Original Article

FUTURE JOURNAL OF PHARMACEUTICALS AND HEALTH SCIENCES

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Screening of important factors using factorial design to predict simvastatin loaded solid lipid nanoparticles

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Article History:

Received on: 13 Nov 2023
Revised on: 18 Jan 2024
Accepted on: 20 Jan 2024

Keywords:

Simvastatin,
Solid Lipid Nanoparticles,
Factorial Design,
Lipid concentration,
Surfactant concentration,
Homogenization speed

Abstract

This study aims to optimize Simvastatin-loaded Solid Lipid Nanoparticles (SLNs) using a 2^k factorial design approach. Simvastatin, a widely used cholesterol-lowering drug, faces bioavailability challenges, prompting the use of nanotechnology for drug delivery. The study focuses on lipid concentration, surfactant concentration, and homogenization speed as critical factors influencing SLN characteristics. These factors were chosen based on their potential impact on SLN physicochemical properties like particle size, polydispersity index, and drug entrapment efficiency. Through systematic variation of factor levels, a matrix of experiments will be created, measuring responses (particle size, polydispersity index, and drug entrapment efficiency) for each run. Statistical analysis, including ANOVA, will assess factor significance and interactions. The study aims to reveal critical parameters affecting Simvastatin-loaded SLN formulation. The optimized formulation targets uniform and stable nanoparticles with enhanced drug entrapment, enhancing Simvastatin bioavailability. The factorial design method offers a systematic, resource-efficient approach for simultaneously screening and optimizing multiple factors, streamlining the experimental process.

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eISSN: 2583-116X
DOI: https://doi.org/10.26452/fjphs.v4i1.581

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INTRODUCTION

Simvastatin, also known as Zocor, is an HMG-CoA reductase inhibitor that lowers lipid levels and thereby lowers the risk of cardiovascular disease [1]. It is derived synthetically from *Aspergillus terreus* and competitively inhibits HMG-CoA Reductase, a crucial enzyme in the synthesis of cholesterol [2].

Statins like Simvastatin are routinely used after cardiac events, particularly for people at risk, due to their demonstrated efficacy and low side effects. Because of the global incidence of cardiovascular

disease, they are a top choice for dyslipidaemia treatment [3].

Simvastatin, like other statins, is critical for lowering cholesterol levels, particularly LDL, and lowering the risk of CVD and mortality [4]. Despite differences in potency, clinical results are only marginally varied. Lipophilic statins, such as Simvastatin, enter cells by diffusion, whereas hydrophilic statins employ transport proteins such as OATP1B1 to reach hepatocytes [5].

Simvastatin is a prodrug that converts into an active metabolite comparable to HMG-CoA, a major enzyme in the manufacture of cholesterol. It competes with HMG-CoA for reductase, lowering liver cholesterol synthesis [6]. This effect increases hepatic LDL absorption while decreasing plasma LDL and VLDL levels. The mechanism of simvastatin maintains required mevalonate levels while also exerting vasculoprotective effects beyond lipid lowering, such as improving endothelial function, stabilizing plaques, and decreasing inflammation [7]. It also binds to 2 integrin, which influences leukocyte trafficking. Peak plasma concentrations occur 1.3 to 2.4 hours after administration. The therapeutic range is 10 to 40 mg/day, with no significant variation from linearity up to 120 mg. Its profile is unaffected by fasting or post-meal administration [8].

METHODOLOGY

Simvastatin was procured from Yarrow Chemicals Pvt. Ltd., stearic acid from S.D. Fine Chem Ltd., Poloxamer from Ozone Chem Ltd., acetonitrile from Merck Ltd., ethanol (imported), Span 80, Disodium hydrogen phosphate, and potassium dihydrogen phosphate.

Quality by Design (QbD)

Quality by Design (QbD) is a popular method for improving nanoparticles that emphasizes the significance of building quality into the product rather than testing it later [9]. DoE, particularly factorial designs, easily analyses the impact of formulation and process parameters on responses, minimizing the need for expensive and time-consuming tests [10]. QbD goals include meeting relevant clinical performance-based product quality criteria, lowering variability and faults, increasing product and process design efficiency, and improving root cause analysis. Identifying critical quality attributes (CQAs), critical material attributes (CMAs), critical process parameters (CPPs), and defining a control strategy are critical factors [11].

Setting clear objectives, selecting relevant process variables and responses, selecting an appropriate experimental design (e.g., factorial or response designs), accurate execution, data evaluation, results analysis using ANOVA, and interpretation for informed decision-making comprise experimental design execution [12].

FTIR

FTIR (Fourier Transform Infrared) spectroscopy is an important technique for obtaining molecular fingerprints of substances by comparing infrared radiation absorption vs wavelength. It is used to detect the component amounts in mixes, to evaluate sample quality and consistency, and to identify unknown components [13].

Statistical Analysis

The experimental design findings were analysed using specialized software, which confirmed the considerable impact of selected independent parameters stearic acid and Poloxamer concentrations, as well as sonication time—on particle size, Zeta potential, and % Entrapment efficiency [14]. There were two levels for each factor, resulting in eight unique SLN formulations using solvent evaporation and micro-emulsification processes, which were optimized using 2^3 factorial designs. The analysis revealed that F-4 was the best formulation [15]. The improved formulation had a particle size of 89.6 nm, a zeta potential of 15.5 mV, and a 45.6% entrapment efficiency.

RESULTS AND DISCUSSION

FTIR of Simvastatin:

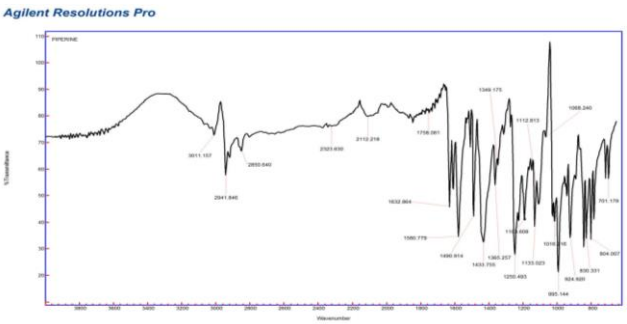

Figure 1 FT-IR Spectrum of Simvastatin

EVALUATION OF SIMVASTATIN LOADED SOLID LIPID NANOPARTICLES

1. Particle Size:

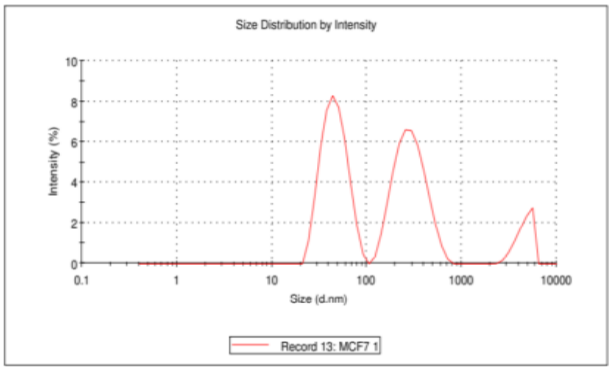

Figure 2 Particle Size determination

The optimized formulation of Simvastatin loaded Solid lipid nanoparticles were analysed for particle size and was found to be 89.6nm. Polydispersity index was found to be 0.677 and the nanoparticles were found to be polydispersity.

2. Zeta Potential:

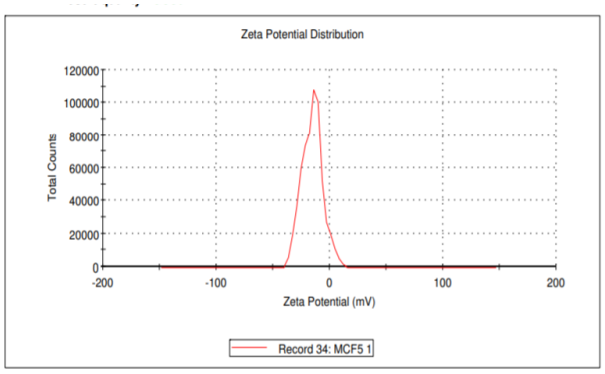

Figure 3 Zeta Potential Determination

3. Entrapment Efficiency (%EE):

Table 1 Drug Entrapment Efficiency (%EE)

Formulation	%EE
F-1	41.62
F-2	33.43
F-3	27.55
F-4	45.65
F-5	26.73
F-6	37.12
F-7	34.54
F-8	27.38

The % Entrapment Efficiency (%EE) of the optimized formulation was found to be 45.65%. The result reveals the drug was successfully entrapped in the nanoparticles and the encapsulated drug loaded into unit weight of the nanoparticles.

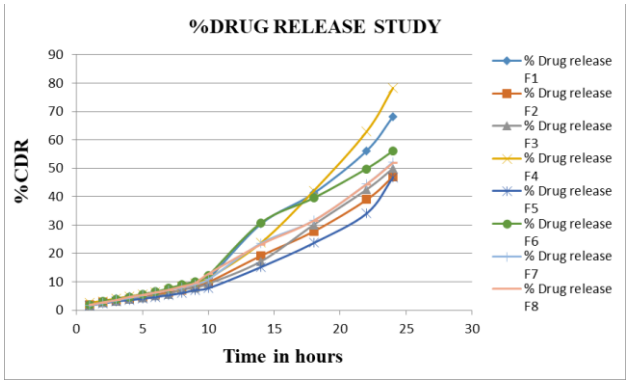

Figure 4 Percentage Drug Release Study

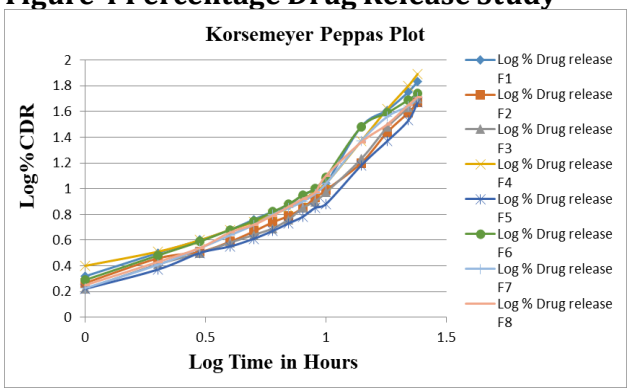

Figure 5 Korsemeyer Peppas Plot

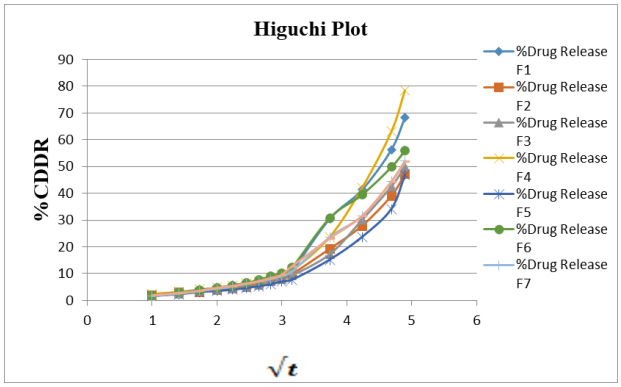

Figure 6 Higuchi Plot

CONCLUSION

Results from the statistical studies indicate the significant impact of all three factors (A, B, C) on Y1 (Particle size). Factor C has a less significant effect on Y2 (Zeta potential), while Factors A and B exhibit significant effects on Y2.

For Y3 (Sonication time), Factors A and C have a less significant impact, whereas Factor B demonstrates a significant effect on Y3.

Table 2 In Vitro Drug Release

Time (hr)	%CDR							
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	2.0	1.8	1.6	2.5	1.6	1.9	1.7	1.8
2	3.1	2.9	2.5	3.2	2.3	3.0	2.6	2.7
3	4.0	3.1	3.2	4.0	3.1	3.9	3.5	3.5
4	4.8	3.9	3.9	4.8	3.5	4.7	4.4	4.6
5	5.7	4.7	4.4	5.5	4.0	5.6	5.3	5.3
6	6.6	5.5	5.0	6.3	4.6	6.5	6.2	6.2
7	7.4	6.2	5.7	7.1	5.3	7.7	7.1	7.2
8	9.0	7.1	7.0	8.2	6.0	9.0	8.0	8.3
9	9.8	8.6	7.9	9.6	7.1	10.1	9.1	9.5
10	11.2	9.8	9.3	11.1	7.7	12.3	10.9	12.7
14	30.0	19.2	17.2	23.7	15.2	30.8	23.6	23.1
18	41.1	27.8	30.1	42.1	23.7	39.5	31.5	31.5
22	56.3	39.0	42.5	63.0	34.1	49.8	44.4	44.3
24	68.1	47.1	49.9	78.4	46.8	56.0	52.1	51.8

Solid lipid nanoparticles containing Simvastatin were created using the micro-emulsification and solvent evaporation procedures. The use of 23 factorial designs aids in the creation of an ideal formulation with the smallest nanometric size and the maximum entrapment efficiency. All three parameters (A, B, and C) have a significant impact on Y1 (Particle size). Factors A and B have a greater impact on Y2 (Zeta potential) than Factor C. Factor B has a significant impact on Y3 (Sonication time), while Factors A, C, and D have a minor impact.

ACKNOWLEDGEMENT

The authors are thankful to the Principal and Management of sri venkateswara college of pharmacy, chittoor for providing the necessary infrastructure and facilities to conduct this research work.

Funding Support: The Author declares that there is no funding.

Conflict of Interest: The Author declares that there is no conflict of interest.

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