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Formulation and Optimization of Tween 80 Cholesterol Based Atorvastatin Loaded Niosomes Prepared by the Ether Injection Method: *In Vitro* Assessment of Drug Content, Entrapment Efficiency, Dissolution Characteristics, and Stability

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ABSTRACT

Background: Atorvastatin calcium is one of the commonly used drugs for lowering lipids, but it has challenges with absorption as it is classified as BCS class II with low permeability and site-specific absorption. Moreover, its conventional oral dosage forms are known for fast drug release. Vesicular drug delivery systems, such as niosomes, represent an attractive strategy for improving the entrapment, stability, and controlled release of drugs.

Objective: This research had the objective of preparing and testing atorvastatin loaded niosomes using the ether injection method in a bid to improve the drug release characteristics compared to existing products.

Methodology: Niosomal formulation A-F was developed by using Tween 80 and cholesterol in various proportions. Formulations were tested for in vitro drug release, potency, entrapment efficacy, stability, release kinetics, and comparison of dissolution profiles of atorvastatin commercial products (X-Z). Drug release profiles were analyzed for various kinetic models, and similarity factor (f_2) and dissimilarity factor (f_1) were determined for optimized formulation.

Results: Compared to commercial products, which had quick release of drugs in less than 90 minutes, the release of drugs in all the niosomal preparations was slow. The preparations B and F had higher potency (99.4% and 99.2%), entrapment efficiency (95.3% and 99.9%), and cumulative drug release (84.67% and 73.94% at 90 minutes). The results after 30 days had little variation in drug content and entrapment efficiency; there was enhanced stability in chilled conditions. Diffusion-controlled release was evident by the release kinetic data of optimized formulations, which were in agreement with Higuchi's equation. Results of fit factor test proved significant differences between the commercial formulation and optimized niosomal formulations.

Conclusion: From this study, it was concluded that atorvastatin-loaded niosomes prepared by the ether injection method, especially formulation B and F, show controlled release properties, entrapment efficiency, and stability, which reveal their potential for alternate delivery systems for Atorvastatin.

Keywords: Atorvastatin; Cholesterol; Dissolution; Drug Entrapment Efficiency; Ether Injection Method; Kinetics Release; Nanocarrier; Niosomes; Potency; Stability; Surfactants; Tween.

1.0. Introduction

The proposed drug delivery mechanism will generate microscopic lamellar structures, facilitating the process of drug encapsulation in order to deliver the drug to the necessary area effectively. This will make it possible for the drug to be localized within the necessary area, making it possible for the intended action to occur. Thus, there will be no threat of the drug to neighboring body parts. Moreover, the drug will remain localized to its specific area without being wasted. Numerous carriers have been used for focused drug administration, including artificial polymers, immunoglobulins, liposomes, blood proteins, niosomes, microspheres, and erythrocytes [1-2]. Amongst these carriers, niosomes are thought to be very resilient and efficient. The spontaneous organization of non-ionic surfactants into vesicle-like structures was first documented by the cosmetics industry during the 70s. Hydration of a composition containing cholesterol and non-ionic surfactants (alkyl/dialkyl ethers of polyglycerol) leads to the formation of microscopic lamellar vesicles termed niosomes [3-4]. Through the concourse of exogenous forms of energy like heat or swirling, non-ionized surfactants accumulate to form closed bilayer vesicles in a state of

aqueous. The hydrophilic parts of the bilayer remain accessible to the solvent, while the hydrophobic domains are oriented away from water. Vesicles' composition, concentration, lamellarity, surface charge, size and tapping volume can all be tuned to adapt their characteristics. There are various forms of interactions that occur inside the vesicle, ranging from van der Waals interactions between the surfactant molecules to electrostatic repulsions between charged bodies, entropic repulsion by head groups, and a lot more kinds of repulsions. These interactions are important for the stability of the vesicular form of niosomes. Nevertheless, the nature of the surfactants, drug characteristics, storage conditions, presence of detergents, membrane lipids, interfacial polycondensation reaction, as well as their charged property can influence the stability of the niosomes. The niosomes can be employed to transport drugs that are differently soluble because of their composition of amphiphilic, hydrophilic, and lipophilic portions [5]. These systems act as reservoirs for drugs that can be released in a regulated way. Additionally, owing to their localized effect, decreased rate of elimination, and protection against degradation by the biological system, these systems enhance drug efficacy [6]. Atorvastatin Calcium is among the statins drugs that work as HMG-CoA reductase inhibitors, used to reduce triglycerides and cholesterol in the body. This helps avoid heart disorders as it prevents the formation of cholesterol [7-8]. Atorvastatin Calcium falls under the category of BCS Class II because of low intestinal permeability and high first-pass effect, hence low oral bioavailability at 14%. The poor solubility of atorvastatin calcium (<1 mg/mL) makes it difficult to achieve oral absorption of the drug. An efficient method to increase the solubility, stability, and absorption of atorvastatin calcium is to formulate it in niosomes [9–10]. The niosome is an advanced drug delivery system that may improve the solubility and bioavailability of insoluble drugs such as Atorvastatin due to its ability to deliver the drug inside a bilayer lipid membrane, thereby increasing its stability and reducing its degradation [11].

1.1. Study Objectives

For the preparation, characterization and optimization of atorvastatin-loaded niosomes via the ether injection method and assessment of their suitability as a sustained release carrier. The specific objectives are as follows:

a) Preparation of atorvastatin-loaded niosomal systems through the use of varying concentrations of Tween 80 and cholesterol via the ether injection technique.

b) In vitro dissolution studies of the prepared atorvastatin loaded niosomes compared to commercial formulations of atorvastatin.

c) Drug content (potency) determination in the prepared niosomal formulations and commercial formulations.

d) Entrapment efficiency of the prepared niosomes to be determined to select the optimized formulation(s).

e) Release kinetics to be studied for the optimized niosomes using different kinetic models such as Zero order, first order, second order, Hixson-Crowell and Higuchi models.

f) Short term stability studies of optimized niosomal formulations under room temperature and refrigeration storage conditions.

g) Comparison of the dissolution pattern of optimized niosomal formulations with that of commercial products using similarity (f2) and dissimilarity (f1) factors.

h) Selection of optimized Tween 80-cholesterol ratio which can enhance entrapment efficiency, stability and sustained release of atorvastatin.

2.0. Literature Review

Niosomes possess numerous advantages over traditional dosage forms including drug stabilization, high entrapment efficiency, control over drug release profile, increased bioavailability, and reduction of systemic toxicity. Flexibility of niosome structure and relatively low production costs have made them a good alternative to liposomes in pharmaceutical industry [12-14].

Recent reviews conducted in 2025 emphasized that physicochemical properties of niosomes were greatly influenced by type of surfactant, cholesterol content, preparation method, and ratio of surfactant to cholesterol. Cholesterol inclusion in vesicular bilayers increases their rigidity, reduces the leakage of entrapped drugs and enhances the stability of niosomal formulation. Moreover, surfactants such as Tween 80 were widely used due to their advantageous hydrophilic-lipophilic balance and ability to form stable vesicular system with high drug-loading capacity [14-16].

Ether injection method remains the most popular among all methods of niosomes production due to simplicity, reproducibility, and possibility to obtain homogenous vesicles. In this method, the mixture of surfactant, cholesterol, and drug in organic solvent is added into aqueous medium leading to spontaneous formation of vesicles as a result of solvent evaporation. Recent research works have indicated that niosomes produced by ether injection have exhibited better drug loading and release properties. For instance, a 2026 work dealing with preparation and characterization of niosomes loaded with stavudine and produced by use of Tween 80 and the ether injection technique has shown that they have exhibited better entrapment efficiency, stability and diffusion-controlled drug release than conventional ones [17].

The interest to niosomes as carriers in drug delivery has been rising significantly due to their capability to improve the oral bioavailability of poorly soluble drugs. In a 2026 study on the pharmacological evaluation of hybrid niosomes, there was shown improvement in oral bioavailability and pharmacokinetics. Similar results have been achieved in recent studies regarding optimization of the formulation with the aim of improving the sustained release property and enhancing the therapeutic effect and stability of the formulation [18].

Atorvastatin has been investigated in niosomal systems by several authors. For example, Alam et al. (2025) produced atorvastatin-loaded niosomes using the ether injection method and found that the developed system had better drug entrapment, sustained release properties and stability than those of conventional dosage forms [9]. In recent advances in niosomal drug delivery technology, there is optimization of vesicular composition and investigation of drug release mechanism. In particular, diffusion-controlled drug release described by the Higuchi model has been frequently observed in niosomes. In addition, it has been found that there is an important role played by the optimization of surfactant and cholesterol content in drug release rate, entrapment efficiency and stability [13,16,18].

It may be concluded from the literature survey that niosomes appear to be a promising carrier system for improvement in the delivery of poorly water-soluble drugs like atorvastatin. Nevertheless, more studies are required

to optimize the formulation variables as well as evaluate the rate of drug release, entrapment efficiency, stability, and release kinetics of atorvastatin loaded niosomes formulated with various ratios of surfactants and cholesterol. Accordingly, the current study was aimed to formulate and optimize atorvastatin loaded niosomes using Tween 80 and cholesterol as surfactants by ether injection method [19-22].

3.0. Materials and Methods

3.1. Materials

The atorvastatin calcium was collected from one of the free samples of the top pharmaceutical industries. The Tween 80, Cholesterol, Chloroform, and 0.1 N Hydrochloric acid (HCl), which were utilized in preparing the solution, were obtained from the Pharmacy Department Laboratory, Bangladesh University. The chemicals utilized in this experiment are research chemicals, and the solvent utilized in this experiment is distilled water. A Shimadzu UV-1800 double-beam spectrophotometer (Japan), a dissolution apparatus, and an electronic balance (AS 220.R2 PLUS) were used, and statistical data were processed using Microsoft Excel.

3.2. Preparation of Atorvastatin-loaded niosomes by ether injection method

Weighed amounts of cholesterol and Surfactants (Tween-80) were heated in a water bath at 55–60 °C. A Atorvastatin-chloroform solution was prepared separately and added dropwise using a microsyringe at 1 mL/min under constant stirring. Then the solution was stirred continuously with magnetic stirrer and the difference in temperature between the phases caused vaporization, resulting in the formation of niosomes [11,23]. Each formulation was prepared using different ratio of surfactant and coded for in-vitro evaluation.

3.3. Calibration curve preparation

A stock solution was created by dissolving 10 mg of atorvastatin calcium in 100 mL of 0.1 N HCl in a volumetric flask. From this solution, 10 mL was filtered and further diluted to 100 mL with distilled water to obtain a working concentration of 10 µg/mL. Specific concentrations (1, 3, 5, 7, and 9 µg/mL) were then prepared through serial dilution. The absorbance of each standard solution was recorded at 246 nm using a single beam UV-Visible spectrophotometer. A calibration curve of concentration versus absorbance was constructed to evaluate linearity and determine the concentrations of unknown samples [11,23].

3.4. Drug content determination

Ten tablets from each brand were selected, and the powder was made by thoroughly combining and crushing the tablets into a fine powder. A weight of powder equivalent to 10 mg of atorvastatin was measured and placed in a 100 ml volumetric flask. A sufficient quantity of 0.1 N HCl was added to the sample, and ultrasonication was used to ensure that it is evenly distributed. The sample was subsequently filtered. A volume of 10 ml from the filtered solution was then taken and further diluted with 100 ml of distilled water. The absorbance of this solution was then measured using a UV-Vis spectrophotometer at 246 nm [11,23]. Additionally, the same analytical methodology was used to assess the drug content of the niosomal preparations.

$$\text{Potency}=\frac{10\times\text{Concentration of sample}\times\text{Absorbance of sample}}{\text{Absorbance of standard}} \quad \text{----------(1)}$$

3.5. Entrapment efficiency determination

The entrapment efficiency of all niosomal formulations was determined by centrifuging the samples at 3000 rpm for 45 minutes to separate the unentrapped drug. The absorbance of the collected supernatant was then measured at 246 nm using a UV–Vis spectrophotometer. [13-14,23].

3.6. Dissolution studies

To find the percentage of atorvastatin release at various intervals, the study of in-vitro drug release for niosome formulations A, B, C, D, E, and F, and commercial products X, Y, and Z was carried out using the USP Apparatus II (paddle type). The procedure was done using 900 mL of 0.1 N HCl at a temperature of 37 ± 0.2°C.

The speed of rotation of the paddles was kept constant at 100 rpm, and the experiment was conducted for 90 minutes. At regular intervals (15, 30, 45, 60, 75, and 90 minutes), samples of 10 mL were withdrawn and replaced with an equal volume of fresh dissolution medium to maintain sink conditions throughout the experiment.

The collected samples were subjected to filtration, and their absorbance was determined at 246 nm by means of a UV-Visible spectrophotometer, to determine the extent of drug release [11-13]. The amount of drug in solution was determined using the calibration graph. The experiment was done thrice, and only the average readings were taken into consideration [12,24].

3.7. Model dependent methods for kinetics of drug release

The optimally designed formulations (B and F) were further evaluated to investigate their release kinetics. The dissolution profiles of these optimized atorvastatin niosomal formulations were analyzed using five model-based approaches, including the zero-order, first-order, second-order, Hixson-Crowell and Higuchi dissolution models, represented by Equations 2–6, respectively. The dissolution patterns corresponding to these five models are described by the following equations.

Zero order kinetics: $D_t = D_o + kt$ ----------(2)

First order kinetics: $\ln D_t = \ln D_o + kt$ ----------(3)

Second order kinetics: $D_t^{-1} = D_o^{-1} + kt$ ----------(4)

Hixson-Crowell model: $D_t^{1/3} + D_o^{1/3} = kt$ ----------(5)

Higuchi model: $D = K\sqrt{(t-t_o)}$ ----------(6)

Where, Do is primary quantity of drug, Dt is the drug quantity at t time and K is the constant of the kinetic drug release [15].

3.8. Stability studies

The optimally designed formulations (B and F) were stored in individual glass tubes, sealed with aluminum foil, at room temperature and under refrigeration (4 °C) for 30 days. After one month, the samples were evaluated and

compared with the initial measurements in terms of percentage drug content and entrapment efficiency of niosomal atorvastatin [16].

3.9. Fit factors determination

A model-independent approach was employed using the fit factors f1 and f2, representing the difference and similarity factors, respectively, calculated by comparing the test and reference brands as shown in Equations (7) and (8). For evaluating the equivalence of two dissolution profiles, f1 values should fall within the range of 0–15, while f2 values should lie between 50 and 100. The f_1 and f_2 defined as-

$$f1=\left\{\frac{\sum|Rt-Tt|}{\sum Rt}\right\}\times 100 \text{----------(7)}$$

$$f2=50\log\{1\div\sqrt{[1+\frac{1}{n}\sum(Rt-Tt)(Rt-Tt)]\times 100}\} \text{--------(8)}$$

Here, The number of sampling time points is represented by n during dissolution, while Rt and Tt represent the drug's dissolution percentage from the reference and test formulations, respectively [16].

4.0. Result and Discussion

4.1. Formulations of the Atorvastatin loaded niosomes

Atorvastatin-loaded Niosomes have been successfully prepared using the ether injection method with varying concentrations of Tween 80 and cholesterol (Table 1). The varying concentrations of the surfactant were used to study the influence of concentration on the release, entrapment efficiency, potency, and effectiveness of the niosomal formulation.

Table 1. Formulations of the Atorvastatin loaded niosomes prepared by ether injection method.

Formulation Code	Drug (mg)	Tween 80 (mg)	Cholesterol (mg)	Drug: Tween: Cholesterol Ratio	Chloroform (ml)	Total Volume (ml)
A	100	100	100	1:1:1	10	300
B	100	150	100	1:1.5:1	10	350
C	100	200	100	1:2:1	10	400
D	100	250	100	1:2.5:1	10	450
E	100	300	100	1:3:1	10	500
F	100	350	100	1:3.5:1	10	550

4.2. Standard calibration curve of atorvastatin

Standard calibration curve of atorvastatin (Fig. 1) showed a good linear relationship in the concentration range of interest, thus ensuring that the analytical method used was accurate for quantitative analysis of atorvastatin in the dissolution studies, potency, and entrapment efficiency.

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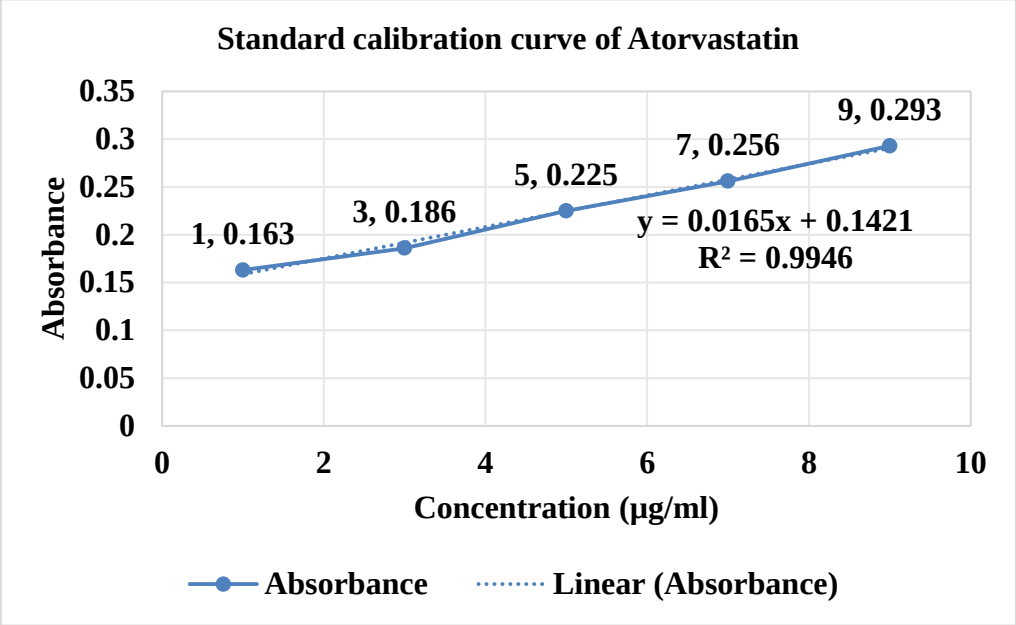

Figure 1. Standard Calibration Curve of Atorvastatin.

4.3. Potency analysis

There was a noticeable difference among the prepared samples based on the values of comparative potency (Table 2 and Fig. 2). As with samples Y (99.8%) and Z (98.4%), samples B (99.4%) and F (99.2%) had higher values than other niosomal samples. Values above 100% could be sensitive, variable, or indicative of micro-heterogeneity during preparation. Samples C and D had low values, possibly due to entrapment or loss of drug during preparation.

Table 2. Comparative potency (%) of niosomal (A–F) and marketed (X–Z) products.

Formulation	A	B	C	D	E	F	X	Y	Z
Potency (%)	78.96	99.4	69.9	66.8	83.5	99.2	96.8	99.8	98.4

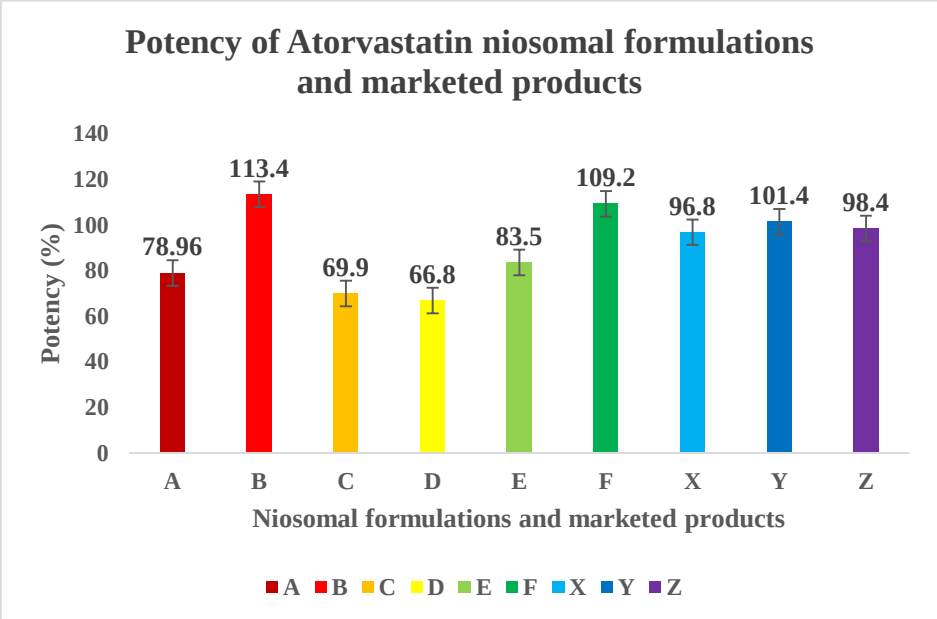

Figure 2. Comparative potency of niosomal formulations (A-F) and marketed products (X-Z).

4.4. Drug entrapment efficiency

Entrapment efficiency is an important characteristic of vesicular delivery systems for drugs. As depicted in Table 3 and Fig. 3, the highest entrapment efficiency of 99.9% and 95.3% was found in formulation F and formulation B, respectively. The rise in entrapment efficiency with the increase in surfactant concentration can be ascribed to the increased formation of vesicles and the ability of the bilayer to accommodate the drug. Formulations with lower amounts of Tween 80 (A, C, D, and E) showed relatively lower entrapment efficiency, which may be due to the reduced stabilization of the bilayer.

Table 3. Drug entrapment efficiency (%) of prepared niosomal formulations (A–F).

Formulation	A	B	C	D	E	F
Drug entrapment efficiency (%)	62.96	95.3	57.9	56.2	59.8	99.9

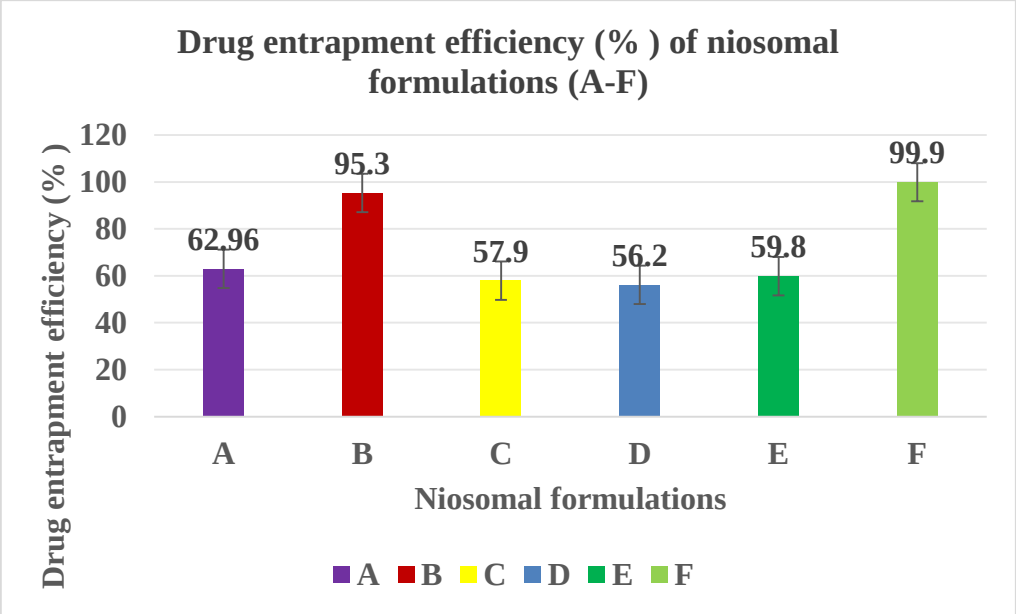

Figure 3. Comparative drug entrapment efficiency (%) of niosomal formulations (A-F).

4.5. In vitro dissolution study

The comparative dissolution profiles of niosomal formulations (A-F) and commercial formulations (X-Z) are shown in Table 4 and Fig. 4. The result shows that all niosomal formulations have shown slow and controlled release of the drug, while the commercial formulations have shown fast and almost complete release of the drug (> 97%) in 60-90 minutes. The fast release of the drug from commercial formulations can be attributed to the direct contact of free drug with the dissolution medium.

Among the niosomal formulations, formulation B showed maximum cumulative drug release (84.67% at 90 min), and second was formulation F (73.94%). Contrarily, formulations A, C, D, and E showed low drug release values, indicating that they retain more drug within the vesicular system. The enhanced drug release in formulation B and F may be attributed to their optimal Tween 80 and cholesterol concentration ratio, which may result in a stable and permeable bilayer structure of niosomes, thus facilitating controlled drug diffusion of atorvastatin.

Table 4. Comparative study of dissolution profile among six formulations (A-F) and three marketed samples (X-Z).

Formulations	Percentage of drug release over time					
	15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**
A	3.76	9.76	17.40	21.76	25.58	29.95
B	15.2	20.31	29.12	63.4	78.58	84.67
C	17.40	21.76	25.58	26.67	32.12	41.12
D	2.67	9.21	21.76	29.40	41.94	49.03
E	7.58	14.12	17.94	23.40	31.03	37.58
F	5.94	8.67	22.84	57.76	67.95	73.94
X	38.5	61.4	84.8	97.7	99.2	99.4
Y	42.3	63.3	87.9	90.1	92.3	98.1
Z	40.7	76.3	85.8	97.4	98.1	99.9

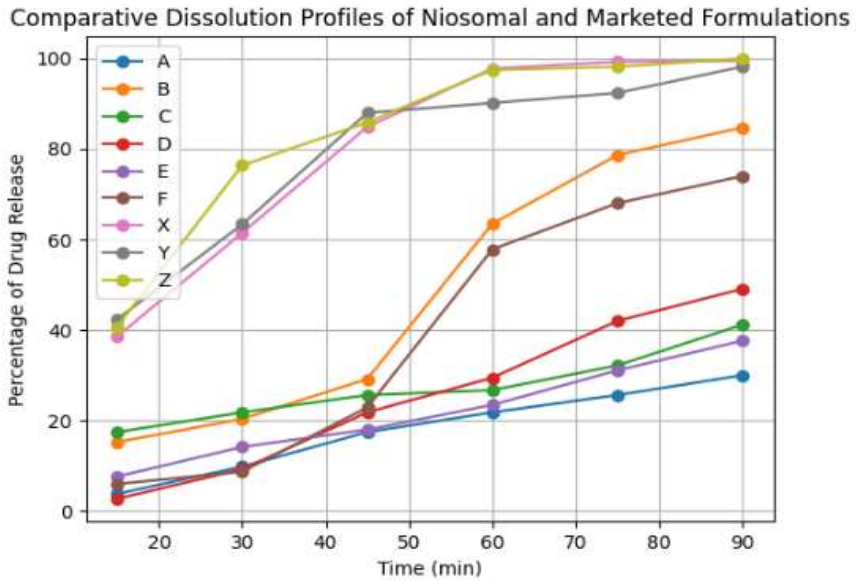

Figure 4. Comparative dissolution profiles of all samples showing percentage drug release over 90 minutes.

4.6. Stability studies

Stability studies were also done for optimized formulations B and F (Table 5), in order to determine the physical and chemical stability for 30 days when stored in room temperature as well as in refrigerated conditions. The two formulations were found to retain very little amount of the drug as well as entrapment efficiency when stored, showing that they were very stable. However, the two were found to retain more when stored in refrigerated temperatures compared to room temperatures, showing that lower temperatures reduce vesicle aggregation as well as release of the drug.

Table 5. Comparative stability studies data for fresh samples with 1 month stored optimized samples at room temperature and refrigerator (4^0C).

Formulation	% Drug content			% Drug entrapment efficiency		
	Initial data	Data after 30 days		Initial data	Data after 30 days	
		Room temp.	4^0c temp.		Room temp.	4^0c temp.
B	99.4	97.3	93.3	95.3	86.9	94.8
F	99.2	93.1	90	99.9	95	99.5

4.7. Drug release kinetics

The data on the release kinetics of an improved formulation B and F is presented in Table 6. The maximum value of R^2 is achieved in the Higuchi equation (0.9702 for B and 0.9329 for F), confirming the fact that the release of the drug in the niosomal formulation is diffusion-controlled. The best-fit result of the data in the Hixson-Crowell equation confirms the fact that the change in the surface area of the vesicles is an important factor in the release of the drug. This confirms the fact that the niosomes have been able to provide an effective controlled release of the drug.

Table 6. Kinetics release data (R^2 value) for optimized (B and F) formulations.

Model	Statistics	Optimized formulations	
		B	F
Zero order	R^2	0.8659	0.8407
First order		0.8710	0.9634
Second order		0.0069	0.7812
Hixson-Crowell		0.9097	0.9021
Higuchi		0.9702	0.9329

4.8. Fit factor analysis

The fit factor analysis (Table 7) indicated low similarity ($f_2 < 50$) and high dissimilarity ($f_1 > 15$) between optimized niosomal formulations (B and F) and the reference product Z. The result further strengthens the fact that the dissolution profile of niosomal formulations differs significantly from that of the reference product, which further supports the controlled release characteristics of the prepared niosomal formulation.

Table 7. Fit factors for optimized (B and F) formulations compared with marketed product (Z).

Fit factor		
Brand	**f_1**	**f_2**
Z/B	41.53	20.88
Z/F	52.41	16.7

4.9. Overall interpretation

On the basis of the dissolution profiles, potency, entrapment efficiency, and kinetic analysis, the optimized niosomal formulation would be formulation B and F. The data indicate the importance of the ratio of Tween 80 and cholesterol in the optimization of the entrapment of the drug, potency, and the release of atorvastatin. The study concludes that the atorvastatin-loaded niosomes prepared by the ether injection method show great promise as an alternative delivery system, which can lead to better therapeutic efficacy than the conventional formulation available in the market.

5.0. Conclusion and Future studies

Atorvastatin-loaded Niosomes have been successfully prepared using the ether injection method with distinct ratios of Tween 80 and cholesterol. The results showed that all the niosomal formulations had a controlled release of the drug compared to the commercial formulations. Formulations B and F were found to be better in terms of potency, entrapment efficiency, stability, and diffusion-controlled release of the drug using the Higuchi model. Fit factor analysis confirmed the lack of similarity with commercial formulations, thus underlining the sustained release capabilities offered by the niosomal formulation. Optimized niosomes appear as a promising choice over conventional dosage forms of atorvastatin. This current study indicated the possibility of utilizing atorvastatin-loaded niosomes formulated with Tween 80 and cholesterol for controlled release drug delivery system. Nonetheless, more research is necessary to validate their pharmaceutical and therapeutic applications.

These are some of the proposed future studies:

1) Physicochemical properties of optimized niosomes (size, zeta potential, SEM/TEM).
2) Pharmacokinetics and bioavailability in vivo.
3) Pharmacodynamics study on animal models of hyperlipidemia.
4) Long-term and accelerated stability tests according to ICH guidelines.
5) Design of experiments optimization of formulation parameters.
6) Cellular uptake and intestinal permeability investigation.
7) Scale-up and industrial manufacture feasibility.
8) Targeting and surface modification of niosomal formulations.
9) Comparison with other non-ionic surfactants.
10) Clinical study of optimized atorvastatin-loaded niosomes.

Declarations

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This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Competing Interests Statement

The authors declare that they have no competing interests related to this work.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contributions

Maksuda Akter Maya and Md. Mahbubol Alam took part in literature review, conceptualization, methodology, investigation, analysis, and manuscript writing, editing and reviewed the manuscript. Mohaiminul Islam, Fahamida Binta Anower and Antu Mozumder analyzed data. Diba Rani Saha and Nowrin Rashid Ratri were involved in the design of the manuscript. All authors have read and approved the final manuscript.

Availability of Data and Materials

Supplementary information is available from the authors upon reasonable request.

Institutional Review Board Statement

Not applicable.

Ethical Approval

Not applicable for this study.

Informed Consent

Not applicable for this study.

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Declaration of Artificial Intelligence

No AI tools were used for this study.

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