Indonesian Journal of Pharmaceutics
IdJP
ISSN : 2597-8748

Vol. 5, Issue 2, 2023 (449-457)
http://journal.unpad.ac.id/IdJP

Study of Formulation, Characteristics, and Evaluation of Self Nanoemulsifying Drug Delivery System (SNEDDS) for Atorvastatin Calcium

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Submitted: 10/11/2023, Revised: 28/12/2023, Accepted: 15/01/2024, Published: 24/01/2025

ABSTRACT

A Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a formulation approach used in the pharmaceutical and biotechnology industries to improve the solubility and bioavailability of poorly water-soluble drugs. Atorvastatin calcium has limited water solubility, which can affect its bioavailability when administered orally. Its solubility can be enhanced by various formulation techniques, such as the use of self-nanoemulsifying drug delivery systems (SNEDDS). The purpose of this study is to determine the formulation and characterization of SNEDDS and determine how it affects the bioavailability of atorvastatin calcium. The data were collected from published journals. The carrier components required in the formulation of atorvastatin calcium with SNEDDS formulation include oils (oleic acid, peceol, capyrol 90, and capmul CMC), surfactants (tween 80, tween 20, labrasol, cremophor RH 40) and co-surfactants (brij 30, propylene glycol, transcutol-P, PEG 400, transcutol HP). Characterization of atorvastatin calcium with SNEDDS formulation showed droplet size 21.6-162.2 nm; zeta potential -1.32 - 24.6±6.47 mV; and polydensity index 0.164 - 0.297. SNEDDS formulation increased the percentage of drug release and increased the bioavailability of atorvastatin calcium.

Keywords: self-nanoemulsifying drug delivery system, SNEDDS, atorvastatin calcium, formulation, characteristics, dissolution, bioavailability

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https://doi.org/10.24198/idjp.v5i2.50996

1. Introduction

The first-choice medication for reducing low density lipoprotein (LDL) cholesterol in the blood is a statin. LDL cholesterol is thought to be the primary cause of many cardiovascular disease (1). When it comes to treating hypercholesterolemia and atherosclerosis, atorvastatin calcium (AT) is one of the most effective statins on the market (2). Atorvastatin calcium is a medication that belongs to a class of drugs known as statins. It is commonly prescribed to lower cholesterol levels in the blood, particularly low-density lipoprotein (LDL) cholesterol, often referred to as "bad" cholesterol. Atorvastatin is known by its brand name Lipitor, among others (3).

Atorvastatin belongs to Biopharmaceutical Classification System (BCS) class II where the nature of the active substance has low solubility and high permeability. Due to the low solubility of atorvastatin in water (0.1 mg/mL), the oral bioavailability of atorvastatin is low (12%) (4). Poor bioavailability may lead to the administration of higher doses to achieve therapeutic goals which may risk liver abnormalities, rhabdomyolysis, arthralgia and renal failure (5).

In recent years, there has been increased interest on lipid-based drug delivery systems, that comprise natural or synthetic lipids as a potential method of enhancing the oral bioavailability of lipophilic, weakly water soluble therapeutic candidates (6). Self-nanoemulsifying drug delivery systems (SNEDDS) is one method that has been proven to improve the solubility and bioavailability of drugs that are not very soluble in water (7). According to Makadia et al. (2013), SNEDDS is an isotropic blend of oils, cosurfactants, and surfactants that may spontaneously generate nanoemulsions when in contact with stomach fluids under modest agitation (8).

A Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a formulation approach used in the pharmaceutical and biotechnology industries to improve the solubility and bioavailability of poorly water-soluble drugs. This technology is particularly important because many drugs with valuable therapeutic properties often have low aqueous solubility, which can limit their effectiveness when administered orally (9). SNEDDS represent an innovative strategy for enhancing the bioavailability of poorly water-soluble drugs. By improving solubility, dissolution, and controlled release, SNEDDS can make a significant difference in the effectiveness of these drugs, ultimately improving patient outcomes (10).

The purpose of this review is to explain how how to formulate and characterize SNEDDS for atorvastatin calcium and show some studies that have been conducted by researchers using the SNEDDS method to increase the bioavailability of atorvastatin calcium.

2. Methodology

The references used are primary and secondary reference sources, namely research journals and books related to the theme of the literature review. In the results of the literature review, the references used are primary reference sources in the form of research journals published in the last 10 years (2013 - 2023). Research journals were obtained from the PubMed journal database with the keywords “atorvastatin calcium”, “atorvastatin”, “formulation”, “characteristics”, “self-nanoemulsifying

Drug Delivery System" and "drug delivery system". The search results obtained from PubMed and GoogleSchoolar database totaled 132 journals. From these search results, the final journals selected for review amounted to 8 journals.

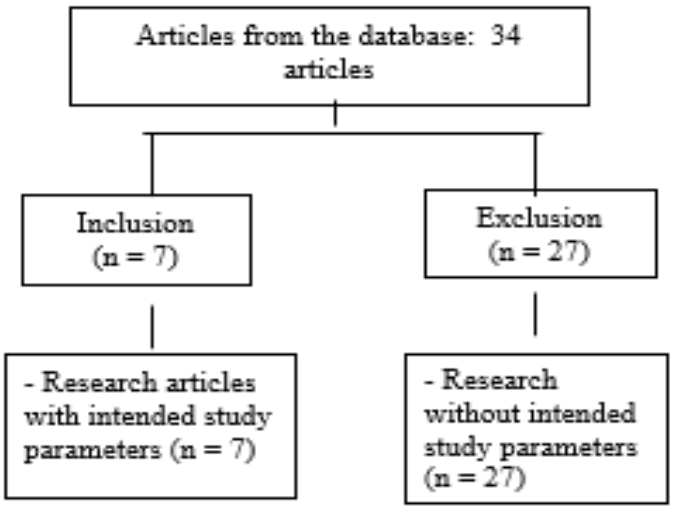

Figure 1. Flowchart of methodology

2.1. Physicochemical properties of atorvastatin calcium

The physicochemical properties of a drug like atorvastatin calcium are important factors to consider when formulating, manufacturing, and analyzing the drug. These properties provide insights into the drug's behavior and characteristics. Here are some of the key physicochemical properties of atorvastatin calcium:

1. Chemical Structure:

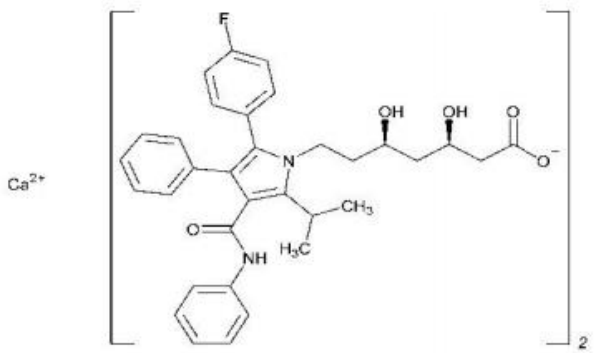

Figure 2. Chemical structure of atorvastatin calcium (11)

2. Molecular Formula: The molecular formula of atorvastatin calcium is $C_{66}H_{68}CaF_2N_4O_{10}$, indicating the number and types of atoms in the compound (11).
3. Molecular Weight: The molecular weight of atorvastatin calcium is approximately 1155.36 g/mol (11).
4. Physical State: Atorvastatin calcium is typically a white to off-white crystalline powder, and it is sparingly soluble in water (11).

5. Solubility: Atorvastatin calcium has limited water solubility, which can affect its bioavailability when administered orally (12).
6. pKa (Acid-Base Dissociation Constant): Atorvastatin calcium has a pKa of approximately 4.46, which is indicative of its ionization behavior at different pH levels. Understanding the pKa can be important for drug formulation and pharmacokinetics (5).
7. Melting Point: Atorvastatin calcium has a melting point around 151-157°C (303-315°F) (13).
8. Log P (Partition Coefficient): The partition coefficient, or Log P, is a measure of a compound's lipophilicity (its tendency to partition into a lipid phase) (14). Atorvastatin calcium has a Log P value of approximately 5.4, indicating its lipophilic nature (15).
9. Stability: Atorvastatin calcium should be stored in a cool, dry place and protected from light to maintain its stability. It can be sensitive to degradation under certain conditions, so proper storage is essential (11).
10. Spectral Properties: Atorvastatin calcium can be characterized by various spectroscopic methods, including infrared (IR) spectroscopy, ultraviolet-visible (UV-Vis) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy (16).
11. Crystalline Forms: Atorvastatin calcium may exist in different crystalline forms, which can impact its solubility, dissolution rate, and stability. Polymorphs of the compound can be a focus of study during drug development (17).

These physicochemical properties play a crucial role in the design and development of pharmaceutical formulations, including tablets, capsules, or other dosage forms. They can influence factors such as drug solubility, dissolution behavior, and bioavailability. Understanding these properties is essential for optimizing drug delivery systems and ensuring the efficacy and safety of medications like atorvastatin calcium.

3. Result and Discussion

Tabel 3.1 Study parameters of atorvastatin calcium formulation SNEDDS

Carrier	% Disolution		Bioavailability (AUC or % absorption)		Droplet Size (nm)	Potential Zeta (mV)	Index Polidipersitas	Source
	A1	A2	B1	B2				
Oleat acid 20% Tween 80 60% Brij 30 20%	56.86	94.12	45.34%	86.67%	162.2	-24.6±6.47	0.297	(18)
Olear acid Tween 80 Propilen glikol	NA	86.53	30249.74	84612.17	73.5	-24.1	NA	(19)

Oleat acid 10% Tween 20 45% Transcutol-P 45%	63.797	96.971	NA	NA	21.6	-17.78	0.315	(20)
Peceol Labrasol PEG 400	Significantly increased (A1<A2)	Significantly increased (A2>A1)	NA	NA	36.22 nm	-1.32	0.164	(21)
Capyrol 90 10% Tween 80 42.71% Transcutol HP Capmul CMC	Significantly increased (A1<A2)	Significantly increased (A2>A1)	59.04 ± 1.07	209.56 ± 2.28	97nm	-9.56	0.238	(22)
Cremophor RH 40 Transcutol-P	57.6±1.0	99.7±0.3	NA	NA	79.85	-23.75	0.250	(23)
Capmul CMC Tween 20	Significantly increased (A1<A2)	Significantly increased (A2>A1)	NA	NA	21.10 ± 4.11	−14.7 ± 2.22	0.293 ± 0.001	(24)

Keterangan: A1 = pure atorvastatin calsium/market product; A2 = SNEDDS atorvastatin kalsium; B1 = AUC% or absorption pure atorvastatin calcium/market product; B2 = AUC% or absorption SNEDDS, NA = not available

3.2. Formulation SNEDDS

The percent dissolution of atorvastatin calcium with a self-nanoemulsifying delivery system after 60 minutes was 94.12%. The carrier components used were oleic acid as oil, tween 80 as surfactant, and brij 30 as co-surfactant. Oil serves as the main carrier of the active substance in SNEDDS formulations, the oil component plays an important role in determining the size of the emulsion formed and the capacity of the active substance that
can be carried(18).

Surfactants reduce the droplet size of the emulsion and keep the active substance in the absorption site for a long time, preventing precipitation in the gastrointestinal tract. The co-surfactant in SNEDDS formulation helps the surfactant to lower the surface tension of water and oil, increase the dissolution of the active substance, and improve the dispersibility and absorption of the active substance.

The percentage release of atorvastatin calcium with self-nanoemulsifying delivery system in Venkatesh and Mallesh's 2013 study was higher than the market product which resulted in a percent dissolution of 56.86%. This is due to the low viscosity and high surfactant concentration of tween 80. Tween 80 also showed the most optimal solubility in other studies (19, 22). This could be due to the high HLB value of tween 80 (HLB = 15), which increases the efficiency of nanoemulsion formation.

Proper component selection is an important first step to create a stable SNEDDS

formulation. To prevent drug precipitation during the shelf life of the formulation and subsequent dilution in gastrointenstinal fluids, the drug must have adequate solubility in the nanoemulsion components. The carrier component was selected based on the ability of the carrier to dissolve atorvastatin calcium and form nanoemulsion spontaneously.

3.3. Characteristics SNEDDS

Droplet size in the studies studied had a size in the range of 21.6-162.2 nm, indicating that all atorvastatin calcium formulations in the SNEDDS studies studied were able to increase the release speed of atorvastatin and reduce surface tension. this is in line with the research of Mohsin et al., (2016) a decrease in droplet size will reduce surface tension and the smaller the droplet size, the greater the surface area so that it is expected that the drug can be absorbed in the digestive system quickly and increase its biaovailability (25).

In addition to droplet size, zeta potential and polydispersity index values are also important characteristics for evaluating SNEDDS formulations. A high zeta potential, which is above 30 mV or less than 30 mV, indicates that the formulation is stable enough to prevent agglomeration of preparation particles caused by repulsive forces. Higher zeta potential values increase repulsion and emulsion stability due to the reduction of particle aggregation, flocculation, coalescence, and coagulation (26). The presence of free fatty acids in negatively charged preparations and preparations, indicated by negative zeta potential values.

The zeta potential values in the study were in the range of -1.32 - 24.6±6.47 mV, indicating that the formulation of atorvastatin calcium with SNEDDS is stable.

The polydispersion index value indicates that the particle size of SNEDDS from temulawak preparation is well distributed or homogeneous. The polydispersity index value in the study reviewed had a value range of 0.164 - 0.297, this value is in accordance with the desired ideal value of <0.5 which indicates a monodisperse formula and identifies the formula has good particle or globule size uniformity

(27).

Other research for SNEDDS formulation studies on oral antihyperlipidemia agents showed that atorvastatin had a polydispersity index value of 0.241 using a combination of two surfactants (Tween 80 and Cremophor RH 40) (22). A lower, or almost zero, polydispersity index value indicates that the droplet size distribution is more homogeneous and better. The particle size distribution in an ideal SNEDDS formula sample can be used to determine the polydispersity index.

3.4. SNEDDS for improving bioavailability

From several studies reviewed, all formulations of atorvastatin calcium using the SNEDDS method showed an increase in percent dissolved when compared to pure atorvastatin calcium/market products. The increase in percent dissolved is predicted to increase the bioavailability of atorvastatin calcium, supported by data on the increase in bioavailability in three studies (18, 19, 22).

4. Conclusion

The carrier components required in the formulation of atorvastatin calcium with SNEDDS formulation include oils (oleic acid, peceol, capyrol 90, and capmul CMC),

surfactants (tween 80, tween 20, labrasol, cremophor RH 40) and co-surfactants (brij 30, propylene glycol, transcutol-P, PEG 400, transcutol HP). Characterization of atorvastatin calcium with SNEDDS formulation showed droplet size 21.6-162.2 nm; zeta potential -1.32 - 24.6±6.47 mV; and polydensity index 0.164 - 0.297. SNEDDS formulation increased the percentage of drug release and increased the bioavailability of atorvastatin calcium.

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