LMJ 5(2) (2026)

Lombok Medical Journal

http://journal.unram.ac.id/index.php/LMJ

The Potency of Atorvastatin Nanoparticles Implementation in Human: A Pharmacokinetic Perspective from Basic to Clinical Literature Review

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DOI: https://doi.org/10.29303/e9cn9w04

Article Info
Received : **20 April 2026**
Revised : **23 May 2026**
Accepted : **29 May 2026**

Abstract: Atorvastatin is a biopharmaceutics classification system class II drug with good permeability but low solubility, thereby limiting its bioavailability and therapeutic efficacy. This study aims to analyze the effect of particle size reduction on the pharmacokinetic parameters (Cmax, Tmax, AUC, t½) of atorvastatin in various drug delivery systems and the potency of its implementation in human through a literature review approach. Literature screening was conducted using online databases including Google Scholar, PubMed, ScienceDirect, and Springer Open, with inclusion criteria of national and international articles published in the last 10 years discussing atorvastatin formulations with various particle sizes and their pharmacokinetics parameters. Analysis of the 11 selected articles showed that nano-based delivery systems can increase the bioavailability of atorvastatin compared to conventional formulations. The results confirmed that particle size reduction through nanotechnology approaches increased the dissolution rate, membrane permeability, and absorption efficiency, thereby optimizing the pharmacokinetic profile of atorvastatin. This review provides evidence that nano-scale formulation strategies have a consistent positive impact on the bioavailability of atorvastatin. Despite these promising preclinical findings, the implementation of atorvastatin nanoparticles in humans remains limited due to the absence of clinical trials, although their potency to improve bioavailability and reduce dose-dependent toxicity at lower doses offers a strong rationale for future translational research.

Keywords: Atorvastatin, Drug delivery system, Nanoparticles, Particle size.

Citation: Haris, V. A. A. S., Tanjaya, S. P., Haiba, S. K., , A'yun, F. Q., & Hamdin, C. D. (2026). The potency of atorvastatin nanoparticles implementation in human: A pharmacokinetic perspective from basic to clinical literature review. *Lombok Medical Journal, 5 (2), 105-113. Doi: https://doi.org/10.29303/e9cn9w04*

Introduction

Cardiovascular disease remains the leading cause of death globally, with hypercholesterolemia serving as a major modifiable risk factor. Pharmacological therapy with statins has become the first-line treatment for dyslipidemia, with atorvastatin being one of the most widely used agents due to its potential to effectively reduce low-density lipoprotein (LDL) cholesterol levels (Putra et al., 2025). Atorvastatin works by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (H-CoA) reductase, thereby suppressing endogenous cholesterol synthesis (Haywood et al., 2022). Beyond its lipid-lowering effects, emerging evidence has revealed additional therapeutic potentials of atorvastatin, including anti-inflammatory, antioxidant, anticancer, and renoprotective activities,

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expanding its possible applications beyond cardiovascular diseases (Lara & Cepeda, 2025).

Despite its broad therapeutic potential, atorvastatin is classified under the Biopharmaceutics Classification System (BCS) as a Class II drug, characterized by low aqueous solubility but good intestinal permeability (Altaani et al., 2020). This poor solubility poses a significant constraint on its oral bioavailability, which can ultimately limit its therapeutic efficacy and necessitate higher doses, increasing the risk of side effects such as myopathy, rhabdomyolysis, and liver dysfunction (Georgescu et al., 2025; Singh et al., 2025). These limitations become particularly critical when atorvastatin is repurposed for non-lipid indications such as cancer or kidney injury, where higher or targeted drug exposure may be required (Clemente et al., 2021).

Overcoming the solubility and dissolution limitations of BCS class II drugs is a primary challenge in pharmaceutical formulation development (Deokate et al., 2024). Conventional approaches are often insufficient to achieve optimal bioavailability (Akour et al., 2025). In the last decade, advances in pharmaceutical nanotechnology have opened a new paradigm in drug delivery systems. Engineering particle size to the nanoscale (1–1000 nm) has been widely proven to enhance the pharmacokinetic performance of poorly soluble drugs (Premkumar et al., 2025). The enhancement of pharmacokinetic performance through particle size reduction to the nanoscale is primarily governed by fundamental physicochemical principles. When particle size is reduced from micrometers to nanometers, the surface area to volume ratio increases exponentially, leading to higher saturation solubility and faster dissolution velocity according to the Noyes-Whitney equations (Liu et al., 2024). Consequently, nanoparticles exhibit improved mucosal adhesion, prolonged gastrointestinal residence time, and enhanced transcellular and paracellular transport, which collectively contribute to superior systemic absorption and more predictable pharmacokinetic profiles (Bhalani et al., 2022).

Various nano-platforms such as polymeric nanoparticles, nanostructured lipid carriers (NLCs), nanocrystals, and self-nanoemulsifying drug delivery systems (SNEDDS), transdermal patches, and targeted nanoparticles have been developed for atorvastatin (Li et al., 2017). Each system offers a unique mechanism for enhancing bioavailability, ranging from improved drug stability in the gastrointestinal tract and increased permeability to bypass first-pass metabolism (Elmowafy et al., 2017). For instance, mannose-anchored solid lipid nanoparticles have been designed for targeted breast cancer therapy, while ROS-responsive nanoparticles have been developed for acute kidney injury treatment (Patil et al., 2024). Additionally, transdermal patches containing atorvastatin nanoparticles offer an alternative route to avoid hepatic first-pass metabolism entirely (Naser et al., 2024). However, the specific impact of variations in particle size and nano-system type on key pharmacokinetic parameters such as peak plasma concentration (Cmax), time to reach Cmax (Tmax), area under the curve (AUC), and elimination half-life (t½) still requires comprehensive mapping and analysis across these diverse applications.

Therefore, this literature review aims to systematically and critically examine the influence of atorvastatin particle size reduction on its pharmacokinetic parameters within various nano-drug delivery systems and its potency for clinical application. By synthesizing findings from recent studies, this review is expected to provide an in-depth scientific understanding from basic to clinical level regarding the relationship between particle size engineering, in vivo performance, and its implications for the development of more effective and safer atorvastatin formulations for clinical use. Furthermore, this review identifies critical knowledge gaps, particularly the absence of human clinical trials, and proposes future research directions to facilitate the clinical translation of nanoformulated atorvastatin.

Methods

This research method employs a literature study approach using a literature review model. Through this method, the author seeks to present a comprehensive summary of research developments and key findings related to the effect of atorvastatin particle size on pharmacokinetic parameters in various drug delivery systems.

The literature search and article selection process followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and reproducibility. As shown in Figure 1, the search strategy yielded a total of 458 articles from four online databases: Google Scholar (n = 187), PubMed (n = 95), ScienceDirect (n = 112), and Springer Open (n = 64). After removing duplicate records (n = 146), 312 articles remained for initial screening.

The literature search process was conducted online using keywords such as "Atorvastatin," "Nanoparticle," "Particle size," and "Drug delivery system." Scientific sources were obtained from several databases, including Google Scholar, PubMed, ScienceDirect, and Springer Open. The inclusion

criteria applied encompassed national and international articles published within the last 10 years, available in full-text format, and comprising original research discussing formulations with varying atorvastatin particle sizes and their resultant pharmacokinetic parameters. Conversely, literature irrelevant to the focus of the study was excluded from the analysis.

Titles and abstracts of the 312 articles were screened based on the inclusion criteria. A total of 247 articles were excluded during this stage for the following reasons: did not discuss atorvastatin (n = 89), did not discuss nanoparticles (n = 76), or did not report pharmacokinetic parameters (n = 82). The remaining 65 articles were assessed for eligibility through full-text review. Of these, 55 articles were excluded because: full text was not available (n = 12), the article was not original research (reviews or editorials) (n = 18), pharmacokinetic parameters (Cmax, Tmax, AUC, t½) were not reported (n = 14), or the publication year exceeded 10 years (n = 10). The complete PRISMA flow diagram is presented in Figure 1.

Following the data selection stage, 11 articles that met all inclusion criteria were analyzed based on title, publication year, abstract, and full text. They were then mapped into a table containing the source, formulation, method, and results of the measured pharmacokinetic parameters (Cmax, Tmax, AUC, t½).

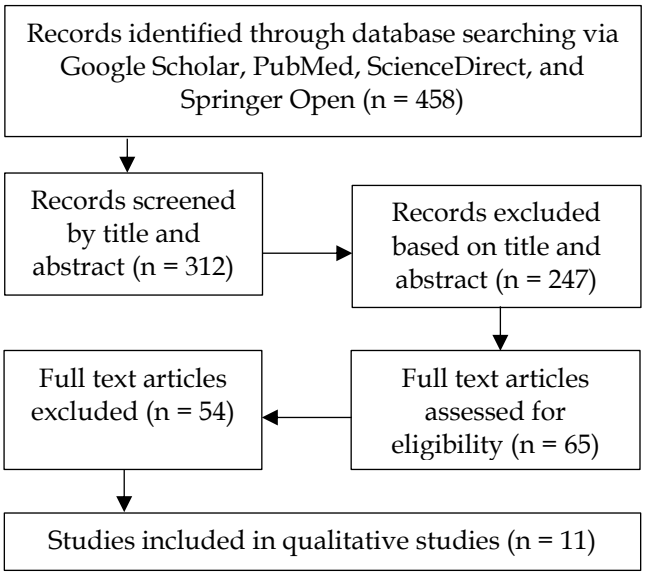

Figure 1. PRISMA flowchart of the article selection process

Result and Discussion

Analysis of various atorvastatin delivery systems indicates that particle size modification significantly influences the drug's absorption and distribution dynamics within the body (Shaker et al., 2020). Overall, nano-based formulations provide a meaningful increase in Cmax and AUC, along with alterations in Tmax and t½, suggesting improved absorption and bioavailability (Patra et al., 2018). This improvement is primarily driven by the fundamental relationship between particle size, surface area, and dissolution rate, which collectively determine the extent and rate of drug absorption from the gastrointestinal tract.

Significant particle size reduction dramatically increases the specific surface area, which directly enhances the dissolution rate following to the Noyes-Whitney equation (Liu et al., 2024). The accelerated dissolution rate subsequently strengthens the concentration gradient for passive diffusion across biological membranes, thereby optimizing systemic absorption (Gigliobianco et al., 2018). As the particle size decreases into the nanoscale range, the exponential increase in surface area allows for greater interfacial contact between the drug particles and the surrounding gastrointestinal fluids, which accelerates the dissolution process and supersaturates the intestinal lumen with dissolved atorvastatin (Shaker et al., 2020). This improved dissolution kinetics not only enhances the pharmacokinetic profile, as evidenced by increased Cmax and AUC values across all nanoformulations in this review, but also translates into superior pharmacodynamic outcomes, including more effective lipid-lowering activity, reduced inflammatory markers, and better target tissue penetration, ultimately leading to enhanced therapeutic efficacy at lower administered doses (Venkatraman et al., 2026; Patil et al., 2024).

Variation among nano-platforms such as polymeric nanoparticles, nanostructured lipid carriers (NLCs), nanocrystals, nanospheres, self-nanoemulsifying drug delivery systems (SNEDDS), and nanosuspensions reveals that the physical characteristics and lipid-polymer composition also determine a formulation's capability to enhance atorvastatin's pharmacokinetic profile (Dewi et al., 2024; Ng et al., 2020). An overview of the selected studies, including their formulations and experimental methods, is presented in Table 1.

Table 1. List of selected Atorvastatin Studies Based on Formulations and Methods

No	Source	Formulation	Method
1.	(Ahmed et al., 2016)	Nanoparticles	In vivo male albino rabbits (HPLC)
2.	(Elmowafy et al., 2017)	Nanostructured Lipid Carriers (NLCs)	In vivo male albino rats (HPLC)
3.	(Sharma and Mehta, 2019)	Nanocrystals	In vivo wistar rats (RP-HPLC)
4.	(Li et al., 2017)	Nanoparticles	In vivo wistar rats, (UPLC-MS/MS)
5.	(Hashem et al., 2015)	Nanospheres	In vivo female albino Wistar rats (HPLC)
6.	(Hashem et al., 2016).	Self-Nanoemulsifying Drug Delivery System (SNEDDS)	In vivo female albino wistar rats (HPLC)
7.	(Hashem et al., 2016).	Nanosuspension	In vivo female albino wistar rats (HPLC)
8	(Liu et al., 2023)	Hybrid Nanoparticles	In vivo wistar rats (HPLC)
9	(Liu et al., 2023)	Polymeric Nanoparticles	In vivo wistar rats (HPLC)
10	(Patil et al., 2024)	Chitosan-PECN Transdermal Patch	In vivo rats (RP-HPLC)
11	(Shinde & Lala, 2023)	Mannose-Solid Lipid Nanoparticles (MSLNs)	In vivo rats (HPLC)

Abbreviations: Self-Nanoemulsifying Drug Delivery System (SNEDDS), Polyelectrolyte Complex Nanoparticles (PECN), High Performance Liquid Chromatography (HPLC), Reverse Phase High Performance Liquid Chromatography (RP-HPLC), Ultra Performance Liquid Chromatography Tandem Mass Spectrometry (UPLC-MS/MS).

The nanoparticle formulation evaluated by Ahmed et al. (2016), demonstrated a Cmax increase up to 219.78 µg/mL which is higher than the marketed formulations 103.3 µg/mL. Besides, the AUC0-48h of 2618.98 µg h/mL also increased, and become the highest values among all marketed formulations in Ahmed's study. This result suggests that particle size reduction plays a role in expanding the surface area, thereby accelerating dissolution and increasing the concentration gradient, which subsequently enhances drug penetration through the intestinal membrane (Ghanem et al., 2021). A similar improvement is observed in the NLC formulation developed by Elmowafy et al. (2017), although its Cmax increase was not as substantial as the polymeric nanoparticles (Abdelkader et al., 2021). The NLC formulation achieved a Cmax of 25 µg/mL and an AUC0–∞ of 599 µg h/mL, indicating that the solid–liquid lipid matrix of NLCs can enhance physical stability as well as drug absorption efficiency. However, the high AUC variability suggests potential particle distribution heterogeneity or differences in physiological responses among test animals (Vasalou et al., 2023).

Nanocrystals studied by Sharma & Mehta (2019), also yielded a substantial peak concentration increase, reaching 1089.78 µg/mL, with a faster Tmax. The advantage of nanocrystals lies primarily in their enhanced dissolution rate through crystal size optimization, where smaller crystalline structures increase solubility pressure, thereby accelerating drug transfer into the solution phase. However, the AUC0-24 in this study was relatively low, potentially due to a different administered dose or a still-substantial contribution from first-pass metabolism.

Among all the nanoformulations analyzed in this review, the PLGA nanoparticle formulation reported by Li et al. (2017) exhibited the lowest Cmax 0.184 ± 0.077 µg/mL and AUC values 0.214 ± 0.058 µg h/mL. Nonetheless, the particle size reduction still resulted in a faster Tmax of 0.37 hours, indicating that the nano-formulation retains an advantage in the initial absorption phase. The low Cmax value in this study may be related to a low administered dose or a polymer composition that was suboptimal for maintaining the drug in a dissolved state.

A series of formulations developed by Hashem et al. (2016), provide an interesting overview of the performance differences among nano-technologies under uniform testing conditions. Nanospheres demonstrated the highest AUC0–∞ among the three tested formulations, at 117.558 µg h/mL, with a t½ reaching 20.84 hours. The SNEDDS formulation exhibited lower bioavailability compared to nanospheres but higher than the nanosuspension. This pattern generally reflects the different mechanisms for enhancing absorption, nanospheres rely on polymeric matrix protection against degradation and solubility enhancement, SNEDDS utilizes spontaneous microemulsion formation to expand contact surface area, while nanosuspensions increase dissolution through particle size reduction without significantly altering the surface structure (Sahumena & Rahmadani, 2019).

Beyond conventional oral formulations, transdermal and targeted delivery systems have also

demonstrated promising results. Patil et al. (2024) formulated atorvastatin-loaded PECN (polyelectrolyte complex nanoparticles) integrated into a chitosan-chondroitin sulfate transdermal patch, exhibiting a particle size of 219.2 nm. Pharmacokinetic studies in Sprague Dawley rats showed a significant improvement in bioavailability, with Cmax of 1.205 µg/mL, AUC0-t of 69.379 µg h/mL, and a half-life reaching 33.95 hours. Notably, the Tmax of this formulation was 11.33 hours, considerably longer than other oral formulations due to the sustained release mechanism through the skin, which bypasses first-pass metabolism. The relative bioavailability of the PECN transdermal patch was 4.76-fold higher compared to oral atorvastatin tablets, demonstrating that the transdermal route is effective in overcoming the first-pass metabolism issues of atorvastatin.

Shinde & Lala (2023) formulated mannose-anchored solid lipid nanoparticles (MSLNs) co-loaded with atorvastatin and vinpocetine for targeted breast cancer therapy. Following mannose conjugation, the nanoparticles exhibited a particle size of 435.4 nm and enhanced the relative bioavailability of atorvastatin by 1.47-fold relative to the commercial formulation. The pharmacokinetic parameters obtained included Cmax of 23.1 µg/mL, Tmax of 2.21 hours, and AUC0-24 of 338.535 µg h/mL. Although the increase in AUC was not as high as other polymeric nanoparticle formulations, the main advantage of this system lies in its targeting ability through mannose receptors expressed on cancer cells, thereby increasing drug accumulation in target tissues and reducing systemic side effects (Sanjaya & Pratiwi, 2026).

Liu et al. (2023) compared two different nano-platforms for atorvastatin delivery polymeric PLGA nanoparticles and lipid-polymer hybrid nanoparticles. Both formulations exhibited particle sizes below 110 nm (98.7 ± 1.2 nm for polymeric NPs and 105.2 ± 2.5 nm for hybrid NPs) with uniform size distribution (PDI < 0.3). Pharmacokinetic evaluation in Wistar rats revealed that hybrid nanoparticles significantly outperformed both polymeric nanoparticles and pure drug suspension. The hybrid NPs achieved a Cmax of 1.584 ± 0.046 µg/mL and an AUCtotal of 14.464 ± 0.055 µg h/mL representing 3.27-fold and 4.26-fold improvements, respectively, compared to pure drug suspension (Cmax 0.484 µg/mL, AUC 0.389 µg h/mL). Polymeric nanoparticles showed moderate improvements, with Cmax of 0.979 ± 0.035 µg/mL and AUC of 0.743 ± 0.018 µg h/mL. Interestingly, all formulations exhibited similar Tmax values (2 hours), suggesting that the enhanced absorption was primarily driven by improved solubility and permeability rather than faster gastric emptying. The superior performance of hybrid nanoparticles can be attributed to the presence of phospholipids in the polymer matrix, which enhances drug entrapment efficiency (77.16%) and facilitates better interaction with intestinal membranes, thereby promoting transcellular and paracellular uptake. These findings highlight that the incorporation of lipid components into polymer-based nanoparticles offers additional advantages for improving oral bioavailability of BCS Class II drugs like atorvastatin. The complete pharmacokinetic parameters for all formulations are presented in Table 2.

Table 2. Pharmacokinetics Profile of Atorvastatin in Various Drug Delivery System

Source	Result			
	Cmax (µg/mL)	Tmax (Hrs)	AUC (µg-h/mL)	t1/2 (h)
(Ahmed et al., 2016)	219.78 ± 2.54	2 ± 0.08	AUC_{0-48h}: 2618.98 ± 2.98	-
(Elmowafy et al., 2017)	25 ± 1.4	2 ± 0.25	$AUC_{0-\infty}$: 599 ± 224.3 AUC_{0-24}: 370.9 ± 65	-
(Sharma and Mehta, 2019)	1089.78 ±59.89	1.00±0.16	AUC_{0-24}: 6.51815±0.10116	5.07±0.08
(Li et al., 2017)	0.184 ± 0.077	0.37 ± 0.14	0.214 ± 0.058	1.08 ± 0.34
(Hashem et al., 2015)	8.65032	2	$AUC_{0-\infty}$: 117.558	20.84
(Hashem et al., 2016).	8.00921	1	$AUC_{0-\infty}$: 84.62117	22.207
(Hashem et al., 2016).	5.90989	2	$AUC_{0-\infty}$: 53.78313	19.28
(Liu et al., 2023)	1.584 ± 0.046	2	14.464 ± 0.055	-
(Liu et al., 2023)	0.979 ± 0.035	2	0.743 ± 0.018	-
(Patil et al., 2024)	1.205 ± 0.101	11.33 ± 1.16	AUC0-t: 69.379 ± 5.600	33.95 ± 4.94
(Shinde & Lala, 2023)	23.1 ± 2.28	2.21 ± 2.15	AUC0-24: 338.535 ± 9.816	-

While all included studies demonstrated improved pharmacokinetics in basic science utilizing animal models, direct extrapolation to human patients requires caution. Significant interspecies differences exist in gastrointestinal physiology, first-pass metabolism, and skin permeability (Liao et al., 2019).

For instance, rats have higher gastric pH and faster transit times than humans, which may overestimate dissolution rate improvements (Berghausen et al., 2016; Šíma et al., 2019). Furthermore, the absence of human clinical trials for nanoformulated atorvastatin represents a major knowledge gap. Future research should prioritize phase I bioavailability studies in healthy volunteers to validate these preclinical findings.

Overall, the data demonstrate that smaller particle sizes and more optimized carrier component engineering lead to greater improvements in pharmacokinetic parameters, particularly Cmax and AUC (Bhalani et al., 2022). Polymeric nanoparticle and nanocrystal formulations tend to yield higher peak concentrations, while lipid-based systems such as NLCs and SNEDDS excel in prolonging the half-life and enhancing drug stability in the gastrointestinal tract (Venkatraman et al., 2026). This relationship confirms that nanotechnology not only modifies dissolution speed but also improves permeation, reduces absorption variability, and, in some platforms, minimizes first-pass effects (Beltrán-Gracia et al., 2019).

Despite promising preclinical results, no nanoformulated atorvastatin product has yet received regulatory approval for clinical use. The path to clinical translation requires addressing several challenges, including scalable manufacturing with batch-to-batch consistency, long-term stability of nanoformulations, potential nanotoxicity concerns, and cost-effectiveness compared to generic atorvastatin (Eftekhari et al., 2017). Given that atorvastatin is off-patent and widely available as low-cost generics, nanoformulations must demonstrate clear clinical advantages, such as reduced dosing frequency, fewer side effects, or improved patient adherence, to justify their development costs (Ahmed et al., 2016). This lack of regulatory approval is further evidenced by the scarcity of completed and published human trials. To date, only one human trial involving atorvastatin nanoparticles has been registered (NCT05583643). Although this Phase 1 trial has been completed, its results have not yet been published in peer-reviewed literature, and no regulatory approval has been granted.

Scientifically, the findings from all articles confirm that modifying atorvastatin dosage forms through a nanotechnology approach consistently yields a positive impact on bioavailability. These findings support the utilization of nano-systems as a strategic approach to optimizing the clinical efficacy of atorvastatin. However, despite these promising preclinical results, the clinical translation of atorvastatin nanoparticles remains in its early stages. The majority of research is still confined to preclinical in vivo studies (Elmowafy et al., 2017). Nevertheless, several innovative formulations are paving the way for future clinical applications, including Mannose-Solid Lipid Nanoparticles (MSLNs) for enhanced brain delivery in breast cancer therapy (Shinde & Lala, 2023) and various oral nanocrystal formulations designed to improve systemic bioavailability (Sharma & Mehta, 2019). These advancements highlight a definitive shift towards developing atorvastatin nanoparticles for specific, high-impact clinical scenarios, though formal regulatory approval and widespread human use have yet to be realized.

To advance the field, future research should focus on head-to-head comparisons of different nano-platforms under standardized conditions, as exemplified by Liu et al. (2023). In addition, well-designed human bioavailability studies are urgently needed. Moreover, long-term toxicity assessments of residual nanocarrier materials in animal and human, development of orally disintegrating or once-weekly formulations to improve patient adherence, and cost-effectiveness analyses comparing nanoformulations to generic atorvastatin.

Conclusion

This review confirms that reducing atorvastatin particle size through nanotechnology enhances its pharmacokinetic parameters. Nano-based formulations consistently showed improved Cmax and AUC values compared to conventional dosage forms. This enhancement is attributed to increased surface area, accelerated dissolution, and improved membrane permeation. Despite these promising preclinical findings, the clinical translation of atorvastatin nanoparticles remains in its early stages, with several challenges including scalable manufacturing, long-term stability, potential nanotoxicity concerns, and cost-effectiveness compared to generic atorvastatin. Taken together, reducing atorvastatin particle size improves bioavailability and has the potential to reduce toxicity at lower doses. However, widespread human implementation is not yet feasible due to the absence of regulatory approval. Future research should prioritize well-designed human bioavailability studies, long-term toxicity assessments, and cost-effectiveness analyses.

Acknowledgements

The authors wish to express their sincere gratitude to all those who have supported the preparation of this manuscript, especially the Faculty of Medicine and Health Sciences, University of Mataram

Conflict of Interest

The authors declare no conflict of interest.

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