Research Article

Optimization of Carboxymethyl-Xyloglucan-Based Tramadol Matrix Tablets Using Simplex Centroid Mixture Design

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The aim was to determine the release-modifying effect of carboxymethyl xyloglucan for oral drug delivery. Sustained release matrix tablets of tramadol HCl were prepared by wet granulation method using carboxymethyl xyloglucan as matrix forming polymer. HPMC K100M was used in a small amount to control the burst effect which is most commonly seen with natural hydrophilic polymers. A simplex centroid design with three independent variables and two dependent variables was employed to systematically optimize drug release profile. Carboxymethyl xyloglucan ($X_1$), HPMC K100M ($X_2$), and dicalcium phosphate ($X_3$) were taken as independent variables. The dependent variables selected were percent of drug release at 2nd hour ($Y_1$) and at 8th hour ($Y_2$). Response surface plots were developed, and optimum formulations were selected on the basis of desirability. The formulated tablets showed anomalous release mechanism and followed matrix drug release kinetics, resulting in regulated and complete release from the tablets within 8 to 10 hours. The polymer carboxymethyl xyloglucan and HPMC K100M had significant effect on drug release from the tablet ($P > 0.05$). Polynomial mathematical models, generated for various response variables using multiple regression analysis, were found to be statistically significant ($P > 0.05$). The statistical models developed for optimization were found to be valid.

1. Introduction

Hydrophilic matrices are an interesting option while developing an oral sustained-release formulation. They can be used for controlled release of both water-soluble and water-insoluble drugs. The release behaviour of drugs varies with the nature of the matrix and it is the complex interaction of swelling, diffusion, and erosion processes [1]. Polysaccharides are the choice of material which has been evaluated as hydrophilic matrix for drug delivery system due to their nontoxicity and acceptance by regulating authorities.

Xyloglucan is a natural polysaccharide isolated from seed kernel of Tamarindus indica. It is used as ingredient in food and pharmaceutical industry. It has been significantly evaluated for use in hydrophilic drug delivery system. It possesses high viscosity, broad pH tolerance, and swelling and binding properties [2]. This led to its application as release retardant polymer and binder in pharmaceutical industry. In addition to these, other important properties of xyloglucan have been identified recently, which include noncarcinogenicity [3], mucoadhesivity, biocompatibility [4], high drug holding capacity [5], and high thermal stability [6]. This led to its application as excipient in hydrophilic drug delivery system [3–6].

Carboxymethyl xyloglucan is a derivative of xyloglucan and the microbial resistance of CM-xyloglucan is much better than that of plain powder. The viscosity of CM-xyloglucan in solutions is higher compared to native gum. Derivatization of xyloglucan, that is, CM-xyloglucan, disrupts the organization and exposes the polysaccharide network for hydration which results in higher viscosity and due to this its swelling index is also higher as compared to Xyloglucan. The presence of carboxymethyl groups makes the molecule resistant toward enzymatic attack [7]. Since carboxymethyl xyloglucan is having improved properties which are required for the retardation of release, the present study was undertaken to elucidate release kinetics of water-soluble drug from the matrix.

Tramadol, a synthetic opioid of the aminocyclohexanol group, is a centrally acting analgesic with weak opioid agonist properties. The half-life of the drug is about 5.5 hours and the usual oral dosage regimen is 50 to 100 mg every 4 to 6
hours with a maximum dosage of 400 mg/day [8]. To reduce the frequency of administration and to improve patient compliance, a sustained-release formulation of tramadol is desirable. The drug is freely soluble in water and hence judicious selection of release retarding excipients is necessary to achieve a constant in vivo input rate of the drug. The most commonly used method of modulating the drug release is to include it in a matrix system [9]. The major objective of the present investigation was to develop a sustained-release drug delivery system using simplex centroid design as an optimization technique.

2. Material and Methods

Carboxymethyl xyloglucan (CM-xyloglucan) was procured from Encore Natural Polymer Private Limited, Ahmedabad. HPMC (K100 M), dicalcium phosphate were purchased from SD Fine Chemicals Ltd (Mumbai, India). PVP K-30 was procured from Loba Chemicals (Mumbai, India). Tramadol HCl was a gift sample from Rantus Pharma Ltd (Hyderabad). All the other chemicals used were of high analytical grade.

2.1. Methods

2.1.1. Preparation of Matrix Tablets. Matrix tablets, each containing 100 mg of Tramadol HCl, were prepared. For determining levels of carboxymethyl xyloglucan, initial trial batches with different concentrations of carboxymethyl xyloglucan were prepared and evaluated for physico-chemical properties of formulation and dissolution studies. In the trial runs, carboxymethyl xyloglucan concentration was varied from 50 to 250 mg. It was observed that as the concentration of carboxymethyl xyloglucan increased, the retarding effect of the formulation also increased, but a phenomenon of burst effect was prominently seen in all the formulations (Figure 1). Hence, to prevent the burst effect HPMC K100M was used. The quantities of other ingredients were kept constant, that is, DCP at 20 mg. Magnesium stearate and talc at 5 mg were used as a lubricant and a glidant, respectively.

Different tablet formulations were prepared by wet granulation technique. All the powders were passed through a sieve of 80 mesh size. Required quantities of drug, polymer, and dicalcium phosphate were mixed thoroughly and a sufficient volume of granulating agent (isopropyl alcohol solution of PVP K-30) was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at room temperature. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Talc and magnesium stearate were finally added as glidant and lubricant, respectively. The tablets were compressed (10 mm diameter, flat punches) using a tablet compression machine, Mini Press-II MT, Rimek. Each tablet contained 100 mg of tramadol HCl and other pharmaceutical ingredients. Prior to the compression, the granules were evaluated for several tests.

2.1.2. Evaluation of Tablets. The tablets were evaluated for different physicochemical parameters such as angle of repose

\[ \text{SI} = \left( \frac{M_t - M_0}{M_0} \right) \times 100, \]  

(1)
where, SI is the swelling index, \( M_t \) is the weight of swollen tablets at respective time intervals, and \( M_0 \) is the weight of tablet at time \( t = 0 \).

**Similarity Factor.** The similarity factor \((f)\) is used for release profile comparison between the test formulation and marketed preparation [21]. It is a logarithmic transformation of the sum squared error of differences between the test \( T_j \) and reference products \( R_j \) over all time points:

\[
f_2 = 50 \times \log \left( 1 + \left( \frac{1}{n} \sum_{j=1}^{n} |R_j - T_j|^2 \right)^{-0.5} \times 100 \right), \tag{2}
\]

where “\( n \)” is number of pull points, “\( R_j \)” is reference profile at time point \( t \), and “\( T_j \)” is test profile at same time point \( t \). The similarity factor fits the result between 0 and 100 as shown in Table 11. It is 100 when test and reference profile are identical and tends to 0 when dissimilarity increases.

**Simplex Centroid Design.** A simplex centroid design [22] was adopted to optimize the formulation variables. In this design three factors were evaluated by changing their concentrations simultaneously and keeping their total concentration constant. The simplex centroid design for a 3-component system \((A, B, \text{and } C)\) is represented by an equilateral triangle in a 2-dimensional space (Figure 2). The amounts of matrixing agent carboxymethyl xylloglucan (carboxymethyl xylloglucan, \( X_1 \)), gelling agent (HPMC K100M, \( X_2 \)), and dicalcium phosphate (DCP, \( X_3 \)) were selected as independent variables as shown in Table 3. Percent release values of drug at 2nd hour and 8th hour were selected as dependent variables. The levels of the three factors were selected on the basis of the preliminary studies carried out before implementing the experimental design.

2.2. Statistical Analysis. The statistical analysis of the simplex centroid design batches was done using Design-Expert 8.0.5 software. To study the influence of each factor on response and behavior of the system within the designed space, response surface plots were generated.

3. Result and Discussion

3.1. Preliminary Trials. In trial batches from \( A_1 \) to \( A_5 \) CM-xylloglucan was used in the range of 50 to 250 mg (Table 1); it displayed a retardation of drug release commensurate to the concentration of polymer.

For the comparison of native xylloglucan and derivative carboxymethyl xylloglucan, trial batches \( M_1 \) and \( M_2 \) each containing 150 mg polymer were prepared (Table 12). Batch \( M_1 \) containing plain xylloglucan sustained-release only for 4 hours while batch \( M_2 \) containing CM-xylloglucan sustained-release up to 7 hours (Figure 10).

The percentage drug release at second hour for \( A_1 \) to \( A_5 \) formulations was in the range of 87.90% to 53.39%, respectively, as shown in Figure 3, while only \( A_3 \) to \( A_5 \) formulations were able to retard drug release up to 7 to 8 hours. It was found from the initial trials that 150 to 250 mg of polymer is required for sustaining drug release up to 8 hours, while only \( A_3 \) to \( A_5 \) formulations were able to retard drug release up to 7 to 8 hours. But at 150 mg concentration (\( A_3 \) batch) release was sustained up to 7 hours so that minimum level should be slightly more than 150 mg, while for 200 and 250 mg concentration release was almost similar, hence, 200 mg was decided as a higher level of the polymer.

The granule characterization of the trial batch formulations \((A_1 \text{ to } A_5)\) was performed. The results of this study are depicted in Table 2 which shows excellent flow properties and compressibility.

3.2. Swelling Study. Swelling study results showed slow and gradual increase in swelling index with time and concentration of CM-xylloglucan, as CM-xylloglucan does not swell instantaneously as soon as it comes in contact with water as shown in Figure 4; this results in burst release due to improper swelling. Therefore, to avoid the burst release effect, we have added HPMC K100 in the small quantity. Swelling
Table 1: Trial batch formulations from $A_1$ to $A_5$.

| Ingredients                   | $A_1$ | $A_2$ | $A_3$ | $A_4$ | $A_5$ |
|-------------------------------|-------|-------|-------|-------|-------|
| Tramadol HCl                  | 100   | 100   | 100   | 100   | 100   |
| TSP                           | 50    | 100   | 150   | 200   | 250   |
| HPMC K100M                    | —     | —     | —     | —     | —     |
| DCP                           | 20    | 20    | 20    | 20    | 20    |
| Talc                          | 5     | 5     | 5     | 5     | 5     |
| Magnesium Stearate            | 5     | 5     | 5     | 5     | 5     |
| PVP K-30                      | 30    | 30    | 30    | 30    | 30    |
| Isopropyl alcohol             | qs.   | qs.   | qs.   | qs.   | qs.   |
| **Total**                     | 210   | 260   | 310   | 360   | 410   |

All quantities in mg.

Table 2: Dissolution model for formulations from $A_1$ to $A_5$.

| Batch code | Release exponent ($n$) | Kinetic constant ($K$) | $R$ | Best fit model |
|------------|------------------------|------------------------|-----|---------------|
| $A_1$      | 0.6948                 | 32.71                  | 0.9692 | Matrix       |
| $A_2$      | 0.7634                 | 28.67                  | 0.9736 | Matrix       |
| $A_3$      | 0.7791                 | 25.36                  | 0.9795 | Matrix       |
| $A_4$      | 0.8372                 | 19.82                  | 0.9817 | Matrix       |
| $A_5$      | 0.6834                 | 15.26                  | 0.9854 | Matrix       |

Non-Fickian.

3.3. Optimization of the Release Rate of Tramadol HCl. The simplex mixture designs are useful when the performance of formulation depends upon relative proportion of ingredients and not on the concentration. The amount of ingredients can be varied keeping the total concentration constant. This design is useful in formulation situations.
before implementing the experimental design. 7 formulations ($F_1$–$F_7$) were prepared as per the experimental design and evaluated for chosen response variables (Tables 4 and 6).

Hence, it was decided to optimize the amount of CM-xyloglucan between 180 to 200mg per tablet in order to have a sustained and complete release of drug at the end of eight to twelve hours. The amounts of matrixing agent carboxymethyl xyloglucan (CM-xyloglucan, $X_1$), gelling agent (HPMC K100M, $X_2$), and dicalcium phosphate (DCP, $X_3$) were selected as independent variables. A statistical model incorporating 7 interactive terms was used to evaluate the responses:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_8X_1X_2 + b_{23}X_2X_3 + b_{13}X_1X_3 + b_{63}X_1X_2X_3,$$  \hspace{1cm} (3)

where $Y$ is the dependent variable, $b_0$ is the arithmetic mean response of the 7 runs, and $b_i$ is the estimated coefficient for the factor $X_i$. The main effects ($X_1, X_2,$ and $X_3$) represent the average result of changing one factor at a time from its low to high value. The interaction terms ($X_1X_2, X_2X_3, X_1X_3,$ and $X_1X_2X_3$) show how the response changes when two or more factors are simultaneously changed. The $rel_2$ Hr and $rel_8$ Hr, respectively, for all 7 batches ($F_1$–$F_7$) showed a wide variation (Figure 5). The data clearly indicate that the values of drug release are strongly dependent on the selected independent variables.

To demonstrate graphically the effect of release modifying polymers on the dissolution profile, contour plots and 3D graphs were generated. The 3D graph (as shown in Figure 6(a)) for $rel_2$ Hr shows that percent drug release at second hour is plotted on $y$-axis where as the concentrations of excipients were plotted on $x$- and $z$-axis. As the concentration of carboxymethyl xyloglucan and HPMC K100M increased from 180 to 200 mg and 10 to 30 mg, respectively, the percent drug release decreased signifying that the polymers have definite effect on drug release, and especially along the axis region of HPMC-K-100M the effect was greater at lower concentration which indicate its effectiveness in controlling burst release is prominent at lower level, whereas the increasing concentration of DCP shows significant effect on drug release at lowest concentration. The contour plot (as shown in Figure 6(b)) for $rel_8$ Hr justifies that optimum formulation complying with the acceptance criteria can be achieved by selecting the formulations near to the upper left side of the triangle-shaped contour plot which is the diagram obtained from the evaluation result of ($F_1$–$F_7$) formulations. Almost similar results were observed with 3D graph (as shown in Figure 7(a)) and contour plot (as shown in Figure 7(b)) for $rel_8$ Hr. Here as the concentration of carboxymethyl xyloglucan increased release retardation effect, also increases due to increase in the diffusion path length and DCP is showing its effect at lower concentration but not at higher concentration, while HPMC-K-100 M is helping to control burst release in initial hours but not showing any release retarding effect at eight hour because it is used in a smaller quantity.

From the dissolution study of seven batches (Figure 5), percent release of drug at two hours ($rel_2$ Hr) was found to be in range of 27.93% to 38.33% and percent release of drug at eight hour ($rel_8$ Hr) was found to be in range of 84.90% to 100.21%.

### Table 4: Composition of $F_1$ to $F_7$ formulations.

| Ingredients                  | $F_1$ | $F_2$ | $F_3$ | $F_4$ | $F_5$ | $F_6$ | $F_7$ |
|------------------------------|-------|-------|-------|-------|-------|-------|-------|
| Tramadol HCl                 | 100   | 100   | 100   | 100   | 100   | 100   | 100   |
| Carboxymethyl xyloglucan     | 200   | 180   | 190   | 180   | 190   | 186.67|
| HPMC-k-100M                  | 10    | 30    | 20    | 20    | 10    | 20    | 16.67 |
| DCP                          | 30    | 30    | 50    | 30    | 40    | 40    | 36.67 |
| Talc                         | 5     | 5     | 5     | 5     | 5     | 5     | 5     |
| Magnesium stearate           | 5     | 5     | 5     | 5     | 5     | 5     | 5     |
| PVP K-30                     | 30    | 30    | 30    | 30    | 30    | 30    | 30    |
| Isopropyl alcohol            | qs.   | qs.   | qs.   | qs.   | qs.   | qs.   | qs.   |
| Total                        | 380   | 380   | 380   | 380   | 380   | 380   | 380   |

All quantities in mg.
TABLE 5: Dissolution model for $F_1$ to $F_7$ formulations.

| Batch code | Release exponent ($n$) | Kinetic constant ($K$) | $R$      | Best fit model |
|------------|------------------------|------------------------|----------|----------------|
| $F_1$      | 0.5919                 | 30.8556                | 0.9874   | Matrix         |
| $F_2$      | 0.5030                 | 36.2863                | 0.9828   | Matrix         |
| $F_3$      | 0.5171                 | 31.8826                | 0.9845   | Matrix         |
| $F_4$      | 0.5008                 | 29.6438                | 0.9870   | Matrix         |
| $F_5$      | 0.5301                 | 27.1364                | 0.9897   | Matrix         |
| $F_6$      | 0.5814                 | 36.9647                | 0.9955   | Matrix         |
| $F_7$      | 0.5049                 | 36.9443                | 0.9957   | Matrix         |

Non-Fickian.

![Graph showing percent drug release at 2nd hour](image1)

**Graph 6**: 3D graph of percent drug release at 2nd hour using different combinations of $X_1$, $X_2$, and $X_3$. The contour lines show percentage of drug release at the end of second hour.

**Graph 6**: Contour plot showing amount of drug release at second hour ($Y_1$) using different combinations of $X_1$, $X_2$, and $X_3$. The contour lines show percentage of drug release at the end of second hour.
Table 6: Pre- and postcompression properties of optimization batches $F_1$-$F_7$.

| Parameters                        | $F_1$    | $F_2$    | $F_3$    | $F_4$    | $F_5$    | $F_6$    | $F_7$    |
|-----------------------------------|----------|----------|----------|----------|----------|----------|----------|
| Bulk density (g/mL)               | 0.387 ± 0.22 | 0.355 ± 0.17 | 0.303 ± 0.11 | 0.409 ± 0.30 | 0.343 ± 0.11 | 0.318 ± 0.16 | 0.366 ± 0.15 |
| Tapped density (g/mL)             | 0.442 ± 0.14 | 0.416 ± 0.35 | 0.426 ± 0.03 | 0.493 ± 0.26 | 0.428 ± 0.05 | 0.374 ± 0.04 | 0.412 ± 0.04 |
| Angle of repose                   | 27.78 ± 0.14 | 26.05 ± 0.08 | 25.55 ± 0.12 | 29.85 ± 0.02 | 28.08 ± 0.16 | 27.08 ± 0.08 | 26.06 ± 0.04 |
| Carr's index                      | 13.44 ± 0.14 | 12.66 ± 0.11 | 12.3 ± 0.16 | 14.43 ± 0.13 | 14.06 ± 0.12 | 13.97 ± 0.17 | 12.17 ± 0.15 |
| Hausner's ratio                   | 1.14 ± 0.18 | 1.17 ± 0.28 | 1.41 ± 0.07 | 1.21 ± 0.28 | 1.24 ± 0.08 | 1.17 ± 0.13 | 1.13 ± 0.11 |
| Hardness (kg/cm²)                 | 5.1 ± 0.33 | 5.3 ± 0.26 | 5.5 ± 0.18 | 5.4 ± 0.34 | 5.7 ± 0.17 | 5.5 ± 0.32 | 5.4 ± 0.13 |
| Friability                         | 0.74 ± 0.21 | 0.70 ± 0.11 | 0.57 ± 0.22 | 0.62 ± 0.16 | 0.42 ± 0.12 | 0.52 ± 0.23 | 0.67 ± 0.22 |
| Uniformity of weight (mg)         | 378.29 ± 0.34 | 379.78 ± 0.45 | 378.98 ± 0.55 | 381.19 ± 0.36 | 382.4 ± 0.12 | 378.56 ± 0.24 | 381.78 ± 0.13 |
| Drug content (%)                  | 100.22 ± 0.22 | 100.62 ± 0.11 | 99.14 ± 0.18 | 98.34 ± 0.39 | 98.72 ± 0.21 | 101.16 ± 0.67 | 98.52 ± 0.89 |
| Thickness (mm)                    | 4.40 ± 0.014 | 4.17 ± 0.016 | 3.89 ± 0.026 | 3.89 ± 0.026 | 3.89 ± 0.026 | 3.89 ± 0.026 | 3.89 ± 0.026 |

±SD (standard deviation) $n = 3$.

Design-Expert software
Component coding: actual
Release in 8hr (%)
- Design points above predicted value
- Design points below predicted value

(a) 3D graph and Contour plot of percent drug release at 8th hour

Design-Expert software
Component coding: actual
Release in 8hr (%)
- Design points

(b) Contour plot of percent drug release at 8th hour

Figure 7: Contour plot showing amount of drug release at twelfth hour ($Y_2$) using different combination of $X_1$, $X_2$, and $X_3$. The contour lines showing percentage of drug release at the end of twelfth hour.
Table 7: Composition of optimum formulations B₁, B₂, and B₃.

| Composition (mg)         | B₁  | B₂      | B₃  |
|-------------------------|-----|---------|-----|
| Tramadol HCl            | 100 | 100     | 100 |
| Carboxymethyl xyloglucan | 194.39 | 190.606 | 200 |
| HPMC-K-100M             | 15.610 | 19.394 | 10  |
| DCP                     | 30  | 30      | 30  |
| Talc                    | 5   | 5       | 5   |
| Magnesium stearate      | 5   | 5       | 5   |
| PVP K-30                | 30  | 30      | 30  |
| Isopropyl alcohol       | qs. | qs.     | qs. |

Table 8: Pre- and post compression properties of optimized carboxymethyl xyloglucan matrix tablets.

| Parameters                | B₁           | B₂           | B₃           |
|---------------------------|--------------|--------------|--------------|
| Bulk density              | 0.312 ± 0.19 | 0.331 ± 0.22 | 0.376 ± 0.16 |
| Tapped density            | 0.351 ± 0.24 | 0.348 ± 0.13 | 0.397 ± 0.09 |
| Angle repose              | 25.03 ± 0.07 | 27.31 ± 0.11 | 29.27 ± 0.03 |
| Carr’s index              | 13.01 ± 0.20 | 13.22 ± 0.17 | 14.21 ± 0.13 |
| Hausner’s ratio           | 1.12 ± 0.21  | 1.05 ± 0.19  | 1.06 ± 0.14  |
| Hardness                  | 5.2 ± 0.03   | 5.1 ± 0.01   | 5.3 ± 0.04   |
| Friability                | 0.542 ± 0.07 | 0.481 ± 0.16 | 0.768 ± 0.18 |
| Weight variation          | 365 ± 1.79   | 387 ± 0.93   | 395 ± 1.04   |
| Drug content              | 99.69 ± 0.17 | 98.61 ± 0.02 | 98.14 ± 0.11 |
| Thickness (mm)            | 3.82 ± 0.03  | 3.96 ± 0.06  | 4.17 ± 0.01  |

±SD (standard deviation) n = 3.

Figure 8: Linear correlation plot for release at 2nd hour.

The equation for percent drug release at the end of the second hour is

\[ Y_1 = +45.15 \times A + 54.19 \times B + 51.44 \times C - 28.40 \times A \times B - 9.78 \times B \times C + 232.81 \times A \times B \times C \]  

(4)

where, A is the carboxymethyl xyloglucan, B is the HPMC, C is the DCP, \( Y_1 \) is the % release at second hour.

3.3.2. Percent Drug Release at Eighth Hour (rel₈ Hr). Model adequacy was checked for percent drug release at eighth hour (rel₈ Hr). Model gave the highest order polynomial where the additional terms were significant and the model was selected. The SCM suggested by the software followed for (rel₈ Hr), with P-value 0.0004 and this indicated the model was highly significant. In order to find out contribution of each component and their interaction, ANOVA for SCM was carried out. The model F-value of 326887 implied that the model was highly significant. Value of P less than 0.05 indicates that model terms were significant. In this case, linear mixture components AB, AC, and A²BC were significant of the analysis of variance (ANOVA), which was used to generate mathematical models. The model F-value (344.65) implied that the model was significant. Value of probability (P) less than 0.05 indicates that model terms were significant. In this case, linear mixture components, AB, BC, and ABC, were significant model terms.
Table 9: The predicted and experimental values of response variables, and their percentage prediction error for $B_1$, $B_2$, and $B_3$ formulations.

| Optimized formulation | Response variable | Experimental value | Predicted value | Percentage prediction error |
|-----------------------|-------------------|--------------------|-----------------|-----------------------------|
| $B_1$                 | $Y_1$             | 41.33%             | 41.95%          | −1.44                       |
|                       | $Y_2$             | 83.78%             | 83.98%          | −0.238                      |
| $B_2$                 | $Y_1$             | 42.52%             | 42.32%          | +0.47                       |
|                       | $Y_2$             | 84.92%             | 84.56%          | +0.425                      |
| $B_3$                 | $Y_1$             | 45.49%             | 45.14%          | +0.775                      |
|                       | $Y_2$             | 87.39%             | 87.89%          | −0.568                      |

Table 10: Analysis of variance (ANOVA) for all two responses.

| Source                | Source | % Release at 2 hour | % Release at 8 hour |
|-----------------------|--------|--------------------|--------------------|
|                       | F-value | P value         | F-value            | P value         |
| Model                 | 344.65  | 0.0409            | 272.39             | 0.004           |
| Linear mixture        | 389.03  | 0.0358            | 162.92             | 0.0003          |
| $AB$                  | 490.78  | 0.0287            | 56.11              | 0.0003          |
| $BC$                  | 58.17   | 0.0830            | 23.94              | 0.0005          |
| $ABC$                 | 741.53  | 0.0234            | 19.97              | 0.0006          |

Table 11: Similarity factor determination.

| Optimized formulations | $f_2$ value | Consideration |
|------------------------|-------------|---------------|
| $B_1$                  | 75          | Similar       |
| $B_2$                  | 70          | Similar       |
| $B_3$                  | 61          | Similar       |

The optimization batches were subjected to short-term stability studies at 40°C and 75% relative humidity (RH) for 3 months. Samples withdrawn after 3 months showed no significant change in dissolution studies and drug content.

4. Conclusion
Sustained drug release following matrix kinetics attained in the current study indicates that the hydrophilic matrix tablet
prepared using carboxymethyl xyloglucan and HPMC-K-100M can successfully be employed sustain the drug release up to 8 to 12 hours as shown in Table 5. carboxymethyl xyloglucan played major role in sustaining release of tramadol at later stage of release profile, whereas HPMC-K-100M prevented the burst effect by controlling the sudden release of drug from the dosage form at the initial stage of the release profile. It was concluded that appropriate balancing between various levels of the polymers may contribute better results. High degree of prognosis obtained using RSM corroborates that a simplex centroid design is quite efficient in optimizing drug delivery systems.

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Table 12: Trial batch formulations of plain xyloglucan and carboxymethyl xyloglucan.

| Ingredients       | Formulations | $M_1$ | $M_2$ |
|-------------------|--------------|-------|-------|
| Tramadol HCl      | 100          | 100   |       |
| TSP               | 150          |       |       |
| CM-TSP            | —            | 150   |       |
| DCP               | 20           | 20    |       |
| Talc              | 5            | 5     |       |
| Magnesium stearate| 5            | 5     |       |
| PVP K-30          | 30           | 30    |       |
| Isopropyl alcohol | qs.          | qs.   |       |
| Total             | 310          | 310   |       |

Figure 10: Dissolution profile for batches $M_1$ to $M_2$.  

![Dissolution profile for batches $M_1$ to $M_2$.](image-url)
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