# Development And Optimisation Of Magnesium Alumino Metasilicate Loaded Tacrolimus Extended Release Tablets By Qbd Approach For Management Of Oragan Transplantation



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## Abstract
The current present study was planned to formulate tacrolimus extended-release tablets to enhance drug activity. Tacrolimus is a calcineurin inhibitor used to treat mild to moderate atopic dermatitis and preclude organ transplant rejection. However, tacrolimus consists of low bioavailability and shorter half-life. Therefore, it was intended to formulate an extended release formulation with suitable polymers to upregulates its therapeutic response.The melt granulation method was used for the preparation of tacrolimus extended release tablets. The central composite design was employed for optimization at two level three factors. Crucial materials properties were the concentration of glyceryl behenate (X1), the concentration of Hypromellose (X2), and the concentration of PEG 6000 (X3).ANOVA has been implemented to interpret the data and design space.The tacrolimus extended release tablet was successfully formulated using melt granulation method and invitro profile of optimized batch compared with marketed formulation. The outcome of the study revealed that optimized formulation of tacrolimus shows 100% release at 12 h. Whereas, marketed formulation (Envarsus XR) also shows 100% release at12 h. Thus, the findings revealed that the optimized formulation was successfully prepared and suitable for extended release nature.

**Keywords:** Tacrolimus, Central Composite Design, Drug release, Extended release tablet
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## Introduction
In the last decades, empirical and systematic approaches are adopted in pharmaceutical development, and remarkable growth in pharmaceutical quality has been observed[1]. The Quality by design (QbD) is a risk-based, all-encompassing approach to pharmaceutical development that begins with stated goals and underlines performance and operational understanding and accountability based on strong science and quality risk management. In addition,QbD is an appropriate approach for the production of pharmaceutical products[2,3]. The international conference on harmonization (ICH) guidelines operates the perception of the QbD by following the precisely ICHQ8 (Pharmaceutical Development), Q9 (Quality Risk Management), and Q10 (Quality Management) (Pharmaceutical Quality System)[4]. It enhances the integrity of the drug product by analyzing the risk of developing the drug product. The QbD principle is founded on prior knowledge of process and product understanding and risk assessment[5]. A poorly formulated pharmaceutical product will not demonstrate proper efficacy and safety, and many tests will not strengthen it. From 2013, the FDA recommended that the pharmaceutical industry implement QbD[6]. In April 1994, US Food and Drug Administration approved Tacrolimusto prevent organ rejection in patients undergoing allogeneic liver transplants. Tacrolimusis marketed under the brand name Prograf[7]. It is now widely prescribed to prevent organ rejection in patients undergoing allogeneic liver, heart or kidneytransplants[8]. Tacrolimus is a popularly

used immunosuppressive drug in kidney transplantation. Tacrolimus is a white to off-white powder with the molecular formula $C_{44}H_{69}NO_{12}$,and 804 g/mol molecular weight[9]. It is a macrolide antibiotic known as FK506 or Fujimycin. It works as an immunosuppressant. It has been shown in primates to be effective in suppressing cardiac allograft rejection. Tacrolimus binds to the FK 506-binding protein-12 (FKBP-12), which is similar to cyclophilin and is found intracellularly. Later complexes of tacrolimus-FKBP-12 inhibit the activity of calcineurin phosphatase, which inhibits T-cell activation[10]. Secondary antibody responses, natural killer or antibody-dependent cytotoxic cell function, and IL-2-stimulated cell proliferation are not inhibited, but primary antibody responses to T cell-dependent antigens. Absorption in the gastrointestinal tract is variable and incomplete. After oral administration, tacrolimus bioavailability ranges from 10% to 60%, often with maximum serum concentrations reaching at 1 to 2 h[11]. It is metabolized to various metabolites by the cytochrome P450 enzyme system in the liver and the intestinal wall. Several metabolites have been discovered, some of which are active. Tacrolimus is used to suppress the immune system during kidney, lung, pancreas, and liver transplants. Following treatments, nephrotoxicity, neurotoxicity, headache, gastro intestinal disturbances, and other side effects have been observed. Immunosuppression after solid organ transplantation is a complicated process. Immunosuppressant researchers have seen significant advancements in patient care over the last 50 years. Enhanced regimens improve clinical therapy and survival prospects; unfortunately, immunosuppressant side effects and the risks of long-term immunosuppression offer various problems for health care providers, including metabolic abnormalities, toxicities, contamination risk, and malignancy[12]. Numerous new immunosuppressants have recently been discovered and developed for transplantation. Corticosteroids, Janus Kinase inhibitors, calcineurin inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, and inhibitors of the enzyme inosine monophosphate dehydrogenase (IMDH) are currently available drug classes.To avoid toxicity and improve bioavailability, an extended release dosage form should be prepared once a day using innovative, simple technology to scale up[13-15]. This study aims to create a Tacrolimus extended release tablet formulation using a quality by design approach to better understand the process and formulation parameters.



## Materials and Methods

### Materials

Tacrolimus was obtained from Biocon (Bangalore, India), Glyceryl behenate (Compritol 888 ATO)were purchased from Gattefosse, Magnesium Alumino metasilicate received from Fuji chemical, Polyethylene glycol (PEG 6000) received from Dow, hypromellose (HPMC K4M) received from colorcon, Lactose monohydrate (Flowlac 100) received from Meggle and magnesium stearate received from Crestcellulose. All other chemicals used in the study were of analytical grades.

### Study of quality target product profile (QTPP)for tacrolimus extended release tablets

Implementing QbD in drug product development necessitates a thorough understanding of the CQA of the drug substance and drug product, which leads to successful product development with a predefined quality target product profile (QTPP). QTTP describes the properties of the drug product in terms of safety and efficacy. To identify the primary quality characteristics of the fabricated system, preliminary investigations were performed based on the quality target product profile. The first step in creating a product by applying this excellent approach is establishing and validatingthe QTPP. It contained a set of quality attributes (QAs) that must be included in the finished product. The components utilized and the variables of the manufacturing process have an impact on certain QAs. As a result, critical material attributes (CQAs) and critical process parameters (CPPs) must be defined[16].

### Study of critical quality attribute (CQA) for tacrolimus extended release tablets

CQA is a physicochemical, biological characteristic of the product, and it is controlled to ensure the safety and efficacy of the patient. Identification of the CQA was done based on the risk assessment and prior knowledge of the drug product.In drug substance particle size

distribution, polymorphic forms, moisture content and flow properties are the factors that need to be assessed. This may affect the quality of the product assay, content uniformity, and dissolution.Various assessment factors are involved in drug formulation, like controlled release polymer, lipid material, and surfactant[17].

## Statistical design of experiments

Risk formulation variables were evaluated and identified in the initial risk assessment during formulation development. The study looked at the effect of the lipid material (glyceryl behenate) / adsorbent (magnesium aluminum metasilicate) ratio, hypromellose (controlled release polymer) level, and surfactant (polyethylene glycol; PEG 6000) level on the critical quality attributes of the drug product (CQAs).The objective of the development of drug product was to choose the lipid (glyceryl behenate) / adsorbent[18-20] (magnesium aluminum metasilicate) ratio, hypromellose (controlled release polymer) level, the surfactant (polyethylene glycol; PEG 6000) level and to see whether these formulation elements interact with the pharmaceutical active substance. The robustness of the proposed formulation is established in this study. Table 1 shows how a central composite design was used to investigate the effect of these variables on the responses.The primary goal of this study was to assess the effect of theoretical polymer level, lipid material, and surfactant on drug release from extended release tablets. Invitro release was performed using USP type II apparatus, at 100 rpm in 0.005 percent HPC (hydroxyl propyl cellulose) in water with 0.50 percent SLS (sodium lauryl sulphate) adjusted to pH 4.5 at three different time intervals [T (2.5 h, 6.5 h, and 12 h)]. The initial response target ranges were based on the drug release profile obtained for the reference listed drug (RLD). The study design and experimental results are summarized in Table 2.

## Preparation of granules by melt granulation technique

The excipients were selected according to the pharmacopoeial monograph of drugs. The granules were prepared by the melt granulationmethod[21-24]. The raw materials glyceryl behenate (compritol 888ATO) and polyethylene glycol (PEG 6000) were placed into a rapid mixture granulator provided with hot water circulation. Hot water was circulated in a rapid mixer, granulated, and heated upto 85 °C till all materials were melted. Then tacrolimus was added into the molten mixture under impeller to form a homogenous molten mixture. Magnesium aluminum metasilicate was added in rapid mixer granulator under both impeller and chopper on. The material was allowed to cool at room temperature by circulating cold water. Granules were milled through co mill fitted with a 40G screen (1016 µm). Milled granules were sifted through #30 mesh (ASTM 600 µm). Milled granules were pre-lubricated with hypromellose and Lactose monohydrate (Flowlac 100) in a blender for 15 min followed by blending with magnesium stearate in a blender for 5 min.

## Evaluation of granules flow properties

### *Bulk density and tapped density*

Bulk density is the weight of powder in a given volume. The bulk density of a powder increases as its compactness increases[25]. On the other hand, Tapped density is a powder weight to the volume occupied after tapping for a specified period. The higher the tapped density, the higher the packing density[26]. The compressibility index is a metric that measures the flow properties of the powder. The relationship between bulk and tapped density indicates the flowing nature of the powder; the greater the difference between bulk and tapped density, the poorer the flow of the blend. The compressibility index ranges from approximately 10 (excellent flow) to approximately 38 (poor flow)[27].

### *Tablet compression*

The compression parameters were evaluated after the tablets were compressed with oval-shaped plain tooling. Compression of the tablets is a crucial parameter, higher the compression effects dissolution of the finished product. Therefore, optimum pressure is required for compression of granules. During in-process control, the tablets' hardness, friability, thickness, and weight variation were assessed. Because this was an extended release formulation, dissolution tests were the primary criterion.

### *In vitro dissolution studies*

The solution of tacrolimus extended release tablets was doneusing USP type II apparatusat 100 rpm in 0.005% HPC in water with 0.50% SLS, and the pH (4.5) was adjusted. The temperature of the dissolution apparatus was maintained at 37 ± 0.5°C. The samples were withdrawn at regular intervals (0.5, 1, 2.5, 4.5, 6.5, 8.5 and 12 h). The withdrawn samples were replaced withan equal volume of fresh medium to maintain sink condition. The samples were analyzed by high-performance liquid chromatography[28].

## Results and Discussions

### Study of QTPP for tacrolimus extended release tablets

To establish physicochemical similarities, QTTP was performed compared to the physicochemical characterization of the reference product (Envarsus XR 4 mg) and in vitro studies to provide equivalent product quality. The QTPP for the formulation is described in table 3.

### Study of critical quality attribute (CQA) for Tacrolimus extended release tablets

CQA refers to the physiochemical and biological properties of a product monitored to ensure the patient's safety and efficacy. The CQA was identified based on the risk assessment and prior knowledge of the drug product. Dissolution, assay, tablet size, identification, and degradation products are identified as product CQAs that can impact product quality and safety.

### Evaluation of granules

Physical properties of granules from various formulations were evaluated. The 17 batches were prepared, and each batch was investigated for the physical parameters like tapped density, bulk density, and compressibility index.Table 10 highlights the obtained results. All of the batches had an acceptable compressibility index.

### Evaluation of tablets

The prepared extended release tacrolimus tablets were investigated for hardness, friability, and thickness, and results indicate that all formulation were within acceptable limits. The lower flow of the blend leads to weight variation on the higher side of batches containing more glyceryl behenate. Table 4 lists the evaluation parameters for tablets.

### Interpretation of design expert software data

Three-tier dissolution specifications were established to optimize the extended release tablets with similar release kinetics as the reference. A central composite design was implemented following an initial assessment and a review of the literature[29,30]. According to the literature review, it has been identified that the hydrophilic and hydrophobic matrix containing insoluble drugs. In terms of dissolution profile, three major factors that will impact product quality are hypromellose (HPMC K4M), glyceryl behenate (compritol 888ATO), and polyethylene glycol (PEG 6000). The factor levels were created based on the results of a design expert software run. Drug release specifications were established in drug product CQA and were set at three different time intervals. A total of 17 experiments with three center points were carried out.A lower release profile was observed in formulations D-3 and D-4 that contained a higher level of controlled release polymer (HPMC and Glyceryl behenate). In contrast, a dump in the release profile was observed in formulation D-11, which contained a low level of controlled release polymer (HPMC and Glyceryl behenate) and a high level of poly ethylene glycol. These formulations did not meet the dissolution specification. The remaining formulations have a good controlled release profile that lasts up to 12 h.

### Analysis of variance (ANOVA)

The data were statistically interpreted using analysis of variance (ANOVA) and design expert software. The sum of squares, P-value, and lack of fit test was used to select the design model for analyzing the response. The model's adequacy is confirmed by the fact that the P-value was less than 0.05 percent. The statistical design assisted in evaluating important factors influencing responses. ANOVA details are provided in table 5 for responses Y1, Y2, and Y3, respectively. Response Y1 shows that the model has an F-value of 106.77, indicating that it is substantial. An F-value this large could occur due to noise only 0.01 percent of the time. If the

P-value is less than 0.05, the model terms are significant. A, B, C, AC, BC, and $C^2$ are all significant terms in this case. The predicted $R^2$ of 0.9465 agrees reasonably with the adjusted $R^2$ of 0.9754. (the difference is less than 0.2). $C^2$ demonstrates the curvature effect based on the final equation in terms of coded factors. Response Y2 shows that the model has an F-value of 85.54, demonstrating that it is significant.Only 0.01 percent of the time might such a large F-value be attributed to noise. If the P-value is less than 0.05, the model terms are significant. In this situation, the terms A, B, C, AB, AC, BC, and $A^2$ are noteworthy.The predicted $R^2$ of 0.8731 agrees reasonably with the adjusted $R^2$ of 0.9737 (the difference is less than 0.2). $A^2$ illustrates the curvature effect based on the final equation in terms of coded factors. Response Y3 displays that the model has an F-value of 21.40, signifying that it is significant.Only 0.01 percent of the time might such a large F-value be owing to noise. If the P value is less than 0.05, the model terms are significant. The terms A, B, C, AB, and C2 are all relevant in this situation.The predicted $R^2$ of 0.7701 agrees reasonably with the adjusted $R^2$ of 0.8644. (the difference is less than 0.2). $C^2$ demonstrates the curvature effect based on the final equation in terms of coded factors.

## Perturbation plots

The perturbation plots aid in comparing the effects of factors at a single point in the design space. The response is determined by changing one factor throughout its range while keeping the other factors constant. Design-Expert sets the reference point to be the midpoint of all the factors. A factor with a steep curvature indicates that the response is sensitive to that factor. A flat line denotes insensitivity to change in that factor.In more than two factors, the perturbation plot assists in determining which factors have the greatest influence on the response. According to the perturbation plots (fig.1), any deviation from the center point causes all three factors (A, B, and C) to be sensitive to responses; however, factor C (polyethylene glycol; PEG 600) has a greater impact on responses than the other two factors (factors A and B), and a slight change in PEG 6000 concentration has a greater impact on the dissolution profile.

## Response surface 3D plot

Figures 2, 3, and 4 show the relationship between significant input factors and response. Responses Y1 (released after 2.5 h), Y2 (released after 6.5 h), and Y3 (release at 12 h). For each of the three responses, fit summary data were generated. The adjusted R2 denotes the number of terms in the model, whereas the predicted $R^2$ denotes how well the model predicts the response. Table 6 shows that the best model for all responses is quadratic as $R^2$ nearer to 1.

## Defining design space

The combination and interaction of various input factors, variables, and process parameters that demonstrate quality assurance is defined as design. Any changes in the design space will not affect product quality[31]. The greater the range of design space, the more robust the product in terms of quality. Graphical optimization was used with an overlay plot to optimize all three responses with the desired range, as shown in Figure 5. The yellow shaded area represents an acceptable operating range. All three factors (A, B, and C) should be within a certain range to ensure patient safety and therapeutic effectiveness.

## Characterization of the optimized formulation of tacrolimus extended release tablets

The in vitro drug release profile of tacrolimus extended release tablets showed sustained release throughout 12 h, similar to the reference product (Envarsus XR 4 mg). All three optimized formulations (three centre point batches, D5, D6, and D14) have a similar release profile (Fig. 6), indicating reproducibility in batches with the same composition. Optimized batch D5, assessed for different kinetics models, and based on the various kinetics models, higher values of coefficient of correlation for zero-order were observed[32-34].From the in-vitro release profile, it has been identified that the results obtained forzero-order release, there was maximum correlation coefficient than first order; hence the release was the zero-order type.

**Table 1:** Factors for design layout of central compsite design

| Factors: Formulation Variables | | Levels | |
|---|---|---|---|
| | | -1 | 1 |
| X1 | % glyceryl behenate (lipid material) to magnesium alumino metasilicate (Adsorbent) in combination | 65 | 85 |
| X2 | Controlled release polymer (%)- Hypromellose | 10 | 30 |
| X3 | PEG 6000 (%) | 1 | 5 |
| **Responses** | | **Acceptable Ranges** | |
| Y1 | Dissolution at 2.5 h | NMT 25% | |
| Y2 | Dissolution at 6.5 h | Between 40-60% | |
| Y3 | Dissolution at 12 h | NLT 80% | |

**PEG:** Polyethylene Glycol, NMT: Not More Than

**Table 2:** Design runs and experimental values

| Run | Factors: Formulation Variables | | | Responses | | |
|---|---|---|---|---|---|---|
| | A | B | C | Y1: 2.5 h | Y2: 6.5 h | Y3: 12 h |
| | (%) | (%) | (%) | (%) | (%) | (%) |
| D-1 | 75 | 10 | 3 | 15 | 60 | 100 |
| D-2 | 65 | 10 | 1 | 10 | 42 | 90 |
| D-3 | 85 | 30 | 5 | 9 | 35 | 90 |
| D-4 | 85 | 30 | 1 | 5 | 25 | 85 |
| D-5 | 75 | 20 | 3 | 14 | 52 | 99 |
| D-6 | 75 | 20 | 3 | 12 | 51 | 99 |
| D-7 | 65 | 30 | 1 | 8 | 44 | 90 |
| D-8 | 65 | 30 | 5 | 20 | 60 | 100 |
| D-9 | 65 | 20 | 3 | 15 | 58 | 100 |
| D-10 | 75 | 30 | 3 | 8 | 45 | 94 |
| D-11 | 65 | 10 | 5 | 30 | 75 | 100 |
| D-12 | 85 | 10 | 1 | 10 | 42 | 90 |
| D-13 | 75 | 20 | 5 | 20 | 60 | 100 |
| D-14 | 75 | 20 | 3 | 12 | 52 | 95 |
| D-15 | 85 | 20 | 3 | 9 | 44 | 92 |
| D-16 | 85 | 10 | 5 | 19 | 61 | 100 |
| D-17 | 75 | 20 | 1 | 10 | 45 | 90 |

**Table 3:** Qttp for tacrolimus extended release tablets

| QTPP Features | Target | Reasons |
|---|---|---|
| Dosage form | Tablet | Dosage form should be same to meet pharmaceutical equivalence |
| Dosage design | Extended release tablet | As per the label claim of reference, same design |
| Route of administration | Oral | Route of administration should be in line with the reference |
| Dosage strength | 4 mg | Strength of the dosage form should be same for pharmaceutical equivalence |

**QTTP:** Quality Target Product Profile

**Table 4:** Evaluation of granules and tablets

| Evaluation of granules | | | | | Evaluation of tablets | | |
|---|---|---|---|---|---|---|---|
| Run | Bulk density (g/ml) | Tapped density (g/ml) | Compressibility index (%) | Hardness (kp) | Friability (%) | Thickness (mm) | Weight variation (mg) |
| D-1 | 0.521 | 0.643 | 18.974 | 9.5±0.15 | 0.11 ± 0.15 | 5.30 ± 0.15 | 400±0.15 |
| D-2 | 0.5 | 0.621 | 19.485 | 10.7±0.08 | 0.12 ± 0.12 | 5.28 ± 0.08 | 399±0.54 |
| D-3 | 0.485 | 0.651 | 25.499 | 8.1±0.10 | 0.12 ± 0.13 | 5.35 ± 0.14 | 399±4.11 |
| D-4 | 0.491 | 0.662 | 25.831 | 8.5±0.12 | 0.14 ± 0.16 | 5.33 ± 0.15 | 401±3.54 |
| D-5 | 0.515 | 0.637 | 19.152 | 10.1±0.07 | 0.09 ± 0.13 | 5.28 ± 0.09 | 398±0.34 |
| D-6 | 0.516 | 0.645 | 20.000 | 10.9±0.12 | 0.16 ± 0.10 | 5.29 ± 0.05 | 401±0.44 |
| D-7 | 0.506 | 0.632 | 19.937 | 10.5±0.16 | 0.12 ± 0.14 | 5.31 ± 0.03 | 402±0.66 |
| D-8 | 0.498 | 0.612 | 18.627 | 9.9±0.12 | 0.19 ± 0.14 | 5.33 ± 0.07 | 401±0.43 |
| D-9 | 0.512 | 0.64 | 20.000 | 10.0±0.05 | 0.21 ± 0.13 | 5.36 ± 0.19 | 402±0.87 |
| D-10 | 0.51 | 0.622 | 18.006 | 10.4±0.05 | 0.22 ± 0.10 | 5.34 ± 0.16 | 402±0.65 |
| D-11 | 0.528 | 0.652 | 19.018 | 9.8±0.09 | 0.24 ± 0.16 | 5.31 ± 0.23 | 403±0.55 |
| D-12 | 0.482 | 0.66 | 26.97 | 8.6±0.17 | 0.10 ± 0.09 | 5.32 ± 0.12 | 401±2.99 |
| D-13 | 0.511 | 0.642 | 20.405 | 10.6±0.11 | 0.20 ± 0.15 | 5.31 ± 0.12 | 402±0.87 |
| D-14 | 0.514 | 0.638 | 19.436 | 9.9±0.07 | 0.12 ± 0.11 | 5.32 ± 0.16 | 401±0.98 |
| D-15 | 0.478 | 0.648 | 26.235 | 8.9±0.08 | 0.18 ± 0.11 | 5.31 ± 0.15 | 402±2.19 |
| D-16 | 0.475 | 0.64 | 25.781 | 8.1±0.18 | 0.18 ± 0.12 | 5.37 ± 0.19 | 400±3.52 |
| D-17 | 0.52 | 0.654 | 20.489 | 11.1±0.19 | 0.12 ± 0.11 | 5.30 ± 0.19 | 399±0.95 |

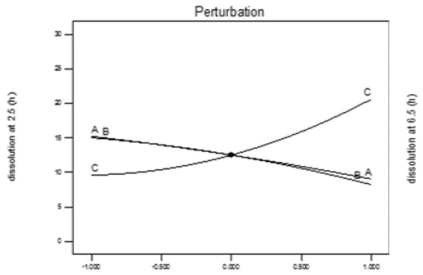
**Table 5:** Summary of anova of response (anova)

| Source | Sum of squares | DF | Mean squares | F value | p-value Prob > F | |
|---|---|---|---|---|---|---|
| Response (Y1) | | | | | | |
| Model | 596.22 | 6 | 99.37 | 106.77 | <0.0001 | significant |
| Residual | 9.31 | 9.1 | 0.9307 | | | |
| Lack of fit | 6.64 | 8 | 0.8301 | 0.6225 | 0.8824 | not significant |
| Pure Error | 2.67 | 2 | 1.33 | | | |
| Response (Y2) | | | | | | |
| Model | 2186.08 | 7 | 312.3 | 85.54 | <0.0001 | significant |
| Residual | 32.86 | 9 | 3.65 | | | |
| Lack of fit | 32.19 | 7 | 4.6 | 13.8 | 0.0692 | not significant |
| Pure Error | 0.6667 | 2 | 0.3333 | | | |
| Response (Y3) | | | | | | |
| Model | 378.07 | 5 | 75.61 | 21.4 | <0.0001 | significant |
| Residual | 38.87 | 11 | 3.53 | | | |
| Lack of fit | 28.21 | 9 | 3.13 | 0.5877 | 0.7639 | not significant |
| Pure Error | 10.67 | 2 | 5.33 | | | |

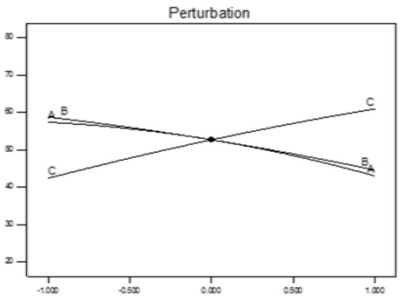
**ANOVA:**Analysis of Variance, DF:Degree of Freedom, Prob: Probability

**Table 6:** FIT summary of responses

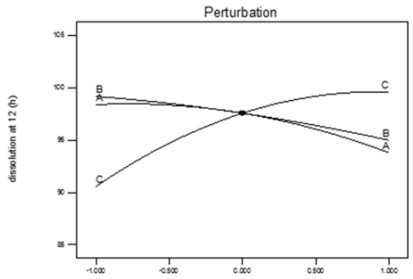
| Source | Y1 | | |
|---|---|---|---|
| | Linear | 2FI | Quadratic |
| Lack of fit p-value | 0.1504 | 0.3763 | 0.8824 |
| Adjusted $R^2$ | 0.8144 | 0.9367 | 0.9825 |
| Predicted $R^2$ | 0.6686 | 0.8628 | 0.9391 |
| Source | Y2 | | |
| | Linear | 2FI | Quadratic |
| Lack of fit p-value | 0.011 | 0.0312 | 0.0663 |
| Adjusted $R^2$ | 0.8161 | 0.939 | 0.9746 |
| Predicted $R^2$ | 0.6564 | 0.6975 | 0.8697 |
| Source | Y3 | | |
| | Linear | 2FI | Quadratic |
| Lack of fit p-value | 0.4077 | 0.4229 | 0.775 |
| Adjusted $R^2$ | 0.6533 | 0.6812 | 0.8699 |
| Predicted $R^2$ | 0.4634 | 0.2183 | 0.59 |




Deviation from reference point (Coded units)




Deviation from reference point (Coded units




Deviation from reference point (Coded units)

**Figure 1:** Perturbation plots for the effect of individual factors on responseY1 (2.5 h), Y2 (6.5 h) and Y3 (12 h)

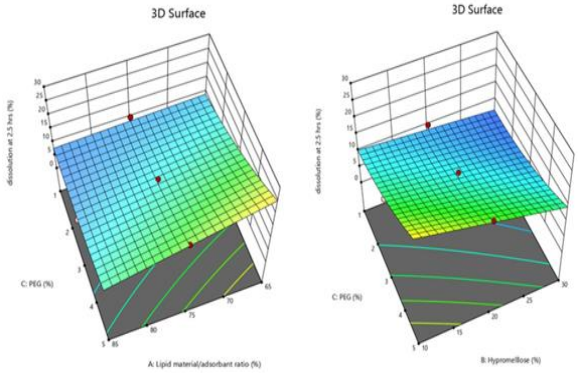


**Figure 2:** 3D contour plot depicting the influence of PEG, Hypromellose and Lipid material/adsorbent on % drug release at 2.5 h

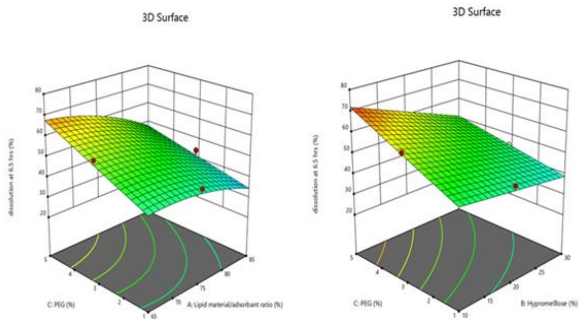



**Figure 3:** 3D contour plot depicting the influence of PEG, Hypromellose and Lipid material/Adsorbent on % drug release at 6.5 h

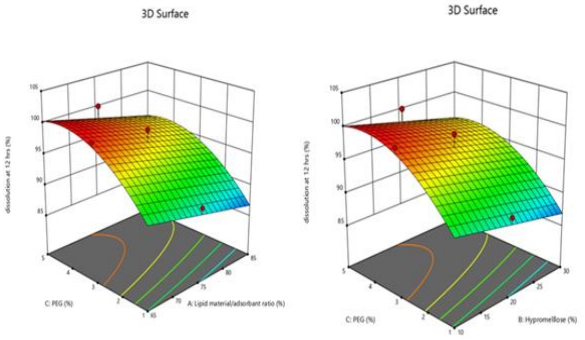



**Figure 4:** 3D contour plot depicting the influence of PEG, Hypromellose and Lipid material/Adsorbent on % drug release at 12 h

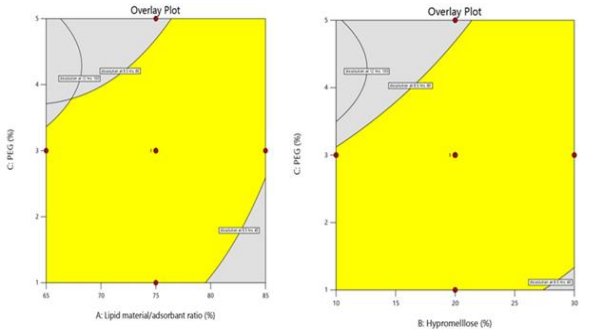



**Figure 5:** Overlay plot

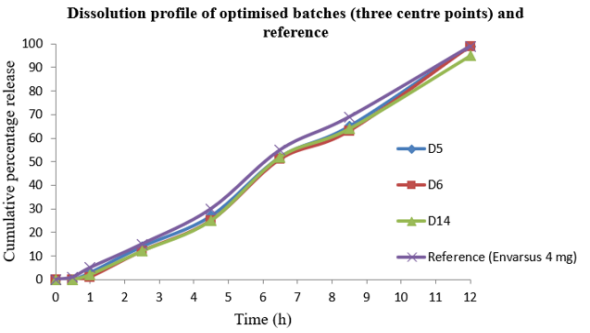



**Figure 6:** Comparison of release profile of optimized batches against reference (Envarsus XR 4 mg)

## Conclusion

Tacrolimus is a calcineurin inhibitor used to treat mild to moderate atopic dermatitis and preclude organ transplant rejection. QbD is an important tool for product development to ensure pharmaceutical quality. By implementing QbD approach in product development, critical material attributes were identified, and control strategies were developed. In the present research, the QbD concept was implemented for a systemic approach for developing extended release tablets of tacrolimus 4mg. In vitro drug release from optimized formulation exhibited zero-order release at 12 h. Initial risk assessment was done for both drug substance and drug product, and justification was provided. Tacrolimus extended release formulation was optimized using a central composite design. ANOVA has been implemented to interpret the data and design space.Thus, the findings revealed that the formulation was suitable for the extended release nature.

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