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# *IN VITRO* RELEASE KINETICS STUDY OF TRAMADOL HCl SUSTAINED RELEASE MATRIX TABLET FROM HPMC K15M

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## ABSTRACT

In the present study, an effort has been made to evaluate of hydroxypropyl methylcellulose HPMC K15M as rate retardant polymer to sustain the release of Tramadol HCl from Tramadol HCl sustained release tablet matrix. Different amount of HPMC K15M were used in formulation of F1 to F5 where drug and polymer ratio were consequently 5:6, 5:5, 5:4, 5:3 and 5:2 in 200 mg tablet matrix. Tablets were prepared by direct compression. The dissolution study of the tablet matrices of different formulations were carried out in the gastric medium (pH 1.3) for first 2 hours and then in the intestinal medium (pH 6.8) for 6 hours using USP dissolution apparatus II. The drug release patterns were simulated in different kinetic orders such as Zero Order release kinetics, First Order release kinetics, Higuchi release kinetics, Korsemeyer-Peppas release kinetics and Hixson-Crowell release kinetics to assess the release mechanism. From the study it was observed that Zero Order release kinetics was the predominant release mechanism than Higuchi and First Order kinetics. Among the formulations of F-1 to F-5, a different amount of HPMC K15M polymer can sustain the release of Tramadol HCl 55.5% to 100% in eight hour.

**INTRODUCTION:** Hydrophilic matrices containing swellable polymers are referred to as hydrogel matrices, swellable sustained release system or hydrophilic matrix tablets. A number of polymers have been investigated to develop *in situ* gel forming systems due to ability of these hydrogels to release an entrapped drug in aqueous medium and to regulate the release of such drug by control of swelling and cross linking [1].

Hydroxy Propyl Methyl Cellulose (HPMC) [5] is the polymer most widely used as the gel forming agent in the formulation of sustained release dosage form. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage form are controlled by the hydration of HPMC which forms a gel barrier through which the drug diffuses [3, 10]. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipientes [7, 8, 9]. The HPMC matrix can modify the drug release rate.

Tramadol is used in the treatment of osteoarthritis when nonsteroidal antiinflamatory drug (NSAIDS), acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. After oral administration, Tramadol is rapidly and almost completely absorbed. Sustained release tablets reach to peak concentration after 4.9 hours and have a bioavailability of 87%-95%. The mean elimination half life is approximately 6 to 8 hours and requires dosing every 6 hours in order to maintain optimal relief of chronic pain.

As a result an attempt made to formulate once daily extended release tablets. Long term treatment with sustained release Tramadol HCl is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated. It has the potential to provide patients more control over the management of their pain, fewer interruptions in sleep and improved compliance.

**MATERIALS AND METHOD:**

**Materials**: Tramadol Hydrochloride from ACI Pharmaceuticals Ltd. Bangladesh, Hydroxy Propyl Methyl cellulose K15M, Lactose, Microcrystalline cellulose (Avicel pH 101), Magnesium Stearate, and Talc was obtained from Dhaka University laboratory [12].

**Preparation of Matrix Tablet:** Drug, polymer and other excipients [1] were weighed separately for each tablet per formulation according to proposed formulations shown in **Table 3**. The proposed formulations were coded as F-1, F-2, F-3, F-4 and F-5. All the amounts of drug and excipients are in milligram unit. Then Active ingredient (Tramadol HCl), polymer (HPMC K15M), and excipients (Avicel, lactose) were blended for 15 minutes and then Magnesium Stearate was added and was blended for another 1 minute. Blended mass was taken in the hopper and then die and punch were adjusted to get the desired weight of the tablet (200 mg). After Direct compression [13] the tablets were weighed and tablet weight was found between 198 mg to 202 mg [18].

**Physical evaluation of Granules:**

1. **Bulk density:** The bulk density of a powder is dependent on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength than a less consolidated one and may therefore be more resistant to powder flow.

   The ease with which a powder consolidates can be used as an indirect method for quantifying powder flow. LBD (Loose Bulk Density) and TBD (Tapped Bulk Density) were determined by 2g of powder from each formula, previously lightly shaken to break any agglomerates formed, was placed into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The reading of tapping was continued until no further change in volume was noted. Using the following equation LBD and TBD was calculating [4].

   LBD = Weight of the powder/volume of the packing

   TBD = Weight of the powder/Tapping volume of the packing

2. **Compressibility index:** The compressibility index of the granules was determined by Carr's compressibility index [2]

   Carr's index (%) = {(TBD-LBD) x 100}/TBD

**TABLE 1: CAR'S INDEX PROPERTIES**

| % Compressibility | Flow description |
|---|---|
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | Fair |
| 23-28 | Poor |
| 28-35 | Poor |
| 35-38 | Very Poor |
| >40 | Extremely Poor |

3. **Total porosity**: Total porosity was determined by measuring the volume occupied by a selected weight of powder (V bulk) and the true volume of granules (the space occupied by the powder exclusive of spaces greater than the intermolecular space (V)

   Porosity (%) = Bulk-V/V bulk x 100

4. **Angle of repose:** The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the power cone was measured and angle of repose was calculated using the following equation

   Angle of repose, $\theta = \tan^{-1} h/r$

Where, h= Height of the powder cone; r= Radius of the powder cone.

5. **Drug content**: An accurately weighed amount of powdered Tramadol HCl (200 mg) was extracted with diluents and the solution was filtered through 0.45 µ membrane filter paper. The absorbance was measured at 271 nm after suitable dilution.

6. **Flow properties**: It is very important parameter to be measured since it affects the mass of uniformity of the dose. It is usually predicted from Hausner ratio and angle of repose measurement.

Hausner Ratio = Tapped Density/Bulk Density

**TABLE 2: HAUSNER RATIO**

| Hausner ratio | Type of flow |
|---|---|
| Less than 1.25 | Good Flow |
| 1.25-1.5 | Moderate |
| More than 1.5 | Poor Flow |

7. **Surface area:** As the shape of the tablet is round flat, it can be compared with a cylinder. Surface area of a cylinder is calculated by

Cylinder surface area = $\pi r^2 h$

Where, r = diameter of tablet in $mm^2$; h= thickness of the tablet in mm

8. **Hardness and Friability**: For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto harness tester and the Roche friabilator respectively.

9. **Thickness**: The thickness of the tablet was determined using a thickness gauge. Five tablets from each batch were used, and average values were calculated.

10. **Weight variation test:** To study weight variation, 20 tablets from each formulation were weighed using an Electronic balance and the test was performed according to the official method.

11. **Drug content (Drug potency)**: Five tablets were weighed individually, and the drug was extracted with diluents. The solution was filtered through 0.45-µ membrane filter paper. The absorbance was measured at 271 nm after suitable dilution.

12. **Preparation of Calibration curve**: Calibration curve for the estimation of Tramadol HCl content in the dissolution medium: To prepare a standard solution, 20 mg of Tramadol HCl was measured in an analytical balance (sartorius, Germany) and dissolved in 1000 ml Distilled water to produce a solution of 20 µg / ml. 1,2,3,4,5,6,7,8 and 9 ml of this solution was taken in test tube and 9,8,7,6,5,4,3,2 and 1 ml water was added to them respectively for the purpose of serial dilution. 10 ml of standard solution is also taken in a volumetric flask. The solutions were mixed well using vortex mixer. These serial dilutions allowed Tramadol HCl concentration to be made in the range of 2 µg / ml to 20 µg / ml. Then absorbance of the solutions was measured at 271 nm using UV spectrophotometer. A plot was constructed showing concentration at X- axis and absorbance at Y- axis.

13. ***In vitro* Dissolution Study of the Tablet Matrix:** Dissolution studies were conducted according to USP method (USP XXII) [17] using apparatus II paddle at a speed of 100 rpm and the temperature was maintained at 37.0±0.5o C. The USP paddle system consisted of six glass vessels. These vessels contained the dissolution medium. The total duration of dissolution was 8 hours in which the tablet matrices were subjected to gastric media (0.1 N HCl pH 1.5) for 2 hours and the later hours the tablet matrices were subjected to intestinal media (Buffer pH 6.8) [14, 15, 16] .

14. **Acid stage**: 900 ml of 0.1 N HCl was placed in each vessel and the apparatus was assembled. Six tablets from one formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 2 hours. After each hour 5 ml of sample solution was withdrawn and same volume of fresh medium was replaced. The released drug was assayed by using UV spectrophotometer at 271 nm. Percentage of drug release was calculated using an equation obtained from the standard curve [11].

15. **Buffer Stage**: 900 ml of intestinal buffer media was placed in each vessel and the apparatus was assembled. Six tablets from each formulation were weighed and placed in the baskets. The operation in the acid stage was carried out for 6 hours. After each hour 5 ml of sample solution was withdrawn and same volume of fresh medium was replaced.

The released drug was assayed by using UV spectrophotometer at 271 nm. Percentage of drug release was calculated using an equation obtained from the standard curve.

16. **Kinetic Study:** Further to understand the order and mechanism of drug release the data was subjected to various kinetic equations and plotted according to zero order, Higuchi, Korsymere's Peppas and Hixson-Crowell. The kinetic values obtained from different plots are listed in **table 7**.

**RESULTS:** The dissolution study of five formulations are given bellow;

F-1: After dissolution of tablets the percent release of drug after 8 hour was 55.44%.

F-2: After dissolution of tablets the percent release of drug after 8 hour was 68.18%.

F-3: After dissolution of tablets the percent release of drug after 8 hour was 85.87%.

F-4: After dissolution of tablets the percent release of drug after 8 hour was 95.94%.

F-5: After dissolution of tablets the percent release of drug after 8 hour was 100%.

The aforementioned dissolution study indicates that with the decrease of drug to polymer ratio; increase the percent of release of drug.

**DISCUSION:** After dissolution study the drug release patterns were simulated in different kinetic orders such as Zero Order release kinetics (**figure 1**), First Order release kinetics (**figure 2**), Higuchi release kinetics [6] (**figure 3**), Korsmeyer-Peppas release kinetics (**figure 4**) and Hixson-Crowell release kinetics (**figure 5**) to assess the release mechanism.

F-1: In this formulation Tramadol HCl and HPMC K15M ratio is 5:6. Best fitted model for this formulation was First order (R2=0.992) and Hixson-Crowell (R2=0.994) model.

F-2: In this formulation Tramadol HCl and HPMC K15M ratio is 5:5. Best fitted model for this formulation were zero order ($R^2$=0.994) and Korsmeyer-Peppas ($R^2$=0.986) model.

F-3: In this formulation Tramadol HCl and HPMC K15M ratio is 5:4. Best fitted model for this formulation were zero order ($R^2$=0.986).

F-4: In this formulation Tramadol HCl and HPMC K15M ratio is 5:3. Best fitted model for this formulation were zero order ($R^2$=0.975) model.

F-5: In this formulation Tramadol HCl and HPMC K15M ratio is 5:2. Best fitted model for this formulation were zero order ($R^2$=0.984) and Korsmeyer-Peppas ($R^2$=0.987) model.

From the study, we observed that Zero Order release kinetics was the predominant release mechanism than Higuchi and First Order kinetics. Among the formulations of F-1 to F-5, a different amount of HPMC K15M polymer can sustain the Release of Tramadol HCl 55.5% to 100% in eight hour.

**CONCLUSION:** The half life of Tramadol HCl is 5.5-7 hour for oral dosage. Due to short half life (5.5-7hr) and its higher water solubility make this drug a suitable candidate for sustained release dosage forms. From this study it was concluded that HPMC K15M CR met the desired sustained release properties.

We also observed that zero order release kinetics was the predominant release kinetics among Higuchi, Korsmeyer-Peppas, Hixson-Crowell, Zero Order, and First Order release kinetics.

Direct compression method may be appropriate for higher productivity, performance, and as results it saves valuable time in manufacturing time, reduce involvement of labor, reduce cost and increase profit.

The proposed formulations may be used for the development of Tramadol HCl release matrix to meet the patient's demand in order to combat against pain more precisely.

**TABLE 3: FORMULATION OF BATCH F1 TO F5**

| Ingredients (mg)/tablet | Formulation no. | | | | | |
|---|---|---|---|---|---|---|
| | Justification | F1 | F2 | F3 | F4 | F5 |
| Tramadol | API | 50 | 50 | 50 | 50 | 50 |
| HPMCK15M | Polymer | 60 | 50 | 40 | 30 | 20 |
| Avicel 101 | Diluent | 25 | 25 | 25 | 25 | 25 |
| Mg Stearate | Lubricant | 5 | 5 | 5 | 5 | 5 |
| Lactose | Diluent | 60 | 70 | 80 | 90 | 100 |
| **TOTAL (in mg)** | | 200 | 200 | 200 | 200 | 200 |

**TABLE 4: THE TABLETS OF DIFFERENT FORMULATIONS (F-1 TO F-5) WERE EVALUATED**

| Formulation no | Weight Variation (mg) | Diameter (mm) | Thickness (mm) | Hardness (kg) | Friability (%) |
|---|---|---|---|---|---|
| F1 | 200 ± 0.97 | 8.40 ± 0.05 | 2.28 ± 0.05 | 6.6 ± 0.2 | 0.62 |
| F2 | 200 ± 0.68 | 8.50 ± 0.06 | 2.31 ± 0.06 | 6.2 ± 0.4 | 0.51 |
| F3 | 200 ± 0.56 | 8.62 ± 0.04 | 2.24 ± 0.04 | 6.3 ± 0.3 | 0.42 |
| F4 | 200 ± 0.02 | 8.36 ± 0.07 | 2.26 ± 0.06 | 6.7 ± 0.3 | 0.31 |
| F5 | 200 ± 0.48 | 8.50 ± 0.06 | 2.34 ± 0.02 | 6.5 ± 0.3 | 0.32 |

**TABLE 5: PHYSICAL PROPERTIES OF GRANULES OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

| Formulation | Loose bulk density (LBD) gm/ml | Tapped bulk density (TBD) gm/ml | Carr's index (%) | Hausner ratio | Total porosity (%) | Moisture content (%) | Angle of Repose( o) |
|---|---|---|---|---|---|---|---|
| F-1 | 0.35±0.02 | 0.50±0.03 | 30.00 | 1.43 | 14.3 | 2.22 | $26^{\circ}$ ±2 |
| F-2 | 0.42±0.03 | 0.54±0.02 | 22.22 | 1.29 | 16.4 | 2.54 | $27^{\circ}$ ±3 |
| F-3 | 0.44±0.02 | 0.49±0.03 | 10.20 | 1.11 | 13.4 | 1.48 | $29^{\circ}$ ±2 |
| F-4 | 0.46±0.01 | 0.55±0.03 | 16.36 | 1.20 | 12.4 | 1.96 | $26^{\circ}$ ±2 |
| F-5 | 0.48±0.02 | 0.52±0.01 | 12.69 | 1.08 | 16.3 | 1.86 | $27^{\circ}$ ± 3 |

**TABLE 7: ZERO ORDER RELEASE PROFILE OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

| Time | Cumulative % of drug release | | | | |
|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 |
| 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 5.23 | 12.65 | 19.79 | 21.84 | 25.67 |
| 2 | 15.41 | 19.55 | 29.69 | 31.80 | 39.41 |
| 3 | 21.63 | 26.78 | 36.08 | 38.20 | 47.39 |
| 4 | 29.23 | 32.66 | 43.34 | 47.34 | 59.45 |
| 5 | 35.48 | 41.16 | 57.43 | 54.59 | 72.97 |
| 6 | 40.65 | 48.74 | 63.64 | 63.36 | 85.18 |
| 7 | 48.78 | 59.33 | 73.87 | 82.69 | 100 |
| 8 | 55.44 | 68.18 | 85.87 | 95.94 | |

**TABLE 8: RELEASE RATE CONSTANTS AND $R^2$ VALUES FOR DIFFERENT RELEASE KINETICS OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

| Formulation No. | Zero order | | First order | | Higuchi | | Korsmeyer-Peppas | | Hixson- Crowell | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $K_o$ | $R^2$ | K1 | $R^2$ | $K_h$ | $R^2$ | n | $R^2$ | $K_{hc}$ | $R^2$ |
| F1 | 6.945 | 0.996 | -0.043 | 0.989 | 20.41 | 0.920 | 1.086 | 0.983 | 0.136 | 0.994 |
| F2 | 8.092 | 0.994 | -0.057 | 0.959 | 23.80 | 0.920 | 0.809 | 0.986 | 0.173 | 0.977 |
| F3 | 9.916 | 0.986 | -0.093 | 0.923 | 29.70 | 0.946 | 0.687 | 0.959 | 0.251 | 0.964 |
| F4 | 10.76 | 0.975 | -0.136 | 0.763 | 31.92 | 0.917 | 0.687 | 0.959 | 0.319 | 0.847 |
| F5 | 13.21 | 0.984 | -0.126 | 0.947 | 36.78 | 0.955 | 0.656 | 0.987 | 0.337 | 0.977 |


**FIGURE 1: ZERO ORDER PLOT PROFILE OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

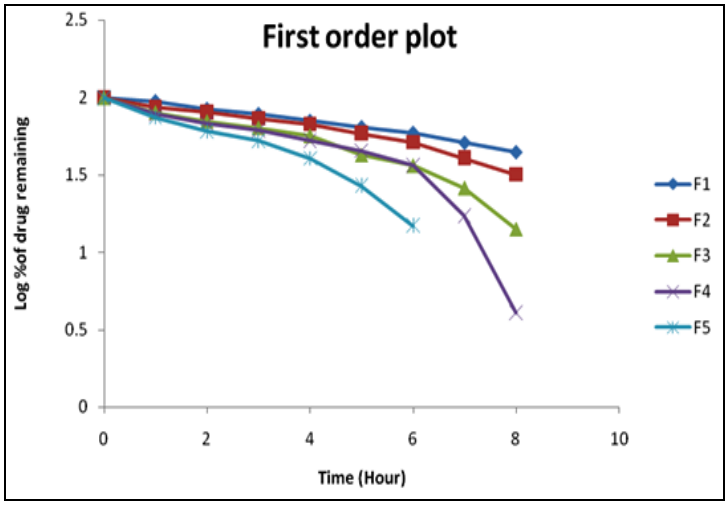


**FIGURE 2: FIRST ORDER PLOT OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

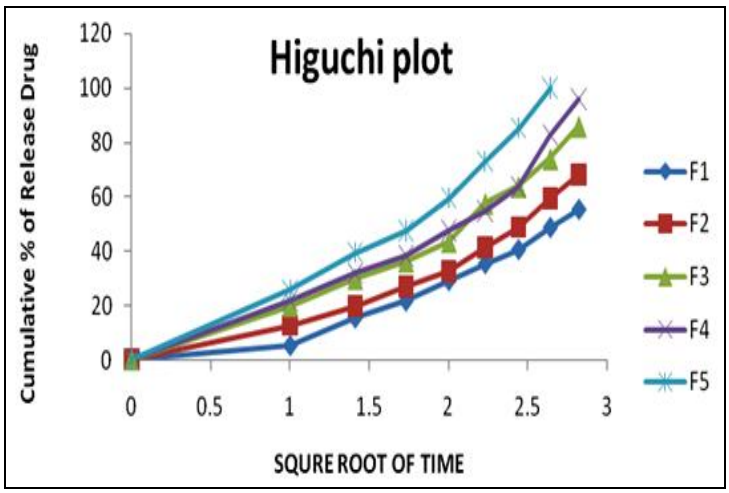


**FIGURE 3: HIGUCHI PLOT OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

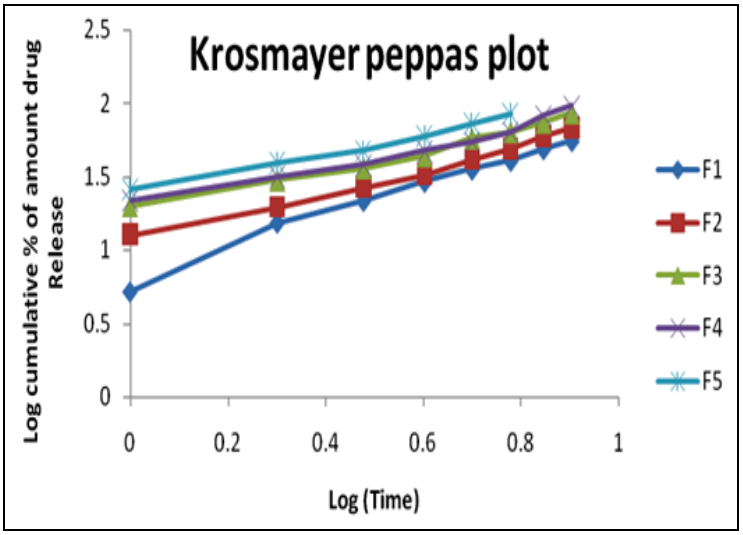


**FIGURE 4: KORSMEYER- PEPPAS PLOT OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

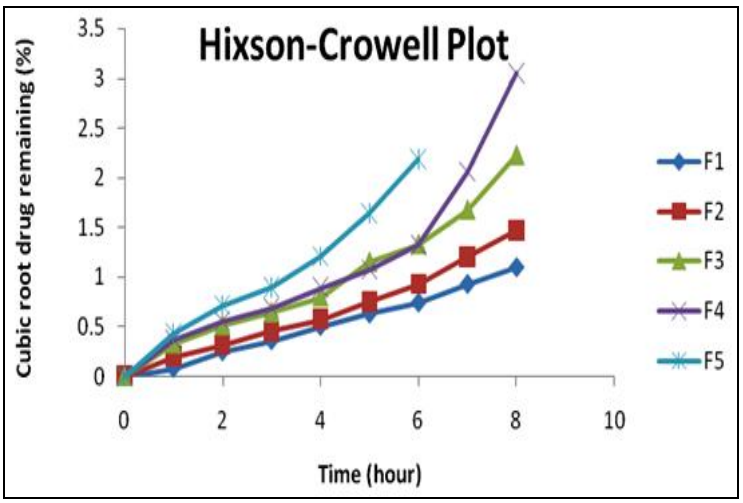


**FIGURE 5: HIXON-CROWELL PLOT OF FIVE FORMULATIONS (F-1 TO F-5) OF TRAMADOL HCl MATRIX TABLETS**

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