# QUALITY-BY-DESIGN DEVELOPMENT OF ORAL DISINTEGRATING TABLETS LOADED WITH EDOXABAN TOSYLATE MONOHYDRATE MESOPOROUS SILICA NANOPARTICLES FOR ENHANCED SOLUBILITY AND DISSOLUTION

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**Abstract**

Edoxaban Tosylate Monohydrate (ETM), a BCS Class IV drug, suffers from both poor aqueous solubility and limited intestinal permeability, and together these properties restrict its dissolution and oral bioavailability. To address this limitation, the current work developed a Quality-by-Design (QbD)-based oral delivery system in which ETM-loaded mesoporous silica nanoparticles (MSNs) were incorporated into oral disintegrating tablets (ODTs) to improve dissolution performance. ETM-loaded MSNs were synthesized using a surfactant-templated sol-gel technique followed by solvent-assisted drug loading, and sixteen nanoparticle formulations were screened before the optimized MSN formulation was selected and incorporated into ODTs prepared by direct compression. Early formulation studies identified polyvinylpyrrolidone K-30 (PVP K-30) and Kollidon® CL-SF as the critical material attributes, and a $3^2$ full factorial design was applied to optimize their concentrations. The resulting optimized formulation displayed satisfactory physicochemical characteristics, including high drug loading, enhanced saturation solubility, and excellent drug–excipient compatibility. Tablets prepared from this formulation possessed acceptable mechanical strength, uniform drug content (99.20 ± 0.51%), rapid wetting (15.44 ± 0.67 s), and a short *In vitro* disintegration time (19.19 ± 0.21 s). Dissolution testing showed rapid drug release, reaching 39.12 ± 0.57% within 3 mins. and 99.29 ± 0.52% within 30 min. The quadratic models fitted to the data were statistically significant ($p < 0.05$) with strong predictive capability, and checkpoint validation produced prediction errors within ±5%, supporting the robustness of the model. Release kinetics pointed to a diffusion-controlled mechanism, in which rapid tablet disintegration was followed by sustained diffusion of ETM from the mesoporous silica network. Across six months of stability testing under ICH storage conditions, the optimized formulation retained its physicochemical characteristics and dissolution performance. This combination of mesoporous silica nanotechnology and a QbD-optimized oral disintegrating tablet platform substantially improved the dissolution behavior of ETM, pointing to a promising strategy for enhancing the oral delivery of poorly water-soluble anticoagulant drugs.

***Keywords:*** Edoxaban Tosylate Monohydrate; Mesoporous silica nanoparticles; Oral disintegrating tablets.

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## INTRODUCTION

Thromboembolic disorders—deep vein thrombosis (DVT), pulmonary embolism (PE), and ischemic stroke—remain leading causes of global morbidity and mortality, driven by pathological intravascular thrombus formation that obstructs blood flow and triggers life-threatening cardiovascular events. Factor Xa plays a pivotal role in coagulation by catalyzing prothrombin-to-thrombin conversion, making it a key anticoagulant target. Direct oral anticoagulants (DOACs), particularly selective Factor Xa inhibitors, have transformed thromboembolic management, offering more predictable pharmacokinetics, fewer food and drug interactions, and no requirement for routine coagulation monitoring compared to conventional vitamin K antagonists.[1] Edoxaban Tosylate Monohydrate (ETM), a potent, selective, and reversible direct Factor Xa inhibitor, is approved for venous thromboembolism treatment and stroke prevention in non-valvular atrial fibrillation. However, its clinical utility is limited by BCS Class IV classification—poor aqueous solubility coupled with low intestinal permeability. Its pH-dependent solubility further declines under intestinal conditions, reducing oral bioavailability and contributing to variable therapeutic performance. Addressing these challenges requires formulation strategies specifically targeting improved dissolution characteristics.[2] Mesoporous silica nanoparticles (MSNs) are promising inorganic nanocarriers for improving the dissolution of poorly water-soluble drugs owing to their high surface area, tunable pore structure, large pore volume, and excellent biocompatibility. Drug confinement within the porous silica matrix minimizes crystallinity, enhances wettability, and promotes molecular dispersion, thereby increasing apparent solubility and dissolution. Incorporation of MSNs into oral disintegrating tablets (ODTs) further enables rapid drug release and improved patient compliance, particularly in elderly and dysphagic patients requiring long-term anticoagulant therapy.[3] Although MSNs and ODTs have individually shown significant potential for enhancing oral drug delivery, their integration, particularly ETM-loaded MSNs incorporated into ODTs, remains largely unexplored within a Quality-by-Design (QbD) framework.[4,5] Therefore, ETM-loaded MSNs were developed, optimized, and incorporated into ODTs, followed by comprehensive physicochemical characterization and evaluation of tablet quality attributes and *In vitro* dissolution performance to establish an improved oral drug delivery system.

## MATERIALS AND METHODS

### Materials

Cetyltrimethylammonium bromide (CTAB), Tetraethyl Orthosilicate (TEOS), and Triethanolamine (TEA) served as the raw materials for synthesis of MSNs, while Polyvinylpyrrolidone K-30 (PVP K-30) and Kollidon® CL-SF functioned as the binder and superdisintegrant, respectively, in the formulation of ODTs. D-Mannitol was incorporated as a diluent, Sodium Lauryl Sulfate (SLS) as a wetting agent, and Aspartame as a sweetener, with Talc and Magnesium Stearate employed as glidant and lubricant, respectively. Methanol, Ethanol, Hydrochloric Acid, Sodium Hydroxide, Phosphate Buffer salts, and all other chemicals and solvents used in the study were of analytical grade and were procured from reputed commercial suppliers; deionized water was used throughout the experimental work.

### Preformulation Studies

Preformulation studies were undertaken to establish the physicochemical and analytical characteristics of ETM in advance of formulation development. These investigations encompassed organoleptic evaluation, melting point determination, UV spectrophotometric method development, calibration curve construction, saturation solubility assessment, and FTIR spectroscopy. Together, the resulting data established the identity, purity, and analytical quantification of ETM, alongside its solubility characteristics and drug–excipient compatibility, thereby providing the foundation for the subsequent development of ETM-loaded MSNs and ODTs.

### Organoleptic Evaluation

The organoleptic characteristics of ETM, colour, appearance, odour, and physical nature, were assessed by visual inspection to confirm the identity and physical properties of the received drug sample prior to formulation development.

### Melting Point Determination

The melting point of ETM was determined using the capillary tube method to verify its identity and purity, and the experimentally observed melting range was compared against reported literature values to confirm the authenticity of the drug prior to formulation studies.[6]

### UV Spectrophotometric Method Development and Calibration Curve

A UV-Visible spectrophotometric method was developed for the quantitative estimation of ETM during preformulation and formulation studies. Standard stock solutions of ETM were prepared separately in distilled water, methanol, 0.1 N hydrochloric acid, and phosphate buffer (pH 6.8), and each solution was scanned on a double-beam UV-visible spectrophotometer to determine the wavelength of maximum absorbance ($\lambda_{max}$). Calibration curves were then constructed over an appropriate concentration range in each medium by plotting absorbance against drug concentration, followed by linear regression analysis. This validated analytical method was subsequently applied for drug content estimation, saturation

solubility studies, and dissolution analysis throughout the investigation.[7,8]

**Fourier-Transform Infrared Spectroscopy**

FTIR spectroscopy was performed to investigate possible molecular interactions between ETM and the silica matrix following drug loading. Spectra of pure ETM, blank MSNs, and ETM-loaded MSNs were recorded on a Bruker Alpha II ATR-FTIR spectrophotometer, and the characteristic absorption bands were compared to evaluate the preservation of functional groups and assess drug–carrier compatibility.[9]

**Preparation of ETM-Loaded MSNs**

MSNs were synthesized by a surfactant-templated sol-gel method to develop a nanoparticulate carrier capable of enhancing the dissolution characteristics of ETM. CTAB functioned as the structure-directing surfactant, TEOS served as the silica precursor, and TEA acted as the catalyst, facilitating hydrolysis and condensation of TEOS under alkaline conditions.

CTAB was first dissolved in purified water under continuous magnetic stirring until a clear solution was obtained. TEA was then added to establish the desired alkaline environment, followed by the dropwise addition of TEOS under continuous stirring. The reaction mixture was maintained under controlled conditions to allow complete hydrolysis and polycondensation, giving rise to silica nanoparticles that formed around the surfactant micelles. The synthesized nanoparticles were recovered by centrifugation, washed repeatedly with purified water and ethanol to remove residual reactants, and dried under controlled conditions.

To identify the most suitable carrier system for ETM incorporation, sixteen nanoparticle formulations (ESM1–ESM16) were prepared by systematically varying the concentrations of the critical formulation components, while the remaining process parameters were held constant.. This preliminary formulation screening was intended to identify an MSN formulation exhibiting optimum physicochemical characteristics for subsequent drug loading and ODT development.[11,12]

**Drug Loading into MSNs**

ETM was incorporated into the synthesized MSNs by a solvent-assisted adsorption technique. An accurately weighed quantity of ETM was first dissolved in methanol to obtain a clear drug solution, into which the optimized blank MSNs were dispersed under continuous magnetic stirring, allowing drug molecules to diffuse into the interconnected mesoporous channels through adsorption. The dispersion was stirred continuously for a predetermined duration to maximize drug incorporation.

Once loading was complete, the organic solvent was removed under controlled conditions, and the ETM-loaded MSNs were separated by centrifugation, washed to eliminate any surface-associated drug, and dried at room temperature. The dried nanoparticles were stored in a desiccator pending further physicochemical characterization and formulation studies.[13]

**Evaluation of ETM-Loaded MSNs**

The prepared ETM-loaded MSN formulations (ESM1–ESM16) were systematically evaluated to determine their physicochemical properties and to identify the formulation most suitable for ODT development. This evaluation encompassed determination of particle size, polydispersity index (PDI), zeta potential, practical yield, drug loading, entrapment efficiency, and saturation solubility, together with characterization by Fourier-transform infrared (FTIR) spectroscopy, and scanning electron microscopy (SEM).

**Particle Size, Polydispersity Index and Zeta Potential**

The mean particle size, PDI, and zeta potential of the prepared MSN formulations were determined by dynamic light scattering (DLS). Prior to analysis, the nanoparticle dispersions were appropriately diluted with deionized water to minimize multiple scattering effects, and measurements were performed in triplicate at ambient temperature, with the mean values recorded. Particle size and PDI served to characterize the size distribution and homogeneity of the nanoparticles, while zeta potential was measured to assess their colloidal stability.[14,15]

**Practical Yield, Drug Loading and Entrapment Efficiency**

The practical yield of each MSN formulation was determined by comparing the experimentally recovered nanoparticle weight against the theoretical weight of the formulation components. Drug loading and entrapment efficiency were determined indirectly using the validated UV spectrophotometric method following separation of the free drug by centrifugation, and the resulting values served as important criteria for selecting the optimized MSN formulation.[16,17]

**Saturation Solubility**

The saturation solubility of Pure ETM and ETM-loaded MSN formulations was determined by the shake-flask method and compared with that of pure ETM. An excess quantity of each formulation was dispersed in the selected dissolution media and equilibrated under constant agitation at 37 ± 0.5 °C. Following equilibration, the samples were centrifuged, filtered through a 0.45 µm membrane filter, suitably diluted, and analysed spectrophotometrically by the validated analytical method.[10]

**Selection of the Optimized ETM-Loaded MSN Formulation**

The prepared ETM-loaded MSN formulations (ESM1–ESM16) were comparatively evaluated on the basis of their physicochemical characteristics, including particle size, polydispersity index, zeta potential, practical yield, drug loading, entrapment efficiency, saturation solubility, and solid-state characterization by FTIR, and SEM analyses. Selection of the optimized formulation took into account the collective performance of all evaluated quality attributes rather than any single response in isolation. Among the developed formulations, ESM11 demonstrated the most desirable combination of physicochemical properties, exhibiting an optimum particle size with narrow size distribution, adequate surface charge, high drug loading and entrapment efficiency, improved saturation solubility, and satisfactory solid-state characteristics. On the strength of this overall performance, ESM11 was selected as the optimized ETM-loaded MSN formulation and was carried forward for the development of ODT and further QbD optimization studies.

**Preliminary Development of ETM-Loaded ODTs**

The optimized ETM-loaded MSN formulation (ESM11) was selected for the development of ODTs. Prior to systematic optimization using QbD approach, preliminary formulation studies were conducted to identify the critical formulation variables governing the quality and performance of the developed tablets. These preliminary investigations guided the selection of suitable excipients and established the basis for subsequent experimental optimization. A series of six trial formulations (EST1–EST6) were prepared by the direct compression method using the optimized ETM-loaded MSN formulation. Their composition was designed to probe the influence of different binders and superdisintegrants on tablet characteristics, while the remaining formulation components were held constant. Powder blends were prepared by accurately weighing and sieving all ingredients through an appropriate mesh sieve, followed by geometric mixing to obtain a homogeneous blend, with talc and magnesium stearate incorporated during the final stage of blending to improve flowability and lubrication prior to compression. The prepared powder blends were compressed on a tablet compression machine equipped with 6 mm flat-faced punches to produce tablets of uniform weight. The trial formulations were then evaluated for pre-compression characteristics—angle of repose, bulk density, tapped density, Carr's compressibility index, and Hausner's ratio—followed by post-compression evaluation comprising weight variation, tablet thickness, hardness, friability, wetting time, *In vitro* disintegration time, drug content, and *In vitro* drug release.[18,19]

**QbD Optimization of ETM-Loaded ODTs by $3^2$ Factorial Design**

Comparative evaluation of the trial formulations revealed that the concentration of PVP K-30, employed as the binder, and that of Kollidon® CL-SF, used as the superdisintegrant, exerted the greatest influence on the critical quality attributes of the developed ODTs. These two formulation variables were accordingly identified as the critical material attributes (CMAs) and selected as the independent variables for subsequent optimization using a $3^2$ full factorial Quality-by-Design experimental design, while ETM-loaded MSN content and other components remained fixed. Four critical quality attributes were evaluated: wetting time ($Y_1$), disintegration time ($Y_2$), and *In vitro* cumulative drug release at 3 mins. ($Y_3$) and *In vitro* cumulative drug release at 30 mins. ($Y_4$). Response surface methodology generated polynomial models relating variables to responses, validated through ANOVA, $R^2$, adjusted/predicted $R^2$, adequate precision, coefficient of variation, and lack-of-fit testing, supported by 3D and contour plots. Desirability-based numerical optimization identified the optimum formulation, which was prepared and experimentally validated against predicted responses.[20,21]

**Precompression Paramaters**

Prior to tablet compression, the powder blends of all factorial formulations (ESMT1–ESMT9) were evaluated to assess their flow and compression characteristics using standard pharmacopeial procedures to establish the suitability of the powder blends for direct compression.

**Bulk Density and Tapped Density:** Bulk density was determined by gently transferring a known quantity of powder blend into a graduated measuring cylinder and recording the initial volume occupied. The cylinder was then mechanically tapped until a constant volume was achieved, from which the tapped density was determined. Bulk density and tapped density were calculated using the following equations:[22]

$$\textbf{Bulk Density} = \frac{\textbf{Bulk weight of powder}}{\textbf{Tapped volume}}$$

$$\textbf{Tapped Density} = \frac{\textbf{Tapped weight of powder}}{\textbf{Tapped volume}}$$

**Carr's Compressibility Index and Hausner's Ratio:** The compressibility characteristics of the powder blends were assessed by calculating Carr's compressibility index and Hausner's ratio using the experimentally determined bulk density and tapped density values. These parameters were employed to evaluate the flowability and compressibility of the powder blends prior to compression.[23]

$$\text{Carr's Index (\%)} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

**Angle of Repose:** The angle of repose was determined using the fixed funnel method. The powder blend was allowed to flow freely through a funnel onto a flat surface to form a conical heap. The height and radius of the powder cone were measured, and the angle of repose was calculated using the following equation: $\tan\theta = \frac{h}{r}$, where **θ** represents the angle of repose, **h** is the height of the powder cone, and **r** is the radius of its base.[24]

**Post compression**

**Evaluation of ETM-Loaded ODTs**

The factorial formulations (ESMT1–ESMT9) were evaluated for their post-compression characteristics to establish their mechanical integrity, uniformity, disintegration performance, and drug release behavior. This evaluation included weight variation, tablet thickness, hardness, friability, wetting time, water absorption ratio, *In vitro* disintegration time, drug content uniformity, and *In vitro* drug release, with all tests performed according to the procedures described in the Indian Pharmacopoeia (IP) and other standard pharmacopeial guidelines.

**Thickness:** Tablet thickness was measured using a digital Vernier caliper on three randomly selected tablets from each formulation, with the average value recorded.[25]

**Weight variation**: The % deviation of each individual tablet weight from the average was then determined, and the formulation was considered to comply with the pharmacopeial limit provided not more than two tablets deviated from the average weight by more than the permissible % ± 10 for tablets weighing 80 mg or less, ± 7.5 for tablets weighing more than 80 mg but less than 250 mg, and ±5% for tablets weighing 250 mg or more—and no tablet deviated by more than twice this permissible percentage.[26]

**Hardness and Friability**: Hardness was determined using a Monsanto hardness tester and expressed as kg/cm², while friability was evaluated using a Roche friabilator by subjecting a pre-weighed sample of tablets to 100 revolutions at 25 rpm. The tablets were then dedusted and reweighed, and percentage friability was calculated using the following equation:

$$\text{Friability (\%)} = \frac{W_1 - W_2}{W_1} \times 100$$

where $W_1$ is the initial tablet weight and $W_2$ is the final tablet weight after the friability test.[27]

**Wetting Time and Water Absorption Ratio:** The wetting time of the prepared tablets was determined using a folded tissue paper method, in which a twice-folded piece of tissue paper was placed in a Petri dish containing a measured volume of distilled water, and a tablet was carefully placed on the wetted surface. The time required for complete wetting of the tablet was recorded as the wetting time.[28]

Following complete wetting, the tablet was carefully removed and reweighed to determine the amount of water absorbed, and the water absorption ratio was calculated using the following

$$R = \frac{W_a - W_b}{W_b} \times 100$$

where **R** represents the **Water Absorption Ratio**, $W_a$ is the weight of the wetted tablet, and $W_b$ is the weight of the tablet before wetting.

***In vitro* Disintegration Time:** The *In vitro* disintegration time of the tablets was determined using the USP disintegration test apparatus, with distilled water maintained at 37 ± 0.5 °C serving as the disintegration medium. One tablet was placed in each tube of the basket assembly, and the time required for complete disintegration without leaving any palpable mass was recorded, with the average disintegration time calculated from sextuplicate determinations.[29]

**Drug Content Uniformity:** Drug content uniformity was determined by randomly selecting tablets from each formulation, accurately weighing them, and reducing them to a fine powder. A quantity equivalent to the required amount of ETM was transferred into a suitable volumetric flask containing phosphate buffer (pH 6.8), and the solution was sonicated to ensure complete extraction of the drug, filtered through a 0.45 µm membrane filter, appropriately diluted, and analyzed by the validated UV spectrophotometric method at the predetermined wavelength. The percentage drug content was then calculated from the corresponding calibration curve.[30]

***In vitro* Drug Release Study:** The *In vitro* dissolution study of ETM-loaded ODTs was performed using the USP Type II (paddle) dissolution apparatus. The study was carried out in 900 mL of phosphate buffer (pH 6.8) maintained at 37 ± 0.5 °C, with the paddle rotated at 50 rpm. At predetermined time intervals, aliquots of the dissolution medium were withdrawn and immediately replaced with an equal volume of fresh medium maintained at the same temperature to preserve sink conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter, suitably diluted where necessary, and analyzed by the validated UV spectrophotometric method. The cumulative percentage drug release was calculated and plotted as a function of time, with all dissolution studies performed in triplicate and results expressed as mean ± standard deviation.[31]

**Drug Release Kinetics:** To elucidate the mechanism of drug release from the optimized

ETM-loaded ODTs, the dissolution data were fitted to various mathematical kinetic models, including the zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models. The regression coefficient ($R^2$) obtained for each model served to identify the kinetic model that best described the release behavior of ETM. For the Korsmeyer–Peppas model, the release exponent (n) was additionally employed to characterize the underlying release mechanism. The release behavior of the optimized formulation was interpreted on the basis of the model yielding the highest correlation coefficient, together with its corresponding release exponent.[32]

**Stability Study:** The optimized ETM-loaded ODTs formulation was subjected to accelerated stability testing in accordance with the International Council for Harmonisation (ICH) guideline Q1A(R2). The tablets were packed in suitable containers and stored under accelerated conditions of 40 ± 2 °C and 75 ± 5% relative humidity for a period of three months, with samples withdrawn at predetermined intervals and evaluated for physical appearance, drug content, *In vitro* disintegration time, and cumulative drug release. The results obtained at each interval were compared with the initial values to assess the stability of the optimized formulation during storage.[33]

**Statistical Analysis:** All experimental studies were performed in triplicate unless otherwise stated, and the results are presented as mean ± standard deviation (SD). Statistical analysis of the factorial design data was carried out, with the significance of the developed polynomial models evaluated by ANOVA; a p-value < 0.05 was considered statistically significant. Response surface methodology, contour plots, three-dimensional surface plots, desirability function analysis, and checkpoint validation were employed to identify and validate the optimized formulation.

## RESULT AND DISCUSSION

### Evaluation of ETM loaded MSN

Particle size ranged from 200.1 to 467.4 nm, with ESM2 exhibiting the smallest particles (200.1 nm), while ESM7 (467.4 nm) and ESM16 (451.3 nm) produced comparatively larger nanoparticles that may compromise dissolution and oral acceptability. The polydispersity index (PDI) varied between 0.198 and 0.498, indicating differences in particle size uniformity. Although ESM14 showed the lowest PDI (0.198), its large particle size (437.8 nm) limited its practical advantage. Zeta potential values ranged from −24.6 to −37.1 mV, with most formulations exceeding the ±30 mV threshold required for colloidal stability. Entrapment efficiency (%EE), drug loading (%DL), and practical yield varied from 54.38–80.94%, 6.71–17.25%, and 52.75–82.04%, respectively, reflecting differences in drug incorporation and process efficiency among the developed batches. Based on the collective evaluation of all physicochemical parameters, ESM11 was identified as the optimized formulation, exhibiting a particle size of 207.6 nm, PDI of 0.263, zeta potential of −37.1 mV, entrapment efficiency of 80.94%, drug loading of 17.25%, and a practical yield of 72.28%. The optimized batch achieved an ideal balance between nanoscale particle size, narrow size distribution, and high surface charge, ensuring excellent colloidal stability while minimizing aggregation. Simultaneously, its superior entrapment efficiency and drug loading confirmed efficient utilization of the mesoporous architecture for ETM incorporation without compromising manufacturing recovery. This combination of favorable micromeritic characteristics, electrokinetic stability, and encapsulation performance established ESM11 as the most suitable formulation for further development into ETM MSN loaded ODT.

**Evaluation of Trial Formulations:** To identify the critical formulation variables affecting the performance of ETM-loaded ODTs, six preliminary trial formulations were prepared and evaluated for their pre-compression and post-compression characteristics. These investigations were intended to establish a suitable formulation platform prior to systematic optimization using the QbD approach.

**Pre-compression Evaluation:** The powder blends of all trial formulations exhibited satisfactory flow and compressibility characteristics, indicating their suitability for direct compression. Bulk density ranged from 0.758 ± 0.0023 to 0.832 ± 0.0042 g/mL, while tapped density varied between 0.923 ± 0.0034 and 1.000 ± 0.0040 g/mL, reflecting minimal variation among the prepared blends. The calculated Carr's compressibility index and Hausner's ratio likewise indicated acceptable compressibility and flow behaviour, suggesting that incorporation of the ETM-loaded MSNs did not adversely affect the processing characteristics of the powder blends. The angle of repose for all formulations was below 30°, confirming good flowability suitable for direct compression. Adequate powder flow is essential for obtaining tablets with uniform weight and consistent drug distribution during compression, and the favorable pre-compression characteristics observed in the present study may be attributed to the combined effect of the directly compressible excipients and the relatively uniform particle characteristics of the optimized ETM-loaded MSN formulation. Comparable flow properties have been reported for mesoporous silica-based tablet formulations prepared by direct compression, where incorporation of silica nanoparticles did not compromise powder handling characteristics but instead contributed to improved blend homogeneity.

**Post-compression Evaluation:** All trial formulations produced tablets with satisfactory

physical integrity and pharmacopeial quality attributes. The average tablet weight remained close to the target weight of 120 mg, demonstrating excellent die filling and blend uniformity during compression, while tablet thickness showed minimal variation (3.20–3.33 mm), confirming uniform compression throughout the formulation batches.

Tablet hardness ranged from 3.47 ± 0.15 to 4.23 ± 0.25 kg/cm², providing sufficient mechanical strength while preserving the rapid disintegration characteristics expected of ODTs . Friability values likewise remained below the pharmacopeial limit of 1%, indicating adequate resistance to mechanical stress during handling, packaging, and transportation. Drug content varied between 98.60 ± 0.18% and 99.67 ± 0.16%, reflecting excellent content uniformity and confirming homogeneous distribution of ETM-loaded MSNs within the tablet matrix.

Across the evaluated formulations, wetting time and *In vitro* disintegration time decreased progressively, accompanied by a corresponding rise in water absorption ratio. Wetting time fell from 38.88 ± 0.45 s for the initial formulation to 25.66 ± 0.93 s for the final trial formulation, while disintegration time decreased from 40.32 ± 0.25 s to 27.89 ± 0.64 s. The water absorption ratio, conversely, increased from 65.83 ± 5.20% to 91.61 ± 1.61%, indicating enhanced penetration of the dissolution medium into the tablet matrix.

These findings suggest that increasing the concentration of the selected superdisintegrant facilitated rapid water uptake, leading to faster tablet swelling and disintegration, while optimization of the binder concentration maintained sufficient tablet hardness without compromising rapid disintegration. The inverse relationship between wetting time and water absorption ratio clearly demonstrates that efficient water penetration accelerated tablet disintegration, a characteristic essential for orally disintegrating dosage forms intended to provide rapid drug release following administration.

Taken together, the comparative evaluation of the six trial formulations demonstrated that binder concentration and superdisintegrant level were the principal formulation variables governing tablet performance. PVP K-30 and Kollidon® CL-SF were therefore identified as the critical material attributes (CMAs) and selected as the independent formulation variables for subsequent optimization using a 3² full factorial QbD experimental design.

***In vitro* Cumulative Drug Release:** All formulations exhibited a progressive increase in drug release with time, although marked differences emerged during the initial stages of dissolution. Among the evaluated formulations, EST4 demonstrated the highest initial drug release (46.08 ± 0.52% at 3 min), whereas EST1 showed the slowest release (19.56 ± 0.20%), indicating that the formulation variables exerted a significant influence on the early dissolution behaviour of the developed ODTs. The enhanced drug release observed in EST4, EST5, and EST6 can be attributed to rapid tablet wetting and disintegration, which facilitated faster exposure of the ETM-loaded MSNs to the dissolution medium. Incorporation of ETM within the mesoporous silica matrix is, in addition, expected to improve drug wettability and dispersion, thereby promoting dissolution of the poorly water-soluble drug—an improvement consistent with reports of similar dissolution enhancement in mesoporous silica-based drug delivery systems owing to their high surface area and porous architecture. At the conclusion of the dissolution study, EST6 exhibited the highest cumulative drug release (99.75 ± 1.44%), followed by EST5 (99.29 ± 1.31%), while EST1 showed comparatively lower drug release (96.53 ± 0.67%). On the basis of the overall tablet characteristics and dissolution performance, PVP K-30 and Kollidon® CL-SF were identified as the critical formulation variables and selected for subsequent optimization using a 3² full factorial QbD approach.

**Quality-by-Design Optimization of ETM-Loaded ODTs**

To achieve a robust formulation with the desired quality attributes, QbD approach employing a 3² full factorial design was adopted. Guided by the findings of the preliminary formulation studies, PVP K-30 ($X_1$) and Kollidon® CL-SF ($X_2$) were selected as the critical material attributes on account of their pronounced influence on tablet hardness, wetting behaviour, disintegration time, and drug release. Nine factorial formulations (ESMT1–ESMT9) were prepared and systematically evaluated to establish the relationship between the formulation variables and the critical quality attributes (CQAs), with the experimental responses further analyzed by response surface methodology to identify the optimized formulation.

**Pre-compression Parameters:** The pre-compression properties of the powder blends (ESMT1–ESMT9) are presented in Table 1.

**Table 1: Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of repose data**

| Batch | Bulk density (gm/ml ± SD) (n=3) | Tapped density (gm/ml ± SD) (n=3) | Carr's index (%± SD) (n=3) | Hausner's Ratio (± SD) (n=3) | Angle of repose (°θ ± SD) (n=3) |
|---|---|---|---|---|---|
| ESMT1 | 0.526 ± 0.000 | 0.533 ± 0.000 | 1.259 ± | 1.013 ± 0.0013 | 29.475 ± |

| Batch | Bulk density (gm/ml ± SD) (n=3) | Tapped density (gm/ml ± SD) (n=3) | Carr's index (%± SD) (n=3) | Hausner's Ratio (± SD) (n=3) | Angle of repose (°θ ± SD) (n=3) |
|---|---|---|---|---|---|
| | 6 | 2 | 0.1239 | | 0.6995 |
| **ESMT2** | 0.529 ± 0.0006 | 0.537 ± 0.0055 | 1.447 ± 0.8879 | 1.015 ± 0.0091 | 29.129 ± 0.5818 |
| **ESMT3** | 0.551 ± 0.0007 | 0.556 ± 0.0002 | 0.857 ± 0.1304 | 1.009 ± 0.0013 | 27.963 ± 0.8806 |
| **ESMT4** | 0.530 ± 0.0006 | 0.549 ± 0.0037 | 3.370 ± 0.5338 | 1.035 ± 0.0057 | 29.215 ± 0.3134 |
| **ESMT5** | 0.530 ± 0.0006 | 0.554 ± 0.0038 | 4.192 ± 0.7742 | 1.044 ± 0.0085 | 27.115 ± 0.4829 |
| **ESMT6** | 0.532 ± 0.0007 | 0.552 ± 0.0002 | 3.729 ± 0.0919 | 1.039 ± 0.0010 | 27.593 ± 0.9334 |
| **ESMT7** | 0.529 ± 0.0013 | 0.553 ± 0.0037 | 4.289 ± 0.4417 | 1.045 ± 0.0048 | 28.188 ± 0.6456 |
| **ESMT8** | 0.532 ± 0.0013 | 0.555 ± 0.0019 | 4.022 ± 0.5632 | 1.042 ± 0.0061 | 28.573 ± 0.5440 |
| **ESMT9** | 0.534 ± 0.0013 | 0.554 ± 0.0002 | 3.681 ± 0.2400 | 1.038 ± 0.0026 | 28.353 ± 0.3656 |

Bulk density and tapped density ranged from 0.526 ± 0.0006 to 0.551 ± 0.0007 g/mL and from 0.533 ± 0.0002 to 0.556 ± 0.0002 g/mL, respectively, indicating minimal variation among the factorial formulations. The calculated Carr's compressibility index (0.857–4.289%) and Hausner's ratio (1.009–1.045) likewise fell within acceptable limits, demonstrating excellent compressibility and flow characteristics of the powder blends. The angle of repose varied between 27.12 ± 0.48° and 29.48 ± 0.70°, confirming good flowability suitable for direct compression. These satisfactory pre-compression properties may be attributed to the balanced composition of the directly compressible excipients together with the favorable flow characteristics of the optimized ETM-loaded MSNs; the resulting flow behaviour ensured uniform die filling during compression, thereby minimizing weight variation and contributing to tablets of consistent quality. Comparable observations have been reported for directly compressed mesoporous silica-based tablet formulations, where appropriate excipient selection contributed to improved powder flow and compression performance. Taken together, the pre-compression evaluation confirmed that all factorial powder blends possessed suitable flow and compressibility characteristics for direct compression, enabling subsequent evaluation of the post-compression properties of the developed ETM-loaded ODTs.

**Post-compression Properties**

The post-compression characteristics of the factorial formulations (ESMT1–ESMT9) are presented in Table 2.

**Table 2: Weight variation, Thickness, Hardness, Friability and Drug content data**

| Batch | Weight Variation (mg ± SD) (n=20) | Thickness (mm ± SD) (n=3) | Hardness (kg/cm² ± SD) (n=3) | Friability (%) (n=3) |
|---|---|---|---|---|
| **ESMT1** | 119.70 ± 1.59 | 3.17 ± 0.06 | 3.57 ± 0.03 | 0.43 ± 0.02 |
| **ESMT2** | 118.60 ± 1.19 | 2.90 ± 0.00 | 3.20 ± 0.20 | 0.56 ± 0.05 |
| **ESMT3** | 119.75 ± 1.29 | 2.73 ± 0.12 | 3.06 ± 0.12 | 0.71 ± 0.04 |
| **ESMT4** | 120.45 ± 1.15 | 2.97 ± 0.06 | 3.92 ± 0.14 | 0.40 ± 0.12 |
| **ESMT5** | 119.60 ± 1.35 | 2.90 ± 0.10 | 3.47 ± 0.12 | 0.47 ± 0.02 |
| **ESMT6** | 119.95 ± 1.10 | 3.03 ± 0.15 | 3.35 ± 0.17 | 0.60 ± 0.10 |
| **ESMT7** | 119.60 ± 1.60 | 3.17 ± 0.12 | 3.72 ± 0.13 | 0.33 ± 0.04 |
| **ESMT8** | 120.05 ± 1.00 | 3.07 ± 0.15 | 3.40 ± 0.01 | 0.51 ± 0.05 |

| | | | | |
|---|---|---|---|---|
| **ESMT9** | 120.10 ± 1.41 | 2.83 ± 0.06 | 3.12 ± 0.10 | 0.64 ± 0.02 |

All formulations produced tablets with satisfactory physical integrity and complied with the pharmacopeial requirements for ODTs. Average tablet weight ranged from 118.60 ± 1.19 to 120.45 ± 1.15 mg, indicating uniform die filling and consistent powder flow during compression. Tablet thickness varied between 2.73 ± 0.12 and 3.17 ± 0.12 mm, reflecting minimal dimensional variation among the factorial batches; the observed differences may be attributed to variations in compression behaviour arising from the different concentrations of PVP K-30 and Kollidon® CL-SF. Nevertheless, thickness remained sufficiently uniform, suggesting reproducible compression characteristics. Tablet hardness ranged from 3.06 ± 0.12 to 3.92 ± 0.14 kg/cm², providing adequate mechanical strength while preserving the rapid disintegration characteristics required for ODTs. Friability values, in turn, varied from 0.33 ± 0.04 to 0.71 ± 0.04%, remaining well below the pharmacopeial acceptance limit of 1% and indicating that all formulations possessed sufficient mechanical resistance to withstand handling, packaging, and transportation without compromising tablet integrity. These results collectively confirmed that the factorial formulations exhibited acceptable physical characteristics and mechanical strength, supporting their subsequent evaluation for performance-related attributes, including wetting time, water absorption ratio, *In vitro* disintegration time, drug content uniformity, and *In vitro* cumulative drug release.

**Tablet Performance Characteristics:** The tablet performance characteristics of the factorial formulations (ESMT1–ESMT9), including drug content, wetting time, *In vitro* disintegration time, and water absorption ratio, are presented in Table 3.

**Table 3: % Drug Content, Wetting time, *In vitro* disintegration time and Water absorption ratio data**

| Batch | % Drug Content (% ± SD) (n=3) | Wetting Time (sec. ± SD) (n=3) | *In vitro* Disintegration time (sec. ± SD) (n=6) | Water Absorption Ratio (%± SD) (n=3) |
|---|---|---|---|---|
| **ESMT1** | 99.12 ± 0.70 | 32.29 ± 0.60 | 35.29 ± 0.53 | 58.66 ± 0.57 |
| **ESMT2** | 99.70 ± 0.29 | 22.38 ± 0.49 | 25.31 ± 0.58 | 68.53 ± 0.66 |
| **ESMT3** | 99.20 ± 0.51 | 15.44 ± 0.67 | 19.19 ± 0.21 | 72.10 ± 0.56 |
| **ESMT4** | 99.43 ± 0.20 | 38.24 ± 0.46 | 41.39 ± 0.62 | 53.52 ± 0.66 |
| **ESMT5** | 97.44 ± 0.55 | 30.26 ± 0.36 | 32.84 ± 0.65 | 60.33 ± 0.57 |
| **ESMT6** | 99.18 ± 0.60 | 24.93 ± 0.49 | 27.78 ± 0.83 | 64.54 ± 0.60 |
| **ESMT7** | 98.37 ± 0.72 | 35.95 ± 0.60 | 38.51 ± 0.90 | 55.34 ± 0.87 |
| **ESMT8** | 98.14 ± 0.95 | 27.68 ± 0.49 | 30.90 ± 0.41 | 62.60 ± 0.85 |
| **ESMT9** | 98.26 ± 0.26 | 20.56 ± 0.81 | 23.64 ± 0.82 | 70.22 ± 0.95 |

All formulations exhibited satisfactory drug content ranging from 97.44 ± 0.55% to 99.70 ± 0.29%, indicating uniform distribution of ETM-loaded MSNs within the tablet matrix and confirming the reproducibility of the direct compression process. Marked differences were observed in wetting time, water absorption ratio, and disintegration time among the factorial formulations, reflecting the significant influence of the formulation variables on tablet performance. Wetting time ranged from 15.44 ± 0.67 to 38.24 ± 0.46 s, while *In vitro* disintegration time varied between 19.19 ± 0.21 and 41.39 ± 0.62 s. Among the investigated formulations, ESMT3 exhibited the shortest wetting and disintegration times, whereas ESMT4 showed the slowest tablet disintegration—differences attributable to variations in the concentrations of PVP K-30 and Kollidon® CL-SF, which govern tablet porosity, water penetration, and structural integrity. The water absorption ratio ranged from 53.52 ± 0.66 to 72.10 ± 0.56%, demonstrating a clear relationship with disintegration behaviour: formulations exhibiting greater water uptake disintegrated more rapidly, owing to enhanced penetration of the dissolution medium into the tablet matrix, which promoted faster swelling of the superdisintegrant and subsequent tablet break-up. Comparable behaviour has been reported for ODTs containing crospovidone-based superdisintegrants, where rapid water uptake is a key determinant of disintegration performance. These findings collectively point to satisfactory tablet performance across the factorial formulations, confirming the suitability of the selected formulation variables for subsequent QbD optimization.

***In vitro* Cumulative Drug Release:** The *In vitro* dissolution profiles of the factorial formulations (ESMT1–ESMT9) are presented in figure 1. All formulations exhibited a rapid and progressive increase in drug release throughout the dissolution

study, although appreciable differences were observed during the initial release period, indicating a significant influence of formulation variables on the dissolution behaviour of ETM-loaded ODTs.

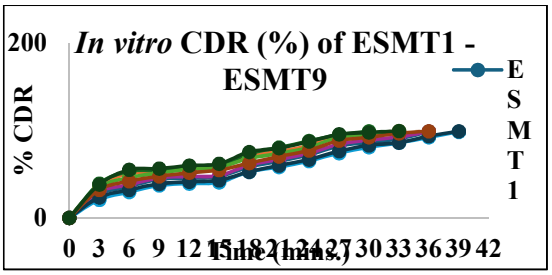


**Figure 1: *In vitro* Cumulative Drug Release profile of batches ESMT1 to ESMT9**

Among the factorial batches, ESMT3 demonstrated the highest dissolution performance, releasing 39.12 ± 0.77% of ETM within 3 mins. and achieving 99.29 ± 0.64% cumulative drug release within 30 min. In contrast, ESMT1 exhibited the slowest dissolution profile, releasing 26.97 ± 0.74% at 3 mins. and 86.56 ± 0.52% after 30 min. The enhanced dissolution observed in ESMT3 may be attributed to the optimized balance between PVP K-30 and Kollidon® CL-SF, which promoted rapid tablet wetting and disintegration, facilitating faster exposure of ETM-loaded MSNs to the dissolution medium. The observed differences among the factorial formulations confirmed that both formulation variables significantly influenced the dissolution characteristics of the developed ODTs. The incorporation of ETM within the mesoporous silica matrix, together with rapid tablet disintegration, contributed to improved drug wettability and dispersion, thereby enhancing dissolution of the poorly water-soluble drug. These findings established cumulative drug release as a critical quality attribute and justified subsequent statistical evaluation using response surface methodology to optimize the formulation.

**Drug Release Kinetics of the Optimized ETM MSN-Loaded ODT:** Dissolution data for the optimized formulation (ESMT3) were fitted to Zero-order, First-order, Higuchi, and Korsmeyer–Peppas models. The formulation released 39.12% of ETM within 3 mins. and 99.29% within 30 min, showing an initial rapid release followed by a diffusion-controlled phase—indicative of biphasic behaviour. The Zero-order model gave the best fit ($R^2$ = 0.9735), followed by Higuchi ($R^2$ = 0.9415) and Korsmeyer–Peppas ($R^2$ = 0.9267), while First-order fit poorly ($R^2$ = 0.7557). The Higuchi correlation and Korsmeyer–Peppas exponent (n = 0.3944) pointed to Fickian diffusion through the mesoporous silica network as the dominant release mechanism, driven by rapid tablet disintegration dispersing the ETM-loaded MSNs, followed by diffusion-controlled release from the nanoporous channels. This dual-stage, diffusion-dominated mechanism with near-Zero-order characteristics confirms the effectiveness of combining MSNs with an ODT system to enhance ETM's dissolution performance.

**Statistical Analysis and Model Evaluation**

Statistical analysis of the $3^2$ full factorial design confirmed that PVP K-30 ($X_1$) and Kollidon® CL-SF ($X_2$) significantly affected all four responses—wetting time, disintegration time, and drug release at 3 and 30 min—with high model F-values (64.56–104.05) and $p < 0.05$ throughout. Both excipients emerged as significant model terms across all responses, while significant quadratic terms ($B^2$ for wetting/disintegration time; $A^2$ and $B^2$ for dissolution) pointed to nonlinear formulation–response relationships, supporting the choice of a quadratic model. The models fit the data well, with $R^2$ values of 0.9908–0.9943 and adjusted/predicted $R^2$ in close agreement (0.9754–0.9847 and 0.8911–0.9325, respectively), reflecting strong predictive reliability. Adequate precision values (22.41–30.84), well above the threshold of 4, confirmed a sufficient signal-to-noise ratio for navigating the design space. Together, these results validated the quadratic models and supported the QbD approach for optimizing the ETM-loaded ODT formulation.

**Statistical Analysis of factorial design batches**

**Effect of Formulation Variables on Wetting Time ($Y_1$)**

Wetting time ($Y_1$) was described by the quadratic equation $Y_1 = 30.39 - 7.59X_1 + 2.35X_2 + 0.3650X_1X_2 + 1.13X_1^2 - 5.43X_2^2$. PVP K-30 ($X_1$) emerged as the dominant variable, its large negative coefficient reflecting a substantial reduction in wetting time with increasing binder concentration. Kollidon® CL-SF ($X_2$), by contrast, exhibited a positive linear coefficient offset by a strong negative quadratic term ($X_2^2 = -5.43$), pointing to a nonlinear, concentration-dependent influence rather than a straightforward monotonic trend. A small positive interaction term ($X_1X_2$) suggested mild synergy between the two excipients, while the modest positive $X_1^2$ term indicated a further, comparatively minor curvature contributed by PVP K-30. These trends were corroborated by the contour (figure 2A) and three-dimensional response surface plots (figure 2B), which showed wetting time diminishing progressively toward higher PVP K-30 levels; the curvature evident along the Kollidon® CL-SF axis further confirmed its nonlinear contribution to the response. The predicted-versus-actual plot (figure 2C), in turn, showed close alignment along the line of unity across the observed range (15.44–38.24 s), affirming the adequacy of the fitted model.

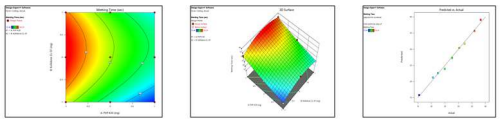

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**Figure 2: Response surface analysis of wetting time ($Y_1$): (A) Contour plot, (B) 3D response surface plot, and (C) Predicted versus actual plot.**

**Effect of Formulation Variables on *In vitro* Disintegration Time ($Y_2$)**

*In vitro* disintegration time ($Y_2$) followed the equation $Y_2 = 33.15 - 7.43X_1 + 2.21X_2 + 0.3075X_1X_2 + 1.28X_1^2 - 5.20X_2^2$. As with wetting time, PVP K-30 ($X_1$) proved the stronger determinant, its negative coefficient signaling a marked drop in disintegration time as binder concentration rose. Kollidon® CL-SF ($X_2$) carried a positive linear term but was counterbalanced by a large negative quadratic coefficient ($X_2^2 = -5.20$), the model's dominant curvature source, confirming that superdisintegrant concentration governed disintegration nonlinearly rather than proportionally. A small positive interaction term hinted synergy between the two excipients, and a $X_1^2$ coefficient added slight curvature. Contour (figure 3A) and 3D surface plots (figure 3B) echoed this pattern: disintegration time fell steadily with rising PVP K-30, while pronounced curvature along the Kollidon® CL-SF axis underscored its nonlinear role. Predicted and actual values plot (figure 3C) tracked closely along the line of unity across the tested range (19.19–41.39 s), affirming the model's predictive accuracy.

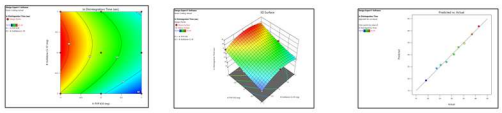

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**Figure 3: Response surface analysis of *In vitro* Disintegration time ($Y_2$): (A) Contour plot, (B) 3D response surface plot, and (C) Predicted versus actual plot.Effect of Formulation Variables on Drug Release at 3 mins. ($Y_3$)**

Cumulative drug release at 3 mins. ($Y_3$) followed the equation $Y_3 = 30.08 + 6.85X_1 - 1.60X_2 + 0.6500X_1X_2 - 2.43X_1^2 + 4.35X_2^2$. Unlike its effect on wetting and disintegration time, PVP K-30 ($X_1$) here showed a positive linear coefficient, indicating that higher binder concentration enhanced early drug release. Kollidon® CL-SF ($X_2$) carried a negative linear coefficient but a large positive quadratic term ($X_2^2 = +4.35$), the model's dominant curvature source, revealing a pronounced nonlinear, concentration-dependent contribution to early-stage release rather than a simple suppressive trend. A negative $X_1^2$ term (−2.43) added further curvature in the opposite direction, while a small positive interaction term suggested mild synergy between the excipients. Contour (figure 4A) and 3D response surface plots (figure 4B) supported these trends, with drug release rising sharply toward higher PVP K-30 levels and pronounced curvature along the Kollidon® CL-SF axis confirming its nonlinear influence; the highest release values occurred at elevated $X_1$ combined with extreme $X_2$ levels. Predicted and actual values plot (figure 4C) aligned closely along the line of unity across the observed range (19.56–46.08%), confirming model adequacy.

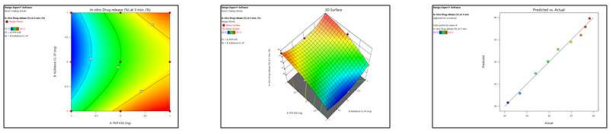

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**Figure 4: Response surface analysis of cumulative drug release at 3 mins. ($Y_3$): (A) Contour plot, (B) 3D response surface plot, and (C) Predicted versus actual plot.**

**Effect of Formulation Variables on Drug Release at 30 mins. ($Y_4$)**

Cumulative drug release at 30 mins. ($Y_4$) followed the equation $Y_4 = 93.48 + 6.90X_1 - 1.59X_2 + 0.4925X_1X_2 - 2.42X_1^2 + 4.40X_2^2$, closely mirroring the pattern seen at 3 min. PVP K-30 ($X_1$) again showed a positive linear effect, with higher binder concentration enhancing drug release. Kollidon® CL-SF ($X_2$) carried a negative linear coefficient outweighed by a large positive quadratic term ($X_2^2 = +4.40$), the dominant curvature source, confirming its persistently nonlinear, concentration-dependent influence at this later time point. A negative $X_1^2$ term (−2.42) added opposing curvature, while a small positive interaction term suggested mild synergy between the excipients. Contour (figure 5A) and 3D surface plots (figure 5B) supported these trends, with release rising sharply toward higher PVP K-30 levels and curvature along the Kollidon® CL-SF axis confirming its nonlinear role; maximal release occurred at elevated $X_1$ combined with extreme $X_2$. Predicted and actual values plot (figure 5C) aligned closely along the line of unity across the observed range (86.56–99.29%), confirming model adequacy.

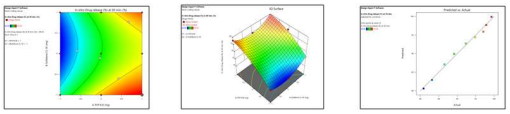

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**Figure 5: Response surface analysis of cumulative drug release at 30 mins. ($Y_4$): (A) Contour plot, (B) 3D response surface plot, and (C) Predicted versus actual plot.**

**Numerical Optimization and Checkpoint Validation**

Numerical optimization was performed using the desirability function in Design-Expert® (Version 13) to identify the formulation that minimized

wetting time and *In vitro* disintegration time while maximizing cumulative drug release at 3 and 30 min. This process identified an optimum design space within which minor variations in the formulation variables were not expected to significantly affect tablet quality, thereby confirming the robustness of the developed formulation. The optimized formulation was predicted at $X_1$ = 0.963 and $X_2$ = 0.116, corresponding to predicted responses of 24.36 s for wetting time, 27.41 s for disintegration time, 34.38% drug release at 3 min, and 94.26% drug release at 30 min. A second checkpoint formulation selected from within the optimized design space likewise satisfied the predefined optimization criteria, further demonstrating the flexibility and reliability of the established design space. To validate the predictive capability of the developed models, two checkpoint formulations were prepared and evaluated experimentally, the graph of overlay plot and checkpoint batches data comparison are shown in figure 6 and table 4 respectively. The observed responses agreed closely with the software-predicted values, yielding prediction errors ranging from −3.85% to 3.94% for checkpoint formulation 1 and from −2.23% to 3.94% for checkpoint formulation 2. In both cases, prediction errors for wetting time, *In vitro* disintegration time, and cumulative drug release at 3 and 30 mins. remained within ±5%, confirming the accuracy and robustness of the developed quadratic models. Taken together, these findings indicate that the optimized design space can reliably predict the critical quality attributes of ETM-loaded ODTs, thereby validating the suitability of the QbD approach for formulation optimization.

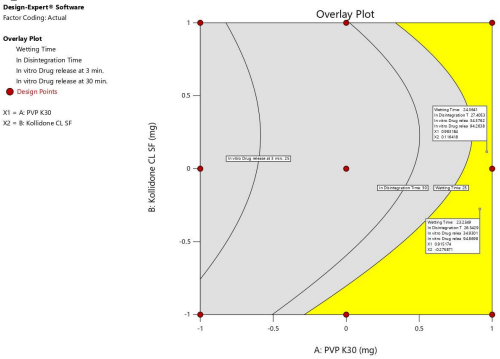


**Figure 6: Overlay plot illustrating the optimized design space obtained by numerical optimization using the desirability function.**

**Table 4: Comparison of predicted and experimental responses of the checkpoint formulations used for validation of the optimization model.**

| Parameter | Checkpoint 1 | | % Error | Checkpoint 2 | | % Error |
|---|---|---|---|---|---|---|
| | **Predicted** | **Observed** | | **Predicted** | **Observed** | |
| Wetting time (sec) | 24.36 | 25.30 | −3.85 | 23.23 | 22.32 | 3.94 |
| *In vitro* disintegration time (sec) | 27.41 | 28.33 | −3.37 | 26.34 | 26.93 | −2.23 |
| % CDR at 3 min | 34.38 | 35.63 | −3.65 | 34.93 | 34.09 | 2.41 |
| % CDR at 30 min | 94.26 | 92.04 | 2.36 | 94.87 | 96.07 | −1.27 |

**Stability Study of the Optimized ETM MSN-Loaded ODTs**

The stability of the optimized ETM-loaded MSNs was evaluated under intermediate storage conditions (40 ± 2 °C and 75 ± 5%) for 6 months in accordance with ICH Q1A(R2) guidelines. The optimized formulation was periodically assessed at 1, 2, 3, and 6 months for hardness, drug content, wetting time, *In vitro* disintegration time, water absorption ratio, and *In vitro* drug release, in order to determine the effect of storage on its physicochemical properties and dissolution performance. Results for various evaluation parameters during the stability testing period are shown in table 5. The formulation remained physically intact throughout the study period, with only minor variation in hardness (3.06–3.88 kg/cm²), indicating that adequate mechanical strength was maintained during storage. Drug content, likewise, remained within acceptable pharmacopoeial limits, declining only slightly from 99.20 ± 0.51% initially to 98.80 ± 1.15% after six months, which confirmed the chemical stability of ETM within the mesoporous silica matrix. Wetting time showed comparably negligible change, rising from 15.44 ± 0.67 s to 16.11 ± 1.02 s, while *In vitro* disintegration time increased marginally from 19.19 ± 0.21 s to 20.89 ± 0.48 s over the same period. Despite these slight shifts, all formulations continued to disintegrate well below the pharmacopoeial limit for ODTs, and the water absorption ratio remained relatively constant throughout the study, pointing to preservation of the tablet's porous structure and hydration characteristics. The dissolution profiles revealed only a modest reduction in the initial drug release rate over the storage period: release at 3 mins. declined gradually from 39.12% initially to 31.24% after six months, whereas cumulative release at 30 mins. remained above 97% throughout, decreasing

only marginally from 99.29% to 97.81%. Results are shown in figure 7. This close similarity between the initial and six-month dissolution profiles indicates that storage exerted only a minimal influence on the release behaviour of the formulation. The slight reduction observed in early-stage dissolution may be attributable to limited moisture uptake during storage, which could transiently slow the penetration of the dissolution medium into the mesoporous network without affecting the overall extent of drug release. It was found that the optimized ETM MSN-ODT demonstrated excellent physicochemical and dissolution stability across the six-month study, with all evaluated quality attributes remaining within acceptable limits. These results confirm that the optimized formulation retained its structural integrity, rapid disintegration characteristics, and dissolution performance under intermediate storage conditions, underscoring the robustness of the mesoporous silica-based formulation and supporting its suitability for further pharmaceutical development.

**Table 5: Stability evaluation of the optimized ETM MSN-loaded ODT under intermediate storage conditions (30 ± 2°C/65 ± 5% RH).**

| Evaluation parameter | Initially | After 1 month | After 2 months | After 3 months | After 6 months |
|---|---|---|---|---|---|
| Hardness (kg/cm² ± SD) (n=3) | 3.06 ± 0.12 | 3.88 ± 0.12 | 3.50 ± 0.10 | 3.35 ± 0.17 | 3.57 ± 0.20 |
| Drug Content (% ± SD) (n=3) | 99.20 ± 0.51 | 98.89 ± 0.76 | 98.02 ± 0.04 | 98.84 ± 0.79 | 98.80 ± 1.15 |
| Wetting Time (sec. ± SD) (n=3) | 15.44 ± 0.67 | 15.95 ± 0.89 | 15.96 ± 1.15 | 15.85 ± 0.52 | 16.11 ± 1.02 |
| *In vitro* Disintegration Time (sec. ± SD) (n=6) | 19.19 ± 0.21 | 19.62 ± 0.17 | 20.03 ± 0.35 | 20.47 ± 0.40 | 20.89 ± 0.48 |
| Water absorption ratio (% ± SD) (n=3) | 72.10 ± 0.56 | 75.22 ± 1.83 | 69.98 ± 1.75 | 71.48 ± 1.57 | 70.40 ± 1.32 |

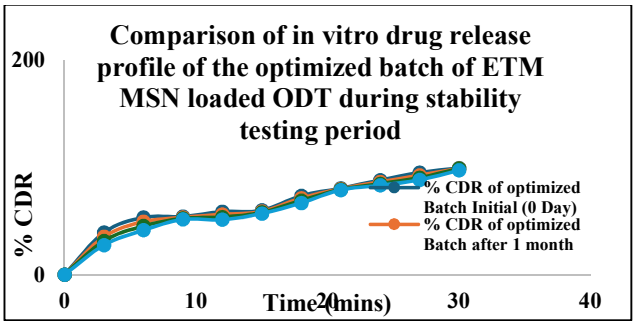


**Figure 7: Comparison of *In vitro* cumulative drug release profiles of the optimized ETM MSN-loaded ODT during the six-month stability study.**

**SUMMARY AND CONCLUSION**

The present study successfully developed and optimized ETM-loaded MSNs and incorporated them into ODTs using a systematic QbD approach. Preformulation studies confirmed the suitability of ETM and the selected excipients for formulation development, while the ETM-loaded MSNs, once prepared and optimized, exhibited desirable particle size, high drug entrapment efficiency, and enhanced drug loading. Physicochemical characterization further confirmed successful drug incorporation into the mesoporous silica matrix, with no evidence of drug–excipient incompatibility. The optimized MSN formulation was subsequently incorporated into ODTs prepared by direct compression. Preliminary formulation studies guided the selection of PVP K-30 and Kollidon® CL-SF as the critical formulation variables for optimization, and a $3^2$ full factorial design established the relationship between these variables and the critical quality attributes of wetting time, *In vitro* disintegration time, and cumulative drug release. Statistical analysis yielded significant and reliable quadratic models with excellent predictive capability, and numerical optimization together with checkpoint validation confirmed the robustness of the resulting formulation. The optimized ETM MSN-loaded ODT exhibited rapid wetting and disintegration, favorable mechanical properties, uniform drug content, and near-complete drug release within 30 min. Release kinetic analysis pointed to a dual-stage, diffusion-dominated mechanism, in which rapid tablet disintegration facilitated immediate nanoparticle dispersion, followed by diffusion-controlled drug release from the mesoporous silica network. Stability studies conducted under ICH Q1A(R2) intermediate storage conditions further demonstrated that the optimized formulation retained its physicochemical characteristics and dissolution performance across the six-month evaluation period. These findings indicate that integrating mesoporous silica nanotechnology with ODTs technology markedly improved the dissolution characteristics of ETM while preserving

excellent formulation stability. The developed ETM MSN-loaded ODT thus represents a promising oral delivery system for poorly water-soluble drugs and offers a robust platform for further pharmaceutical development and potential clinical translation.

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