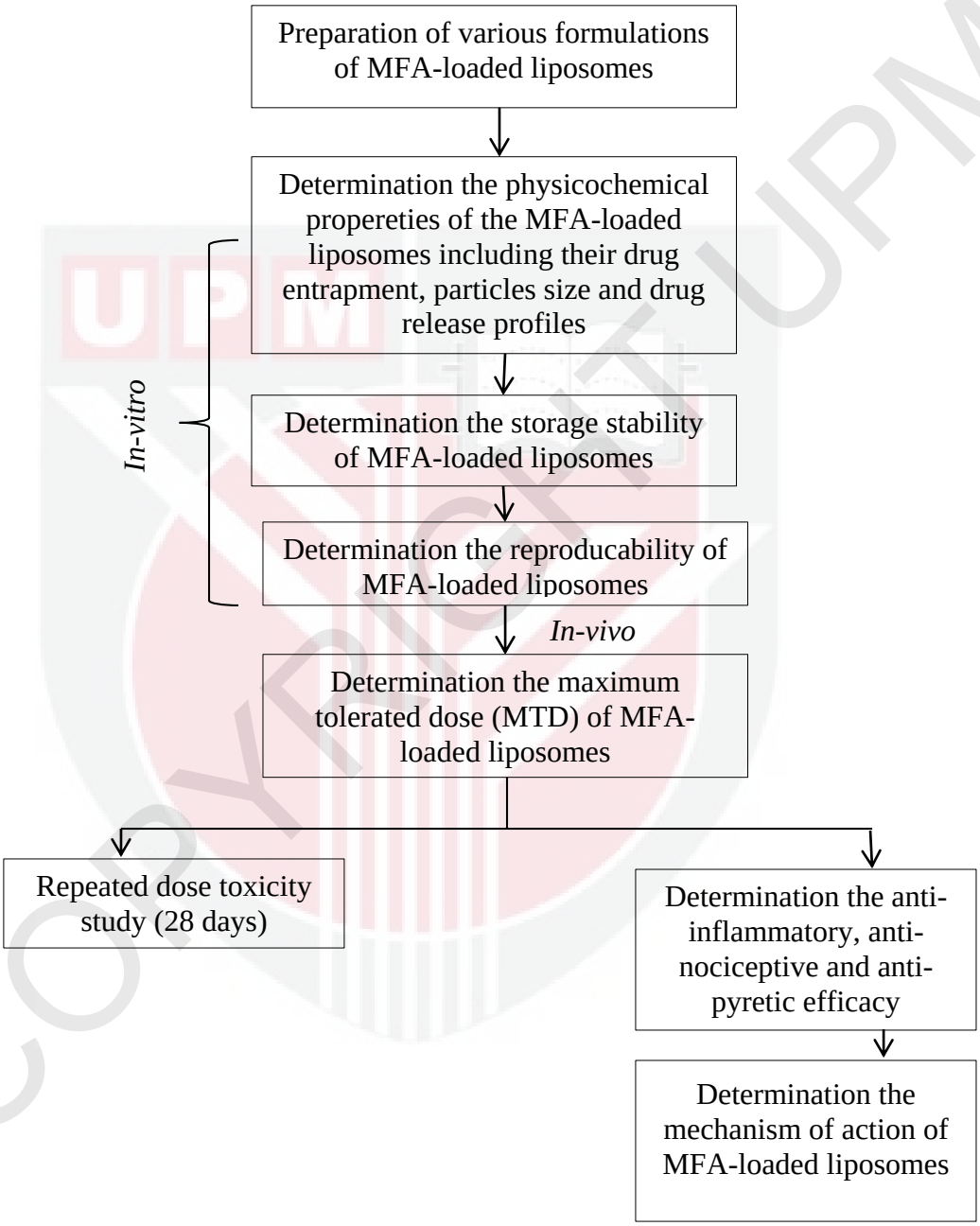

Figure 1.1 :Flow chart of the study design

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