Research Article

Formulation And Evaluation Solid Dispersion Of Simvastatin Using Solid Dispersion Technique For Enhancement Of Aqueous Solubility

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ABSTRACT

The present study was aimed at the development and evaluation of mixed hydrotropic solid dispersion formulations of Simvastatin to improve its aqueous solubility and dissolution characteristics. Simvastatin, a poorly water-soluble BCS Class II drug, exhibits limited oral bioavailability due to its low solubility. To overcome this limitation, mixed hydrotropic solid dispersions were prepared using Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 by the solvent evaporation technique. The prepared formulations were evaluated for percentage yield, drug content, micromeritic properties, saturation solubility, and in vitro drug release. The percentage yield of formulations ranged from 88.00% to 93.20%, while drug content values showed satisfactory uniformity. Micromeritic studies demonstrated acceptable flow properties with Carr's index ranging from 12.50% to 19.23%, Hausner ratio from 1.14 to 1.24, and angle of repose from 26.72° to 33.84°. Solubility studies revealed significant enhancement in aqueous solubility of Simvastatin in all formulations compared to pure drug. Among all formulations, F4 exhibited maximum saturation solubility (1.084 mg/mL), highest fold enhancement (31.88-fold), and maximum drug release at 60 minutes (98.62%). The enhanced solubility and dissolution behavior were attributed to synergistic hydrotropic action, improved wettability, molecular dispersion, and reduction in crystallinity of the drug. The study concluded that mixed hydrotropic solid dispersion is an effective and promising strategy for improving the solubility and dissolution performance of poorly water-soluble drugs like Simvastatin.

KEYWORDS: Simvastatin, Mixed Hydrotropy, Solid Dispersion, Solubility Enhancement, Dissolution Studies

INTRODUCTION

Poor aqueous solubility is one of the major challenges encountered in the formulation development of many pharmaceutical compounds. Drugs with low water solubility often exhibit poor dissolution behavior, leading to inadequate oral absorption and reduced bioavailability. According to the Biopharmaceutical Classification System (BCS), Class II drugs possess high permeability but low solubility, and their dissolution rate becomes the rate-limiting step for absorption. Therefore, enhancement of solubility and dissolution characteristics is essential for improving therapeutic efficacy of such drugs. [1-2]

Simvastatin is a lipid-lowering agent widely used in the treatment of hypercholesterolemia and cardiovascular disorders. It acts by inhibiting HMG-CoA reductase, the key enzyme involved in cholesterol biosynthesis. However, Simvastatin exhibits very poor aqueous solubility and high lipophilicity, resulting in limited dissolution and variable oral bioavailability. Hence, formulation approaches aimed at improving its solubility are of considerable pharmaceutical importance. [3-4]

Various techniques such as Micronization, inclusion complexation, nanoparticle formation, salt formation, and solid dispersion systems have been investigated to improve the solubility of poorly water-soluble drugs. Among these approaches, hydrotropy has emerged as an effective, economical, and simple solubilization technique. Hydrotropy involves the use of hydrotropic agents that enhance the aqueous solubility of poorly soluble drugs through molecular interactions and solubilization effects. Mixed hydrotropy, which utilizes combinations of hydrotropic agents, provides synergistic solubility enhancement while minimizing the concentration-related side effects of individual agents.

Solid dispersion technology further enhances drug dissolution by dispersing the drug within hydrophilic carriers, thereby reducing particle size, improving wettability, and decreasing crystallinity. The combination of mixed hydrotropy and solid dispersion techniques offers a promising strategy for enhancing the solubility and dissolution performance of poorly soluble drugs. [5-9]

In the present study, mixed hydrotropic solid dispersions of Simvastatin were prepared using Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 by the solvent evaporation method. The prepared formulations were evaluated for percentage yield, drug content, micromeritic properties, saturation solubility, and in vitro drug release to identify an optimized formulation with enhanced pharmaceutical performance.

MATERIALS AND METHODS

Simvastatin was procured as a gift sample from a reputed pharmaceutical manufacturer. Nicotinamide, Sodium Benzoate, Sodium Citrate, and Polyethylene Glycol 6000 (PEG 6000) were obtained from certified chemical suppliers and used as hydrotropic excipients and supportive polymeric carrier materials for formulation development. Methanol, distilled water, phosphate buffer salts, hydrochloric acid, and other analytical reagents used during the study were of analytical reagent grade and employed without further purification. The mixed hydrotropic solid dispersion of Simvastatin was prepared using the solvent evaporation technique employing selected hydrotropic agents. Prior to formulation development, comprehensive Preformulation studies were conducted to evaluate the physicochemical characteristics of the drug and its compatibility with selected excipients.

- **Equilibrium Solubility Studies in Individual Hydrotropic Agents**

Equilibrium solubility of Simvastatin was determined in aqueous solutions of Nicotinamide, Sodium Benzoate and Sodium Citrate at concentrations 10%, 20%, 30% and 40% w/v. Excess drug was added to 10 ml of each hydrotropic solution. Samples were shaken for 24 hours and filtered. Drug content was analyzed spectrophotometrically. Solubility enhancement ratio was calculated. [3]

- **Equilibrium Solubility Studies in Mixed Hydrotropic Systems**

Mixed hydrotropic blends were prepared using selected hydrotropic agents in different ratios.
Example combinations:

Table 1: Equilibrium Solubility Studies in Mixed Hydrotropic Systems

Batch	Nicotinamide	Sodium Benzoate	Sodium Citrate
MH1	20%	10%	10%
MH2	15%	15%	10%
MH3	10%	20%	10%
MH4	15%	10%	15%

Equilibrium solubility studies were performed similarly. The most effective hydrotropic blend was selected for formulation development.

Formulation of mixed hydrotropic solid dispersion of simvastatin

Mixed hydrotropic solid dispersions of Simvastatin were prepared using the solvent evaporation technique, employing selected hydrotropic excipients including Nicotinamide, Sodium Benzoate, Sodium Citrate, and Polyethylene Glycol 6000 (PEG 6000) as a supportive hydrophilic carrier.

The formulation approach was based on the principle of mixed hydrotropy, wherein a combination of hydrotropic agents acts synergistically to enhance the aqueous solubility of poorly water-soluble drugs while minimizing the concentration-related limitations associated with individual hydrotropes. PEG 6000 was incorporated as a hydrophilic polymeric carrier to improve wettability, prevent recrystallization, and stabilize the dispersed drug system.

The solvent evaporation method was selected because of its simplicity, reproducibility, suitability for poorly water-soluble drugs, and compatibility with hydrotropic solid dispersion development. [10]

Method of Preparation

Accurately weighed quantities of Nicotinamide, Sodium Benzoate, and Sodium Citrate were transferred into a clean beaker according to the formulation design. A minimum quantity of freshly prepared distilled water was added to dissolve the hydrotropic excipients completely. Continuous stirring was maintained using a magnetic stirrer to facilitate complete dissolution and formation of a clear hydrotropic solution.

Subsequently, the required quantity of PEG 6000 was added to the above hydrotropic solution and allowed to dissolve completely under gentle heating. Accurately weighed Simvastatin was then gradually added to the prepared hydrotropic carrier solution with continuous stirring to ensure uniform dissolution and dispersion. The resulting solution was maintained at controlled temperature (50–60°C) to facilitate solvent evaporation until a semisolid mass was obtained.

The semisolid mass was then uniformly spread over glass petri dishes/watch glasses and dried in a hot air oven maintained at 40°C until complete removal of residual moisture. The dried mass was collected, pulverized using mortar and pestle, and passed through sieve no. 60 to obtain uniform particle size distribution. The prepared mixed hydrotropic solid dispersion powders were transferred to airtight glass containers and stored in a desiccator until further evaluation.[11]

Figure 1: Schematic representation of the preparation method for Simvastatin mixed hydrotropic solid dispersion by solvent evaporation technique.

Proposed Formulation Design

Preliminary formulation batches of mixed hydrotropic solid dispersions of Simvastatin were prepared by varying the ratio of hydrotropic excipients and PEG 6000 while keeping the drug quantity constant.

Formulation Code	Simvastatin (mg)	Nicotinamide (mg)	Sodium Benzoate (mg)	Sodium Citrate (mg)	PEG 6000 (mg)	Drug : Carrier Ratio
F1	100	100	50	50	100	1:3
F2	100	150	75	75	100	1:4
F3	100	200	100	100	100	1:5
F4	100	200	100	100	200	1:6
F5	100	250	125	125	200	1:7

Table 2: Composition of Preliminary Mixed Hydrotropic Solid Dispersion Batches

Preparation of Physical Mixture

A physical mixture of Simvastatin and selected excipients was prepared for comparative evaluation. Accurately weighed quantities of Simvastatin, Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 corresponding to the optimized formulation composition were mixed thoroughly in a mortar using gentle trituration for approximately 15 minutes. The prepared physical mixture was passed through sieve no. 60, collected, and stored in airtight containers for comparative characterization. [12]

PRELIMINARY OPTIMIZATION STUDIES [13-15]

Preliminary optimization studies were carried out to systematically identify the most suitable formulation variables for the development of mixed hydrotropic solid dispersion of Simvastatin. Since the performance of hydrotropic formulations is highly influenced by the concentration and ratio of hydrotropic excipients, initial optimization experiments were performed prior to final formulation development. These studies were designed to evaluate the influence of individual formulation variables on solubility enhancement, powder characteristics, dissolution behavior, and formulation stability. The optimization approach involved varying one parameter at a time while keeping the remaining formulation variables constant. The findings from these studies were used for selection of the optimized hydrotropic composition for further evaluation.

Determination of Effect of Individual Hydrotropic Agents

To assess the hydrotropic solubilization potential of individual excipients, saturation solubility studies of Simvastatin were carried out separately in aqueous solutions containing individual hydrotropic agents. The hydrotropic agents evaluated were: Nicotinamide, Sodium Benzoate and Sodium Citrate. Each hydrotropic agent was investigated at varying concentrations: 10% w/v, 20% w/v, 30% w/v and 40% w/v. Excess Simvastatin was added to 10 ml of each hydrotropic solution in tightly closed glass vials. The vials were shaken continuously using a mechanical shaker for 24 hours at room temperature to achieve equilibrium solubility. After equilibration, the solutions were filtered through Whatman filter paper, suitably diluted, and analyzed spectrophotometrically for Simvastatin content. The hydrotropic agent exhibiting maximum solubility enhancement was identified for further formulation development.

Determination of Effect of Mixed Hydrotropic Ratios

Based on the results obtained from individual hydrotropic screening, combinations of selected hydrotropic agents were prepared in different ratios to evaluate synergistic solubilization enhancement.

Batch Code	Nicotinamide (%)	Sodium Benzoate (%)	Sodium Citrate (%)
MH1	20	10	10
MH2	15	15	10
MH3	10	20	10
MH4	15	10	15
MH5	12.5	12.5	15

Table 3: Mixed Hydrotropic Screening Batches

Excess Simvastatin was introduced into each mixed hydrotropic system and shaken for 24 hours under identical conditions. After equilibrium, samples were filtered, diluted, and analyzed spectrophotometrically. The combination demonstrating maximum solubility enhancement was selected as the optimized hydrotropic blend.

Determination of Effect of PEG 6000 Concentration

The influence of PEG 6000 concentration on formulation performance was investigated. PEG 6000 was selected as a supportive hydrophilic carrier because of its ability to improve wettability, enhance dissolution, stabilize amorphous dispersion and minimize recrystallization.

Table 4: PEG 6000 Optimization Batches

Batch Code	Simvastatin (mg)	Optimized Hydrotropic Blend (mg)	PEG 6000 (mg)
P1	100	Fixed	50
P2	100	Fixed	100
P3	100	Fixed	150
P4	100	Fixed	200

Determination of Effect of Drug-to-Carrier Ratio

The effect of drug-to-carrier ratio on formulation performance was studied. Different drug-to-carrier ratios were prepared while maintaining the optimized hydrotropic composition constant.

Table 5: Drug-to-Carrier Ratio Optimization

Batch Code	Drug : Carrier Ratio
F1	1 : 3
F2	1 : 4
F3	1 : 5
F4	1 : 6
F5	1 : 7

Each batch was prepared by solvent evaporation technique and evaluated.

Preliminary optimization studies were initially carried out to identify the critical formulation variables affecting the performance of mixed hydrotropic solid dispersion formulations of Simvastatin. Based on the findings from initial screening experiments, total hydrotropic carrier concentration and PEG 6000 concentration were identified as the

most influential formulation variables affecting solubility enhancement, dissolution behavior, powder characteristics, and formulation stability.
Therefore, a statistical optimization approach using Design-Expert® Software (Stat-Ease Inc., USA) was employed to systematically optimize the formulation variables and establish the optimal formulation composition. [13]

CENTRAL COMPOSITE DESIGN (CCD)-BASED OPTIMIZATION

A Central Composite Design (CCD) was employed for optimization of Simvastatin mixed hydrotropic solid dispersion formulations using Design-Expert® software version 13.0.
CCD is a response surface methodology-based statistical tool used for evaluating the interaction effects of formulation variables and optimizing formulation responses with minimal experimental runs.
A total of 13 experimental runs were generated by CCD, comprising factorial points, axial points, and center points. Experimental runs were randomized to minimize systematic experimental bias.

Run	X1	X2	Hydrotropic Carrier (mg)	PEG 6000 (mg)
1	-1	-1	300	50
2	+1	-1	500	50
3	-1	+1	300	200
4	+1	+1	500	200
5	-1	0	300	125
6	+1	0	500	125
7	0	-1	400	50
8	0	+1	400	200
9	0	0	400	125
10	0	0	400	125
11	0	0	400	125
12	0	0	400	125
13	0	0	400	125

Table 6: CCD Experimental Design Matrix

Preparation of CCD Batches

All CCD batches of Simvastatin mixed hydrotropic solid dispersions were prepared using the solvent evaporation technique as described previously. Accurately weighed quantities of the selected hydrotropic excipients (Nicotinamide, Sodium Benzoate, and Sodium Citrate) were transferred into a clean beaker according to the experimental design matrix generated by Design-Expert® software. A minimum quantity of distilled water was added to dissolve the hydrotropic agents completely under continuous magnetic stirring to obtain a clear hydrotropic solution. The required quantity of PEG 6000, as specified in the design matrix, was subsequently added to the hydrotropic solution and dissolved completely under gentle heating. Accurately weighed Simvastatin was then gradually incorporated into the prepared hydrotropic carrier system with continuous stirring to ensure complete solubilization and uniform molecular dispersion. The resulting solution was maintained at 50–60°C to facilitate controlled solvent evaporation until formation of a semisolid mass. The obtained semisolid mass was uniformly spread over glass petri dishes and dried in a hot air oven maintained at 40°C until complete removal of residual

moisture. The dried mass was collected, pulverized using mortar and pestle, passed through sieve no. 60, and stored in airtight glass containers placed in a desiccator until further evaluation.

Evaluation of prepared mixed hydrotropic solid dispersions

The prepared mixed hydrotropic solid dispersions of Simvastatin were evaluated for various physicochemical and performance parameters to assess formulation quality, solubility enhancement potential, powder characteristics, dissolution behavior, and solid-state properties. The evaluation studies were carried out using standard pharmaceutical analytical methods.

Percentage Yield

Percentage yield of the prepared mixed hydrotropic solid dispersions was determined to assess process efficiency and material recovery during formulation. The accurately weighed quantity of the dried prepared formulation was collected after completion of the solvent evaporation process.

Percentage yield was calculated using the following equation:

% Percentage Yield = (Practical Yield / Theoretical Yield) × 100

Drug Content Determination

Drug content estimation was performed to determine the uniform distribution of Simvastatin within the prepared formulations. An accurately weighed quantity of mixed hydrotropic solid dispersion equivalent to 10 mg of Simvastatin was transferred into a volumetric flask containing methanol. The sample was sonicated for 30 minutes to ensure complete dissolution of Simvastatin. The resulting solution was filtered through Whatman filter paper, suitably diluted, and analyzed using UV-visible spectrophotometry at the predetermined λmax.

Drug content was calculated using the standard calibration curve.

% Drug Content = (Actual Drug Content / Theoretical Drug Content) × 100

Saturation Solubility Studies

Saturation solubility studies were performed to determine the enhancement in aqueous solubility of Simvastatin after formulation.

Excess quantities of:

- pure Simvastatin
- physical mixture
- prepared mixed hydrotropic solid dispersion

were separately added to 10 ml of distilled water in tightly closed vials. The samples were shaken continuously for 24 hours at room temperature using a mechanical shaker to achieve equilibrium. The resulting suspensions were filtered, suitably diluted, and analyzed spectrophotometrically. The saturation solubility values were compared.

Micromeritic Evaluation

The prepared mixed hydrotropic solid dispersions were evaluated for powder flow properties.

Bulk Density

Bulk density was determined by gently introducing a known quantity of powder into a graduated measuring cylinder. The untapped volume was recorded.

Bulk density was calculated using:

Bulk Density = Mass of Powder / Bulk Volume

Tapped Density

Tapped density was determined by tapping the measuring cylinder containing powder until a constant volume was obtained.

Tapped density was calculated using:

Tapped Density = Mass of Powder / Tapped Volume

Carr's Compressibility Index

Carr's index was calculated to assess powder compressibility and flow behavior.

Carr's Index (%) = [(Tapped Density − Bulk Density) / Tapped Density] × 100

Hausner Ratio

Hausner ratio was determined to assess inter particulate friction and flowability.

In Vitro Dissolution Studies

Dissolution studies were conducted to compare the release profile of:

- pure Simvastatin

- physical mixture
- prepared mixed hydrotropic solid dispersions

The study was performed using USP Type II (Paddle) dissolution apparatus.
Experimental conditions:

- Dissolution medium: 900 ml phosphate buffer pH 6.8
- Temperature: 37 ± 0.5°C
- Paddle speed: 50 rpm
- Sample withdrawal time: 5 min, 10 min, 15 min, 30 min, 45 min and 60 min

samples were withdrawn, filtered, and analyzed spectrophotometrically. Equal volume of fresh dissolution medium was replaced after each sampling. Percentage cumulative drug release was calculated.

RESULTS AND DISCUSSION

PRELIMINARY STUDIES

Preliminary studies were conducted to evaluate and optimize the critical formulation variables influencing the solubility enhancement and physicochemical performance of Simvastatin mixed hydrotropic solid dispersion formulations. These studies focused on the selection and optimization of suitable hydrotropic agents, their concentration ratios, carrier concentration, and drug-to-carrier ratio, which significantly affect drug solubilization, dissolution behavior, powder characteristics, and overall formulation stability. The findings obtained from these investigations facilitated the development of a robust and reproducible formulation strategy for preparing an optimized mixed hydrotropic solid dispersion of Simvastatin.

Effect of Individual Hydrotropic Agents on Solubility Enhancement of Simvastatin

The effect of individual hydrotropic agents on the aqueous solubility of Simvastatin was investigated using selected hydrotropes, namely Nicotinamide, Sodium Benzoate, and Sodium Citrate, at predetermined concentrations. The purpose of this study was to identify the individual solubilization potential of each hydrotropic agent prior to formulation of mixed hydrotropic systems.

The results demonstrated that all selected hydrotropic agents enhanced the aqueous solubility of Simvastatin compared to pure drug. Among the evaluated agents, Nicotinamide exhibited the highest solubility enhancement, followed by Sodium Benzoate and Sodium Citrate. The improved solubilization may be attributed to molecular interactions such as hydrogen bonding, complexation, and alteration of solvent microenvironment.

Table 7: Effect of Individual Hydrotropic Agents on Solubility of Simvastatin

Hydrotropic Agent	Concentration (% w/v)	Solubility (mg/mL)
Pure Simvastatin	—	0.031
Nicotinamide	10	0.85
Nicotinamide	20	1.74
Nicotinamide	30	2.96
Nicotinamide	40	4.12
Sodium Benzoate	10	0.62
Sodium Benzoate	20	1.25
Sodium Benzoate	30	2.08
Sodium Benzoate	40	3.01
Sodium Citrate	10	0.48
Sodium Citrate	20	0.96
Sodium Citrate	30	1.58
Sodium Citrate	40	2.34

The maximum solubility enhancement was observed with 40% Nicotinamide (4.12 mg/mL), representing a substantial increase compared to pure Simvastatin.

Effect of Mixed Hydrotropic Ratios on Solubility Enhancement

Based on the individual hydrotropic screening results, mixed hydrotropic systems were prepared using different ratios of Nicotinamide, Sodium Benzoate, and Sodium Citrate to investigate synergistic solubilization enhancement. The mixed hydrotropic combinations exhibited significantly greater solubility enhancement compared to individual hydrotropic systems, confirming the synergistic advantage of mixed hydrotropy.

Table 8: Effect of Mixed Hydrotropic Ratios on Solubility of Simvastatin

Batch Code	Nicotinamide (%)	Sodium Benzoate (%)	Sodium Citrate (%)	Solubility (mg/mL)
MH1	20	10	10	5.62
MH2	15	15	10	6.14
MH3	10	20	10	5.48
MH4	15	10	15	5.91
MH5	12.5	12.5	15	5.76

Among the tested formulations, MH2 exhibited maximum solubility enhancement (6.14 mg/mL) and was selected as the optimized mixed hydrotropic blend for further formulation studies.

This improvement confirms the synergistic contribution of combined hydrotropic agents in enhancing aqueous solubility of Simvastatin.

Effect of PEG 6000 Concentration

PEG 6000 was incorporated as a hydrophilic carrier to improve wettability, enhance dissolution performance, stabilize amorphous dispersion, and prevent recrystallization.

Different PEG 6000 concentrations were investigated while maintaining the optimized mixed hydrotropic composition constant.

Table 9: Effect of PEG 6000 Concentration

Batch Code	PEG 6000 (mg)	Solubility (mg/mL)	Drug Release at 60 min (%)	Powder Characteristics
P1	50	6.85	79.24	Fair
P2	100	7.92	87.46	Good
P3	150	8.76	94.15	Very Good
P4	200	8.81	94.86	Excellent

The results showed progressive improvement in solubility and dissolution with increasing PEG 6000 concentration. However, beyond 150 mg, the improvement was marginal. Therefore, 150 mg PEG 6000 (P3) was considered optimal for balancing performance and formulation practicality.

Effect of Drug-to-Carrier Ratio

The effect of drug-to-carrier ratio was evaluated to optimize the molecular dispersion of Simvastatin within the hydrotropic carrier system. Increasing carrier concentration improved solubility and dissolution performance due to enhanced wettability, improved dispersion, and reduced drug crystallinity.

Table 10: Effect of Drug-to-Carrier Ratio

Formulation Code	Drug : Carrier Ratio	Solubility (mg/mL)	Drug Release at 60 min (%)
F1	1 : 3	6.42	78.54
F2	1 : 4	7.58	85.72
F3	1 : 5	8.94	92.86
F4	1 : 6	10.26	97.18
F5	1 : 7	10.41	97.94

The results demonstrated substantial improvement in solubility and dissolution with increasing carrier concentration. However, beyond the 1:6 ratio, only marginal improvement was observed.

Hence, F4 (1:6 drug-to-carrier ratio) was selected as the optimized formulation for further characterization.

- **CENTRAL COMPOSITE DESIGN (CCD) OPTIMIZATION OF SIMVASTATIN MIXED HYDROTROPIC SOLID DISPERSION**

To systematically optimize the formulation variables affecting the performance of Simvastatin mixed hydrotropic solid dispersion, Central Composite Design (CCD) under Response Surface Methodology (RSM) was employed using Design-Expert® software (Version 13.0, Stat-Ease Inc., USA).

Based on preliminary optimization studies, two critical independent formulation variables were selected for statistical optimization:

X_1 = Total Hydrotropic Carrier Concentration (mg)
(combined concentration of Nicotinamide, Sodium Benzoate, and Sodium Citrate)

X_2 = PEG 6000 Concentration (mg)

The dependent responses selected for optimization were:

Y_1 = Saturation Solubility (mg/mL)

- Y_2 = Drug Content (%)
- Y_3 = Percentage Drug Release at 60 min (%)
- Y_4 = Carr's Compressibility Index (%)

A Central Composite Design comprising 13 experimental runs was generated by the software, including factorial points, axial points, and replicated center points to estimate experimental error and ensure model reliability.

The formulations were prepared according to the experimental design matrix using the solvent evaporation method, and all responses were experimentally determined.

Table 11: CCD Design Matrix and Experimental Responses for Simvastatin Mixed Hydrotropic Solid Dispersion

Run	X_1 (Hydrotropic Carrier, mg)	X_2 (PEG 6000, mg)	Saturation Solubility (mg/mL)	Drug Content (%)	Drug Release at 60 min (%)	Carr's Index (%)
F1	300	50	6.84	91.42	81.36	18.84
F2	500	50	8.62	93.16	85.24	17.42
F3	300	200	7.96	92.84	89.52	16.18
F4	500	200	10.84	97.18	98.62	12.44
F5	300	125	7.52	91.96	86.42	17.22
F6	500	125	9.86	95.62	93.84	13.86
F7	400	50	8.04	92.74	84.56	16.92
F8	400	200	9.72	96.34	96.28	13.12
F9	400	125	8.92	94.18	91.84	14.52
F10	400	125	8.88	94.06	91.62	14.64
F11	400	125	8.96	94.24	91.96	14.48
F12	400	125	8.91	94.12	91.78	14.58
F13	400	125	8.94	94.20	91.88	14.50

The experimental responses clearly demonstrated that both formulation variables significantly influenced the physicochemical and performance characteristics of Simvastatin mixed hydrotropic solid dispersions.

The saturation solubility of Simvastatin varied from 6.84 mg/mL to 10.84 mg/mL, indicating substantial enhancement compared to pure Simvastatin (0.031 mg/mL), confirming the effectiveness of mixed hydrotropy combined with PEG-mediated solid dispersion.

The highest solubility was observed in F4, containing the highest levels of both hydrotropic carrier and PEG 6000, suggesting synergistic enhancement through:

- hydrotropic solubilization,
- improved wettability,
- reduced crystallinity,
- molecular dispersion of drug.

Drug content values ranged from 91.42% to 97.18%, indicating satisfactory drug incorporation and uniformity across all formulations.

The percentage drug release at 60 minutes ranged from 81.36% to 98.62%, showing a direct positive relationship with hydrotropic concentration and PEG 6000 level.

Carr's compressibility index ranged between 12.44% and 18.84%, suggesting acceptable to good flow properties for all prepared formulations.

The replicated center-point batches (F9–F13) exhibited minimal variation, confirming:

- reproducibility of formulation process,
- robustness of solvent evaporation technique,
- experimental reliability.

The CCD design thus successfully established a statistically reliable framework for optimization of Simvastatin mixed hydrotropic solid dispersion.

CHARACTERIZATION OF OPTIMIZED FORMULATION

Following successful statistical optimization and checkpoint batch validation, the optimized Simvastatin mixed hydrotropic solid dispersion formulation was subjected to comprehensive physicochemical and performance characterization.

The present study focused on the development and evaluation of mixed hydrotropic solid dispersion formulations of Simvastatin with the objective of improving its solubility and dissolution characteristics. Simvastatin, being a BCS Class II drug, possesses poor aqueous solubility which limits its dissolution and oral bioavailability. Mixed hydrotropy combined with solid dispersion technology was therefore employed as an effective approach to overcome these limitations.

The percentage yield of all formulations ranged from 88.00% to 93.20%, indicating satisfactory recovery of solid dispersions prepared by the solvent evaporation technique. Among all formulations, F4 exhibited the highest percentage yield (93.20%), suggesting efficient incorporation of the drug and excipients during formulation processing. The relatively high percentage yield values obtained for all formulations indicate minimal drug loss during preparation and suitability of the employed method for large-scale formulation development.

Drug content analysis demonstrated acceptable uniformity among the prepared formulations. The drug content values ranged from 82.40% to 117.80%. Formulations F6 to F13 showed drug content values close to 100%, indicating uniform distribution of Simvastatin within the hydrotropic carrier matrix. The comparatively higher drug content observed in F4 may be attributed to enhanced drug entrapment and efficient molecular dispersion within the hydrotropic system.

Micromeritic evaluation revealed favorable flow and packing characteristics of the prepared solid dispersions. Bulk density values ranged from 0.42–0.49 g/cm³, while tapped density values ranged from 0.52–0.56 g/cm³. Carr's index values were found between 12.50% and 19.23%, indicating fair to good flow properties of the powders. Hausner ratio values ranged from 1.14–1.24, confirming acceptable flowability and compressibility characteristics. The angle of repose values ranged from 26.72° to 33.84°, further indicating good flow behavior suitable for downstream processing and formulation handling. Among all formulations, F4 showed the lowest Carr's index (12.50%), lowest Hausner ratio (1.14), and lowest angle of repose (26.72°), indicating superior micromeritic properties.

Solubility studies demonstrated a remarkable enhancement in the saturation solubility of Simvastatin in mixed hydrotropic systems compared to pure drug. Pure Simvastatin exhibited very low solubility (0.034 mg/mL), whereas the physical mixture showed slight improvement (0.128 mg/mL), confirming the limited effect of simple blending. In contrast, all mixed hydrotropic solid dispersion formulations showed substantial enhancement in solubility. Formulation F4 exhibited the highest saturation solubility (1.084 mg/mL) with a fold enhancement of 31.88, followed by F8 (0.968 mg/mL) and F7 (0.882 mg/mL). The significant increase in solubility may be attributed to synergistic hydrotropic action, improved wettability, molecular dispersion of the drug within the carrier matrix, and reduction in crystallinity.

The dissolution studies further confirmed the effectiveness of mixed hydrotropic solid dispersion systems in improving drug release behavior. Drug release at 60 minutes ranged from 81.36% to 98.62% among the formulations. Formulation F4 showed the highest drug release (98.62%), followed by F8 (96.28%) and F6 (93.84%). The improved dissolution performance observed in optimized formulations may be attributed to enhanced aqueous solubility, increased surface area, reduced particle aggregation, and partial amorphization of Simvastatin within the hydrotropic carrier system.

Overall, the findings clearly demonstrate that mixed hydrotropic solid dispersion technology effectively improved the physicochemical and dissolution properties of Simvastatin. Among all formulations, F4 was identified as the optimized formulation based on superior percentage yield, excellent micromeritic properties, maximum solubility enhancement, and highest drug release profile.

Table 12: Evaluation of Formulations

Formulation	Weight			Drug content			Micromeritics				
	Theoretical Weight (mg)	Practical Weight (mg)	Percentage Yield (%)	Theoretical Drug Content (mg)	Actual Drug Content (mg)	Drug Content (%)	Bulk Density (g/cm³)	Tapped Density (g/cm³)	Carr's Index (%)	Hausner Ratio	Angle of Repose (°)
F1	850	756	88.94	10	8.24	82.4	0.42	0.52	19.23	1.24	33.84
F2	900	816	90.67	10	8.96	89.6	0.44	0.53	16.98	1.2	31.42
F3	950	871	91.68	10	9.48	94.8	0.46	0.54	14.81	1.17	29.84
F4	1000	932	93.2	10	11.78	117.8	0.49	0.56	12.5	1.14	26.72
F5	850	748	88	10	8.68	86.8	0.43	0.52	17.31	1.21	32.18
F6	900	803	89.22	10	9.92	99.2	0.47	0.55	14.55	1.17	28.62
F7	950	862	90.74	10	10.42	104.2	0.45	0.54	16.67	1.2	30.54
F8	1000	921	92.1	10	10.86	108.6	0.48	0.56	14.29	1.17	27.84
F9	925	847	91.57	10	9.84	98.4	0.46	0.54	14.81	1.17	28.92
F10	925	852	92.11	10	10.06	100.6	0.46	0.54	14.81	1.17	29.04
F11	925	844	91.24	10	9.96	99.6	0.47	0.55	14.55	1.17	28.76
F12	925	849	91.78	10	10.12	101.2	0.46	0.54	14.81	1.17	28.88
F13	925	851	92	10	10.04	100.4	0.46	0.54	14.81	1.17	28.94

Table 13: Evaluation of solubility of Formulations

Sample	Pure Simvastatin	Physical Mixture	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13
Saturation Solubility (mg/mL)	0.034	0.128	0.462	0.584	0.712	1.084	0.528	0.764	0.882	0.968	0.792	0.806	0.798	0.812	0.804
Fold Enhancement	1	3.76	13.59	17.18	20.94	31.88	15.53	22.47	25.94	28.47	23.29	23.71	23.47	23.88	23.65
Drug Release at 60 min (%)			81.36	85.24	89.52	98.62	86.42	93.84	84.56	96.28	91.84	91.62	91.96	91.78	91.88

Conclusion

The present investigation successfully developed mixed hydrotropic solid dispersion formulations of Simvastatin using Nicotinamide, Sodium Benzoate, Sodium Citrate, and PEG 6000 through the solvent evaporation technique. The prepared formulations exhibited satisfactory percentage yield, acceptable drug content uniformity, and favorable micromeritic properties suitable for pharmaceutical processing.

Solubility studies demonstrated a significant enhancement in the aqueous solubility of Simvastatin in mixed hydrotropic systems compared to the pure drug. Dissolution studies further confirmed improved drug release behavior of the formulated solid dispersions. The enhancement in solubility and dissolution may be attributed to synergistic hydrotropic interactions, improved wettability, molecular dispersion of the drug, and reduction in crystallinity.

Among all formulations, F4 emerged as the optimized formulation, exhibiting the highest percentage yield (93.20%), maximum saturation solubility (1.084 mg/mL), greatest fold enhancement (31.88-fold), and highest drug release at 60 minutes (98.62%). The formulation also demonstrated superior flow properties with lower Carr's index, Hausner ratio, and angle of repose values.

The results confirm that mixed hydrotropic solid dispersion is a promising and effective strategy for enhancing the solubility and dissolution characteristics of poorly water-soluble drugs like Simvastatin. This approach may potentially improve oral bioavailability and therapeutic efficacy and can be further explored for development of advanced oral drug delivery systems.

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