RESEARCH PAPER

QUALITY-BY-DESIGN DEVELOPMENT OF A MIXED-SOLVENCY-BASED FAST-DISSOLVING SOLID DISPERSION OF TORSEMIDE USING TAGUCHI FACTOR SCREENING AND BOX–BEHNKEN RESPONSE-SURFACE ANALYSIS

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Abstract

Background: Torsemide is a loop diuretic used in the management of edema and hypertension. Its limited aqueous solubility can constrain dissolution and may affect oral drug absorption. Mixed-solvency-based solubilization, combined with systematic formulation optimization, offers a potential strategy for improving the dissolution performance of poorly water-soluble drugs.

Objective: This study aimed to develop and evaluate a mixed-solvency-based fast-dissolving solid dispersion of torsemide using a Quality-by-Design (QbD) framework integrating Taguchi factor screening and Box–Behnken response-surface methodology.

Methods: Sodium caprylate, sodium citrate, sodium acetate, and β-cyclodextrin were investigated as solubilizing agents. Preliminary screening was performed using a Taguchi L9 orthogonal array, with aqueous solubility designated as the larger-the-better response and pH monitored as a complementary formulation attribute. β-Cyclodextrin, sodium caprylate, and sodium acetate were subsequently evaluated using a three-factor Box–Behnken design, while sodium citrate concentration was maintained at 2.5% w/v. Solubility, pH, and solubility enhancement ratio were assessed to characterize formulation performance. Solid dispersions containing torsemide and solubilizers at drug-to-solubilizer ratios of 1:4, 1:6, and 1:8 were prepared and compared with their corresponding physical mixtures in terms of drug content and *in vitro* dissolution.

Results: The reduced solubility model was statistically significant ($p = 0.0186$), with an R^2 of 0.582 and an adjusted R^2 of 0.469, indicating moderate explanatory capacity. Among the tested mixed-solvency compositions, Taguchi screening run 4, containing sodium caprylate (20% w/v), sodium citrate (2.5% w/v), sodium acetate (2.5% w/v), and β-cyclodextrin (5% w/v), exhibited the highest observed solubility of 56.12 mg/mL and a solubility enhancement ratio of 332.07. The 1:4, 1:6, and 1:8 solid dispersions demonstrated drug contents of 98%, 100%, and 105%, respectively, and corresponding 5-min drug releases of 80%, 75%, and 78%. In comparison, the respective physical mixtures released 40%, 45%, and 50% of the drug within 5 min. Thus, the solid dispersions exhibited absolute increases in 5-min drug release of 40, 30, and 28 percentage points, respectively, relative to their corresponding physical mixtures. The 1:4 formulation demonstrated the highest early drug release, reaching 80% within 5 min.

Conclusion: The findings demonstrate the potential of combining mixed-solvency-based solubilization with a structured QbD approach to develop fast-dissolving torsemide solid dispersions. Among the evaluated drug-to-solubilizer ratios, the 1:4 formulation provided the most favorable combination of drug content and early dissolution performance. Further characterization of solid-state properties, dissolution behavior under biorelevant conditions, and formulation stability is warranted to establish the underlying enhancement mechanism and support subsequent pharmaceutical development.

Keywords: Torsemide; mixed-solvency approach; solid dispersion; Quality-by-Design; Taguchi screening; Box–Behnken design; response-surface methodology; aqueous solubility; dissolution enhancement.

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1. Introduction

Poor aqueous solubility is a persistent challenge in oral drug-product development because dissolution can limit drug availability for absorption. Solid-dispersion approaches have been extensively investigated to increase apparent solubility, dissolution rate, and oral exposure of poorly water-soluble drugs [1, 2].

Torsemide (torasemide) is a loop diuretic whose crystalline form and pH-dependent dissolution behavior can influence formulation performance. Multiple crystal forms of torasemide and differences in their dissolution behavior have been reported [3].

Solid dispersions can improve dissolution through increased drug-carrier contact, improved wetting, reduced aggregation, changes in solid-state organization, and more favorable drug release from the carrier matrix. Their performance depends on carrier composition, drug-carrier interactions, manufacturing method, and drug-to-carrier ratio [1, 2].

Solubility enhancement can also be supported by water-soluble excipients with complementary solubilization mechanisms. Cyclodextrins can increase apparent solubility through inclusion complexation, whereas hydrotropic solubilizers can increase aqueous solubility through concentration-dependent solute-solubilizer interactions. In the present work, sodium caprylate, sodium citrate, sodium acetate, and beta-cyclodextrin were evaluated as mixed-solvency components [4].

Quality by Design (QbD) provides a structured framework for pharmaceutical development through definition of product targets, identification of critical quality attributes, risk-based factor selection, and experimental evaluation of influential variables [5].

The present study used a two-stage experimental design strategy. Taguchi L9 experimentation was applied first for factor screening and ranking, an approach used in pharmaceutical formulation development to reduce experimental burden while identifying influential variables. The prioritized factors were then evaluated in a three-factor response-surface stage using the factor levels planned for a Box-Behnken design. The analyzed matrix, however, contained one duplicated edge condition and omitted one canonical Box-Behnken edge condition; therefore, it is described and analyzed here as a custom three-factor response-surface matrix rather than as a canonical Box-Behnken design. Response-surface methodology provides a structured framework for local multivariable investigation [6, 7].

The formulation objective was to develop a fast-dissolving torsemide solid dispersion. At the mixed-solvency stage, the primary response was equilibrium solubility with pH monitored as an additional response. At the solid-dispersion stage, drug content and in vitro release were used for batch selection. The predefined final performance target was not less than 80% drug release at 5 min. Corresponding physical mixtures were used as comparators, and release-profile interpretation was based on established principles for comparative dissolution assessment [8].

The objective of this study was to develop and evaluate a mixed-solvency-based torsemide solid dispersion using Taguchi factor screening, three-factor response-surface analysis, final solid-dispersion preparation, and in vitro comparison with corresponding physical mixtures.

2. Materials and Methods

The experimental design followed a QbD sequence. The quality target product profile defined the intended product as an oral fast-dissolving torsemide solid dispersion prepared using an aqueous mixed-solvency system. The principal quality objectives were enhanced solubility, rapid in vitro release, and drug content close to the theoretical value [5, 9].

Torsemide was selected as the model poorly water-soluble drug. Sodium caprylate, sodium citrate, sodium acetate, and beta-cyclodextrin were evaluated as mixed-solvency excipients [4].

Critical quality attributes were defined before the design stage. Equilibrium solubility in the mixed-solvency system was the primary response at the solution-screening stage, and pH was monitored. Solubility enhancement ratio (SER) was calculated using an aqueous torsemide solubility reference of 0.169 mg/ml. For the final solid-dispersion stage, drug content and in vitro release were the decisive quality attributes. The development-stage target was drug content close to 100% of theoretical value and not less than 80% release at 5 min.

Before response-surface analysis, formulation factors considered were sodium caprylate concentration, sodium citrate concentration, sodium acetate concentration, beta-cyclodextrin concentration, and total solubilizer load. Process factors considered were equilibration time, agitation, filtration, solvent-evaporation temperature, drying temperature, drying time, and particle-size reduction after drying. Process conditions were held constant during the formulation design experiments.

A Taguchi L9 design was used as the initial factor-screening experiment. Four factors were evaluated at three levels each: sodium caprylate at 5, 10 and 15% w/v; sodium citrate at 0, 2.5 and 5% w/v; sodium acetate at 0, 2.5 and 5% w/v; and beta-cyclodextrin at 0, 5 and 10% w/v. Solubility was treated as the larger-the-better response, and for single-observation runs the signal-to-noise ratio simplifies to 20 log10(Y). pH was retained as a monitored response rather than a response to be maximized.

Taguchi factor ranking was determined from the mean S/N ratio at each factor level. Delta S/N was calculated as the difference between the largest and smallest mean

S/N value for each factor. For screening prioritization, each factor delta was normalized by the sum of all deltas. The resulting normalized delta share was used as a screening metric and not as an ANOVA variance contribution [6].

Based on the Taguchi ranking, beta-cyclodextrin, sodium caprylate, and sodium acetate were selected for the response-surface stage, while sodium citrate was fixed at 2.5% w/v. The three factors were sodium caprylate at 10, 15, and 20% w/v; sodium acetate at 0, 2.5, and 5% w/v; and beta-cyclodextrin at 5, 10, and 15% w/v. Sodium citrate remained fixed at 2.5% w/v throughout this stage. The analyzed 15-run matrix used these intended Box-Behnken factor levels but included a replicate of the A = 0, B = +1, C = -1 edge condition (runs 1 and 15) and did not include the canonical A = +1, B = +1, C = 0 edge condition. Accordingly, the dataset was treated as a custom three-factor response-surface matrix [11, 12].

For each mixed-solvency run, the required quantities of solubilizers were dissolved in the aqueous vehicle, excess torsemide was added, and the system was equilibrated under the same conditions for all runs. After equilibration, samples were filtered and diluted as required before UV spectrophotometric estimation. Equilibrium solubility was recorded in mg/ml. The pH of each solution was recorded. Solubility enhancement ratio was calculated from solubility divided by 0.169 mg/ml.

The three-factor data were analyzed using response-surface methodology. For solubility, a full quadratic model including main effects, two-factor interactions, and squared terms was evaluated. Model selection considered R2, adjusted R2, overall model p value, residual behavior, and interpretability. Because the full quadratic model showed poor statistical support, a reduced linear model was retained for local interpretation. pH was retained as a monitored response and was summarized descriptively rather than used for inferential model selection.

Model diagnostic and response-surface plots were generated from the experimental responses and fitted equations. These included predicted-versus-actual, residuals-versus-predicted, normal-probability, perturbation, contour, and three-dimensional response-surface plots [12].

After the response-surface stage, solid dispersions were prepared by the solvent-evaporation method at drug-to-total-solubilizer ratios of 1:4, 1:6, and 1:8. The selected solubilizer composition was used as the basis of the carrier system. Physical mixtures containing the same drug-to-solubilizer ratios were prepared by direct mixing. The physical mixtures served as comparators for the solid-dispersion formulations.

Drug content was determined spectrophotometrically for each solid dispersion and corresponding physical mixture and was expressed as percentage of theoretical drug content.

In vitro release testing was performed for the three solid dispersions and their matching physical mixtures using Apparatus II (paddle), a pH 6.8 dissolution medium, and a rotation speed of 50 rpm. The selected time points were 1, 3, 5, 10, 15, 30 and 60 min. The primary endpoint for final batch selection was percentage drug released at 5 min. The target criterion was not less than 80% release at 5 min. The physical-mixture comparison criterion was a minimum 30% relative reduction in 5-min release versus the paired solid dispersion [15].

Statistical calculations were performed using the experimental design matrix and measured responses. Solid-dispersion ratios were compared descriptively using drug content, 5-min release, the complete release profile, and release improvement over the paired physical mixture. The selected batch was the formulation meeting the 5-min target with acceptable drug content and a release advantage over its physical-mixture comparator [14].

2.1 QTPP and CQA framework

Table 1. Quality target product profile for the torsemide solid-dispersion project.

Element	Target	Rationale
Product concept	Fast-dissolving torsemide solid dispersion	Improved dissolution for poorly soluble drug
Route	Oral	Consistent with torsemide use
Primary formulation attribute	Enhanced mixed-solvency solubility	Supports dispersion preparation
Final performance target	NLT 80% release at 5 min	Fast-dissolving profile
Assay target	Approximately 100% of theoretical	Development-stage dose-content consistency
Comparator	Corresponding physical mixture	Distinguishes dispersion effect from blending

Experimental design	Taguchi followed by three-factor RSM	Factor screening followed by local response-surface analysis

Table 2. Critical quality attributes and response roles.

Attribute	Role	Criticality	Reason
Equilibrium solubility	Primary mixed-solvency response	High	Direct measure of solubilization
pH	Monitored response/constraint	Medium	Monitored formulation response
SER	Derived response	Medium	Normalizes solubility to aqueous baseline
Drug content	Final formulation CQA	High	Assay/dose-content indicator
5-min release	Final performance CQA	High	Primary fast-dissolution endpoint
Physical-mixture comparison	Discriminatory performance test	Medium	Demonstrates process-related release gain

2.2 Taguchi factor-screening design

Table 3. Taguchi L9 experimental responses and derived metrics.

Run	CP %	SC %	SA %	βCD %	Solubility mg/ml	pH	SER	S/N dB
1	5	0	0	0	2	7	11.834	6.021
2	5	2.5	2.5	5	18	7.2	106.509	25.105
3	5	5	5	10	16.8	7.4	99.408	24.506
4	10	0	2.5	10	23.21	7.4	137.337	27.314
5	10	2.5	5	0	12.23	7	72.367	21.749
6	10	5	0	5	14	7	82.84	22.923
7	15	0	5	5	16	7.4	94.675	24.082
8	15	2.5	0	10	25	7.2	147.929	27.959
9	15	5	2.5	0	21.23	7.3	125.621	26.539

Table 4. Taguchi factor ranking based on larger-the-better solubility S/N ratio; normalized delta share is a screening metric, not an ANOVA variance contribution.

Rank	Factor	Delta	Normalized delta share (%)	Best level
1	βCD	8.49	28.986	10
2	CP	7.649	26.116	15
3	SA	7.352	25.101	2.5
4	SC	5.799	19.798	2.5

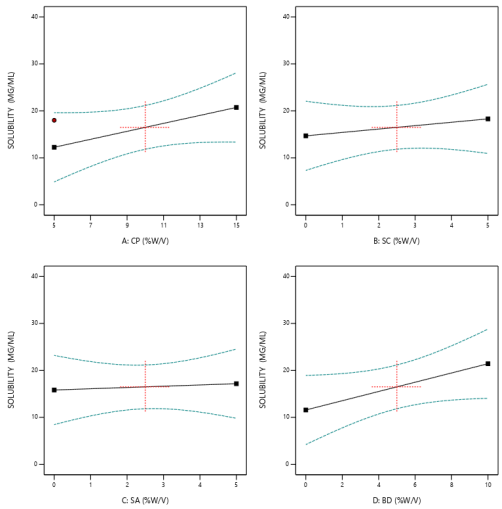


Figure 1. Taguchi main-effects plot for solubility.

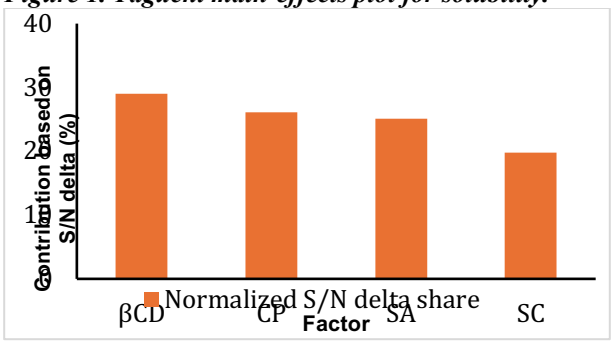


Figure 2. Taguchi S/N delta share used for factor-screening prioritization.

2.3 Three-factor response-surface design

Table 5. Three-factor response-surface design and measured responses.

Run	CP (%w/v)	SA (%w/v)	βCD (%w/v)	CP (%w/v)	SC fixed (%w/v)	SA (%w/v)	βCD (%w/v)	Solubility (mg/mL)	pH	SER
1	0	1	-1	15	2.5	5	5	42.82	7.3	253.373
2	0	1	1	15	2.5	5	15	37.38	7	221.183
3	0	0	0	15	2.5	2.5	10	4.49	7.2	26.568
4	1	0	-1	20	2.5	2.5	5	56.12	7.3	332.071
5	0	0	0	15	2.5	2.5	10	52.191	7	308.822
6	1	-1	0	20	2.5	0	10	49.82	7	294.793
7	0	-1	-1	15	2.5	0	5	44.59	7	263.846
8	1	0	1	20	2.5	2.5	15	32.42	7.2	191.834
9	-1	0	1	10	2.5	2.5	15	9.572	7.4	56.639
10	-1	1	0	10	2.5	5	10	10.07	7.1	59.586
11	-1	-1	0	10	2.5	0	10	10.12	7.2	59.882
12	0	-1	1	15	2.5	0	15	28.35	7.4	167.751
13	0	0	0	15	2.5	2.5	10	26.75	7.3	158.284

14	-1	0	-1	10	2.5	2.5	5	29.77	7.1	176.154
15	0	1	-1	15	2.5	5	5	34.1	7.2	201.775

Table 6. Summary of solubility response-surface model selection.

Model	Model type	R2	Adjusted R2	Model p value	Decision
Selected reduced model	Linear	0.582	0.469	0.0186	Retained for local interpretation and visualization
Full quadratic diagnostic	Quadratic	0.655	0.034	0.504	Not retained because of poor overall statistical support

3. Results

The Taguchi screening stage ranked beta-cyclodextrin, sodium caprylate, sodium acetate, and sodium citrate in descending order of normalized S/N delta share. The best Taguchi level combination was CP 15%, SC 2.5%, SA 2.5%, and beta-cyclodextrin 10%. This combination was used as a factor-screening result rather than as the final formulation.

Sodium citrate showed the lowest normalized delta share and was therefore fixed at 2.5% w/v for the subsequent response-surface stage.

Response-surface-stage solubility values ranged from 4.49 to 56.12 mg/ml. The highest observed solubility was obtained in run 4, corresponding to CP 20% w/v, SC 2.5% w/v, SA 2.5% w/v, and beta-cyclodextrin 5% w/v. This run produced an SER of 332.07. The measured pH values ranged from 7.0 to 7.4 and were treated as monitored observations rather than as a basis for formulation optimization.

The selected reduced model for solubility was: Solubility = 31.788 + 15.798A - 0.032B - 7.547C, where A is sodium caprylate, B is sodium acetate, and C is beta-cyclodextrin in coded units. The model gave R2 = 0.582, adjusted R2 = 0.469, F = 5.11, and p = 0.0186. The positive coefficient for A indicates that increasing sodium caprylate from 10% to 20% increased solubility within the studied experimental region. The negative coefficient for C indicates that the higher beta-cyclodextrin level did not further improve solubility within the analyzed response-surface region under the fixed sodium citrate condition.

The full quadratic model was not retained because it showed poor overall statistical support (R2 = 0.655, adjusted R2 = 0.034, p = 0.504). The reduced linear model was used for local interpretation of the measured response trend.

Predicted-versus-actual and residual plots showed deviations between measured and fitted responses, and the center-region solubility values showed substantial dispersion. Accordingly, the response-surface model was interpreted cautiously and final batch selection was based on observed formulation performance.

At the final dosage-form stage, the three solid dispersions showed drug contents of 98%, 100% and 105% for the 1:4, 1:6 and 1:8 ratios. The corresponding physical mixtures showed drug contents of 99%, 98% and 100%. These assay values indicate that differences in release cannot be attributed simply to underloading of the physical mixtures. The comparison is therefore based primarily on release performance.

The *in vitro* release profiles showed a clear release advantage for solid dispersions over paired physical mixtures at the 5-min primary endpoint. SD-1 at 1:4 released 80% at 5 min, compared with 40% for PM-1. SD-2 at 1:6 released 75% at 5 min, compared with 45% for PM-2. SD-3 at 1:8 released 78% at 5 min, compared with 50% for PM-3. The relative reductions for physical mixtures were 50.0%, 40.0%, and 35.9%, respectively; all three ratios satisfied the predefined criterion of at least 30% lower 5-min release for the physical mixture relative to the paired solid dispersion.

Only the 1:4 solid dispersion met the predefined NLT 80% release target at 5 min. The 1:6 and 1:8 solid dispersions showed useful improvement over corresponding physical mixtures but did not reach the primary 5-min release criterion. Therefore, the final selected batch was the 1:4 solid dispersion, supported by 98% drug content and a 50% relative reduction in 5-min release for its physical mixture comparator.

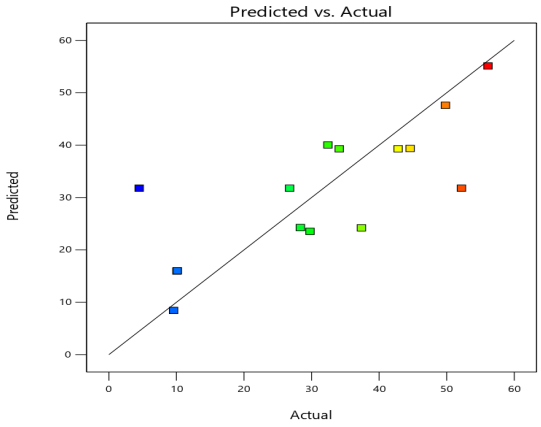


Figure 3. Predicted versus actual solubility for the selected response-surface model.

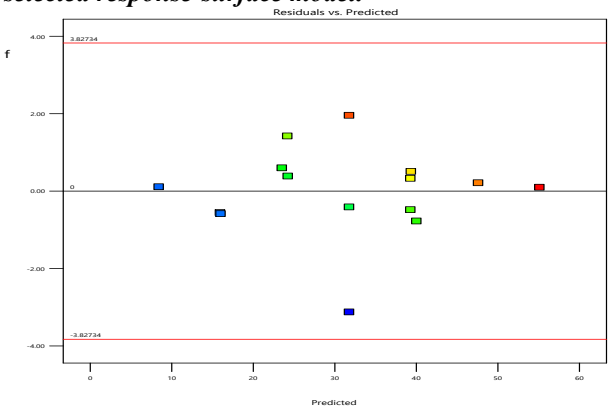


Figure 4. Residuals versus predicted solubility.

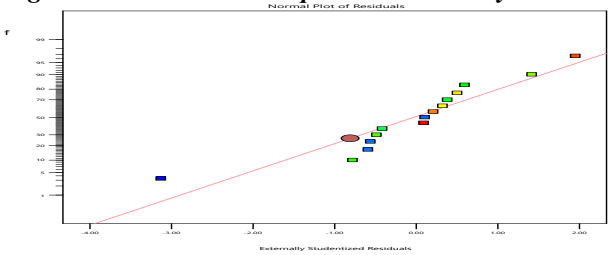


Figure 5. Normal probability plot of residuals.

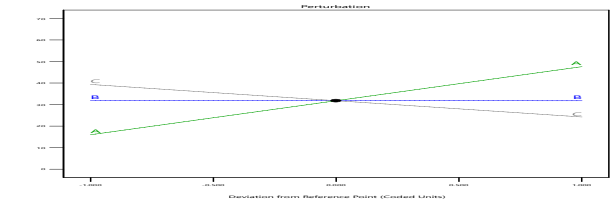


Figure 6. Perturbation plot around the response-surface reference point.

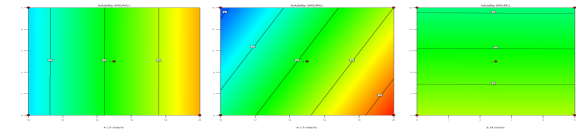


Figure 7. Contour plots for pairwise formulation effects based on the selected model.

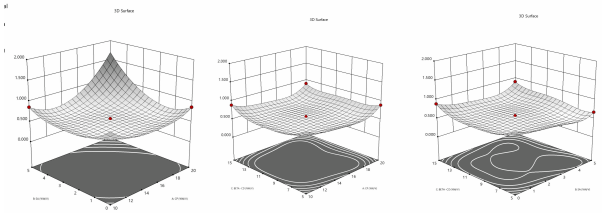


Figure 8. Three-dimensional response-surface plots based on the selected model.

3.1 *In-vitro* release and final batch selection

Table 7. In-vitro release profiles of solid dispersions and physical mixtures.

Batch	Type	Ratio	Drug content (%)	1 min	3 min	5 min	10 min	15 min	30 min	60 min
SD-1	Solid dispersion	1:4	98	30	50	80	85	90	92	98
PM-1	Physical mixture	1:4	99	10	15	40	50	60	70	80
SD-2	Solid dispersion	1:6	100	25	60	75	80	89	94	97
PM-2	Physical mixture	1:6	98	5	20	45	58	67	73	75
SD-3	Solid dispersion	1:8	105	30	68	78	86	92	96	99
PM-3	Physical mixture	1:8	100	10	20	50	55	59	70	80

Table 8. Five-minute release comparison and relative reduction of physical mixtures.

Ratio	SD assay (%)	SD 5-min release (%)	PM assay (%)	PM 5-min release (%)	Gap (points)	Relative reduction (%)
1:4	98	80	99	40	40	50
1:6	100	75	98	45	30	40
1:8	105	78	100	50	28	35.9

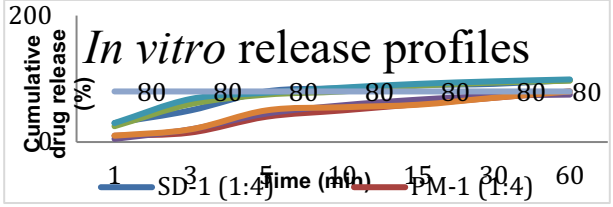


Figure 9. In-vitro release profiles for solid dispersions and physical mixtures.

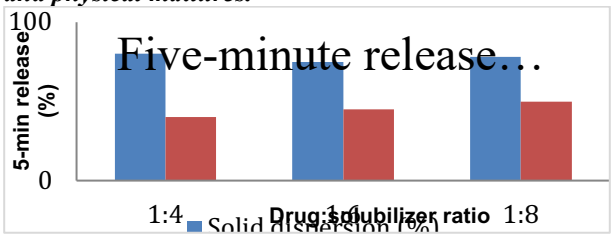


Figure 10. Five-minute release comparison against the NLT 80% target.

4. Discussion

The sequential QbD workflow linked product targets and critical quality attributes with factor screening, local response-surface analysis, and final in vitro release testing. The formulation-design stages focused on the composition of the mixed-solvency system while process conditions were held constant.

Taguchi screening ranked beta-cyclodextrin, sodium caprylate, sodium acetate, and sodium citrate in descending order of normalized S/N delta share. Sodium citrate had the lowest screening contribution and was fixed at 2.5% w/v in the subsequent response-surface stage. The use of Taguchi screening for prioritizing pharmaceutical formulation variables is consistent with prior formulation applications of orthogonal-array design.

Within the studied response-surface region, sodium caprylate showed the largest positive coefficient for solubility, whereas beta-cyclodextrin showed a negative local coefficient in the reduced linear model. These effects are restricted to the tested factor ranges and the fixed sodium citrate level.

The full quadratic model was not retained because its adjusted R2 (0.034) and overall model p value (0.504) indicated poor statistical support. The reduced linear model was statistically significant ($p = 0.0186$) but had moderate explanatory power ($R2 = 0.582$; adjusted $R2 = 0.469$). Therefore, interpretation was based on the observed response trend and measured candidate performance, consistent with cautious use of response-surface methodology when higher-order terms are not adequately supported.

The solid dispersions showed higher 5-min release than their corresponding physical mixtures at all three drug-to-solubilizer ratios, while drug-content values were of similar magnitude. At 1:4, release was 80% for the solid dispersion and 40% for the physical mixture; the corresponding values were 75% versus 45% at 1:6 and 78% versus 50% at 1:8. These results demonstrate a release advantage of the solid-dispersion preparation over simple physical mixing under the tested conditions. Such dissolution enhancement is consistent with established solid-dispersion mechanisms involving improved wetting, drug-carrier contact, and altered drug release behavior.

The final selection of the 1:4 solid dispersion followed the predefined 5-min release endpoint. The 1:6 and 1:8 solid dispersions improved release relative to their physical mixtures but did not meet the NLT 80% 5-min target. The 1:4 batch achieved 80% release at 5 min and had 98% drug content, and it showed the largest relative release difference from its paired physical mixture.

The 1:8 solid dispersion showed a measured drug content of 105%; this value is reported without adjustment.

Using relative reduction in 5-min release, the physical mixtures were 50.0%, 40.0%, and 35.9% lower than their paired solid dispersions at ratios of 1:4, 1:6, and 1:8, respectively. Thus, all three pairs met the predefined 30% relative-reduction comparison criterion, while only the 1:4 solid dispersion met the 80% 5-min release target. Interpretation of the complete time-course remains important because dissolution-profile comparison is more informative than reliance on a single time point alone.

Overall, the experimental sequence identified run 4 as the highest-solubility response-surface candidate and the 1:4 drug-to-solubilizer ratio as the best-performing tested solid-dispersion batch. The conclusion is restricted to the experimental space and in vitro endpoints evaluated in this study.

The reduced response-surface model had moderate explanatory power, and the center-region solubility responses were dispersed. In addition, the selected 1:4 solid dispersion met the 5-min release criterion exactly at 80%. These observations support cautious interpretation of model-predicted behavior beyond the measured runs.

5. Conclusion

Torsemide mixed-solvency solid dispersions were developed using a sequential QbD workflow comprising

Taguchi L9 factor screening and a three-factor response-surface stage. Beta-cyclodextrin, sodium caprylate, and sodium acetate were carried forward, while sodium citrate was fixed at 2.5% w/v. The reduced solubility model identified sodium caprylate as the dominant positive factor within the studied region. The highest observed solubility was 56.12 mg/ml in run 4, corresponding to an enhancement ratio of 332.07.

Final solid dispersions were prepared at drug-to-solubilizer ratios of 1:4, 1:6, and 1:8 and compared with corresponding physical mixtures. The 1:4 solid dispersion showed 98% drug content and 80% release at 5 min. The physical mixture at the same ratio released 40% at 5 min, corresponding to a 50% relative reduction. The 1:6 and 1:8 solid dispersions improved release relative to their physical mixtures but did not meet the NLT 80% 5-min target.

The 1:4 torsemide solid dispersion was selected as the final batch because it combined 98% drug content with 80% release at 5 min and showed the largest relative 5-min release advantage over its physical-mixture comparator.

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