Formulation Development and Optimization of Intermediate Release Metoclopramide HCl Tablets by Central Composite Rotatable Design for IVIVC Studies

Ahmad Khan*, Jallat Khan, Maria Zafar, Muhammad Irfan, Imran Rabbani

Abstract- The objective of this study was development and optimization of intermediate release formulation for IVIVC study of metoclopramide HCl. A four steps simple and cost effective study was performed. The first step was to study the micromeritic properties of different powder blends with and without metoclopramide HCl (Placebo). In second and third step, central composite design (CCRD) was used for intermediate release metoclopramide tablets. In the last step stability studies of three selected metoclopramide HCl tablet formulations which were calculated using R Gui software. Varying concentrations of excipients, HPMC K4M cps, Avicel PH-102, and lactose DC were used as variables in CCRD. Preformulation studies of two blended powders i.e. placebo and metoclopramide HCl were done to evaluate the angle of repose, loose bulk density, tapped bulk density, and compressibility index. Blending rate constant was performed at different mixing times i.e. 5, 7, 12, and 15 minutes. Out of twenty intermediate release formulations, three (F1, F7, F10) were subjected to direct compression on the basis of compressibility index. Physicochemical properties and in-vitro kinetic studies in different dissolution media were measured successfully. Simple experimental studies were performed to determine relative densities, tensile strength of tablets, hardness, weight variation, friability, disintegration and dissolution of tablets. Presence of metoclopramide HCl in the powder blend enhanced all the micromeritics properties. 12 minutes was found to be the best mixing time. The increase in relative density resulted in increase in hardness of tablets containing metoclopramide HCl. The analysis of release pattern was done using model dependent kinetic approaches i.e. zero order kinetics, first order kinetics, Hixon Crowell, Higuchi kinetics, Hopfenberg model, and pappas, Baker and Lonsdale model, Weibull model, Korsmeyer and pappas, Baker and Lonsdale model, Weibull model, Hopfenberg model and pappas Sahlin model; and model independent kinetic models using f1 and f2 values. F10 showed the best result in stability studies having shelf life of 64 months calculated by RGui.

Keywords: Metoclopramide HCl, Intermediate release, stability studies, central composite design, model dependent and model independent kinetic models.

1. INTRODUCTION

Metoclopramide is a medication used for stomach and esophageal problems and in the treatment of nausea and vomiting. It is included in the WHO’s list of essential medicines [1].

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Metoclopramide was one of the top 100 most prescribed medications in the United States in 2012 [2]. The quality control of tablets is judged through various important parameters like micrometric properties of powder blend. Accurate characterization of particle size, physicochemical nature of powders, porosity and hardness of tablets, tensile strength and elastic modules of tablets are best determined through a fundamental property called as true density of powder [3-5]. Micromeritic properties are greatly influenced by the different compositions of powders. Different ratios of excipients used in designing formulations and presence of active ingredient show a change in porosity, relative density, and disintegration. The use of sensitive instruments and complex structure of active ingredients like amorphous, crystalline structure makes the calculations of physicochemical properties a bit difficult. The nature of physicochemical properties of the active ingredient has a fundamental role in formulation development. Different crystalline forms provide an advantage in designing a formulation whereas some unfavourable properties of dosage form lead towards the ideas of different modified release pattern. The literature illustrates a number of examples of accuracy and suitability of using one crystalline form of API inspite of other having unfavourable properties [6, 7]. The crystalline form of metoclopramide exhibits intricacy in predicting its compatibility with excipients. 4-amino-5-chloro-N-(2-(diethylamino)ethyl)-2 methoxybenzamide shows less compatibility and low solubility with most of the excipients. Moreover sensitivity of porosimeter to this compound also added the situation more badly. Various statistical models i.e. central composite designs, full factorial, and fractional factorial are used in the new drug development as well as in optimizing methods used in pharmaceutical drug developments. The selection of central composite rotatable design (CCRD) overcame the drawback of using the excessive concentrations rather than central one [8]. In this study a successful comparison and analysis of micromeritic properties of two blends of powders i.e. placebo blend and metoclopramide containing blend with intermediate release metoclopramide tablets was done. Intermediate release metoclopramide tablets having different concentrations of HPMC, Avicel PH-102 and lactose DC were made through direct compression method. CCRD model was applied to these intermediate release metoclopramide tablets.
Model dependent and model independent approaches were used to study the release pattern of metoclopramide formulations with the help of Microsoft Excel based program DD Solver. Furthermore, freely available software R Gui was used to analyze the results of long term stability studies of three selected intermediate release formulations. The maximum, minimum and median values of excipients are calculated by different formulae as given in table 1 and the values generated by software are given in table 2.

II. MATERIALS AND METHODS

Materials Used
Metoclopramide HCl was gifted by Indus Parma (Pvt) limited Pakistan. HPMC K4M cps and Avicel PH-12 were purchased from Dow chemical Co., US and FMC Corporation, USA. Maxolon® tablets were purchased from local market. The other materials used in the experiments were of analytical grade.

Softwares Used
Stability analysis and shelf life studies were done by using an adds on program in Microsoft excel (DD Solver) and 2.13 version of R Gui (CARNI Packages). Version 8.0.4 of Design-Expert® (Stat-Ease, Inc) was used for formulation development and optimization.

Loose bulk and Tapped bulk densities
Following equations were used to calculate loose and tapped bulk densities using a glass cylinder.

\[ \rho_b = \frac{M}{V_b} \]  
\[ \rho_t = \frac{M}{V_t} \]  

Compressibility index (%) = \( \frac{\rho_l - \rho_t}{\rho_t} \times 100 \)

Where \( \rho \) is the density whereas “b” and “t” denote bulk and tapped values respectively.

Blending rate constant
Blending rate constant was used to analyze the dose uniformity of tablets. The assay was done by using 20 tablets out of 30 randomly selected tablets from each formulation. The experiment was repeated thrice and the results were found within the range (85-110%)

RSD% was calculated by using the following equation.

\[ RSD\% = \frac{S.D}{\text{Mean}} \times 100 \]  

Where S.D is standard deviation.

Preparation of placebo tablets
Single Punch Compression Machine (Korsch, Erweka, Germany) was used to prepare placebo tablets by direct compression method. The powder mixture was blended for 12 minutes with barrel type mixer. Tablets with 135-223 mg weight and varying thickness were prepared using different concentration of excipients as shown in table 3.

Preparation of Metoclopramide HCl tablets
Out of twenty, three formulations F1, F7 and F10 were selected for direct compression method using Single Punch Compression Machine (Korsch, Erweka, Germany). HPMC, Avicel PH-102, and lactose DC all were in their acceptable ranges [9]. They were accurately weighed, mixed for 12 minutes with tumbler mixer and tablets were compressed.

Measurement of tablet tensile strength
Hardness Tester (OSK Fujiwara, Ogawa Seiki Co. Ltd. Japan) was used for the calculations of crushing load. Following equation was used to calculate the Tensile strength (T).

\[ T (\text{MPa}) = \frac{2F}{\pi d^2/4} \times \frac{1}{1000} \]  

Where F (N) is the crushing load, H (cm) and D (cm) are the thickness and diameter of tablet respectively.

Relative Density
Analytical Balance (Sartorius, Germany) was used to measure the mass and Vernier Caliper (Seikobrand, China) was used to calculate the thickness and diameter of placebo and metoclopramide tablets [10]. Following equations were used to calculate the densities and relative densities.

\[ P_t = \frac{M}{\pi h d^2/4} \]  
\[ P_t = \frac{P_{\text{tablet}}}{P_{\text{Powder}}} \]

P is the density in g/cm³.

Porosity of tablets
True density of tablets \( \rho \) (g/cm³) and true density of powders \( \rho_b \) (g/cm³) were used to calculate the percentage porosity of tablets \( \epsilon \) (%) using the following equation.

\[ \epsilon(\%) = \left(1 - \frac{1}{\rho_b}\right) \times 100 \]

A micrometer was used to measure the thickness and diameter of the tablet for the calculation of tablet volume.

Disintegration time
USP Basket Rack Assembly (Erweka ZT2, Heusenstamm, Germany) was used to estimate the disintegration time of metoclopramide HCl tablets. Temperature was maintained at 37±5°C using water as disintegration media.

Multiple point Dissolution studies
USP Dissolution Apparatus II (DT 600 HH, Erweka, Germany) was used to carry out the dissolution studies of metoclopramide HCl tablets. 6 tablets from each formulation were selected for evaluation using USP [11] USP Apparatus type II paddle rotating apparatus at 50 rpm. The dissolution conditions were: 900 ml dissolution medium, distilled water, 0.1 M HCl (pH 1.2), phosphate buffer (pH 4.5 and 6.8). Approximately 10 ml aliquots of the dissolution medium were removed at 0.05, 0.1, 0.5, 0.75, 1, 1.25, 1.50, 2, 3, 3.5, 4, 5, 6, 8, 10 hours for intermediate release formulations and subjected to estimate the drug concentrations by UV/Visible Spectrophotometer (UV-1800, Shimadzu, Japan) at \( \lambda = 309 \) nm. Each time the sample was replaced by fresh media to maintain sink conditions up to 10 hours for intermediate release metoclopramide tablets. The estimation of metoclopramide concentration in intermediate release metoclopramide tablets by HPLC method was already reported by Ahmad et al 2012.

In-Vitro Kinetics
Model Independent approaches
Following formulae were used to calculate the similarity (f₂) and dissimilarity (f₁) factors respectively.
\[ f_1 = \left[ \frac{\sum R_i - T_i}{N^2 - 1} R_i \right] \times 100 \]  
\[ f_2 = 50 \times \log \left\{ 1 + \left( \frac{1}{n} \right) \sum (R_i - T_i)^2 \right\}^{-0.5} \times 100 \]

Model Dependent approaches

An Excel based program DD Solver was used to analyze model dependent kinetics. Following formulae were used for this purpose.

Zero order kinetics

\[ Q = K_o t \]

Where \( Q \) = the drug release at \( t \), \( K_o \) = zero order rate constant and \( t \) = time. \( K_o \) is the slope of the straight line obtained by drawing graph between %age drug release and time.

First order kinetics

\[ \ln Q = \ln Q_0 - K_t \]

Where \( Q \) = the drug release at \( t \), \( Q_o \) = initial drug release and \( K_t \) is constant and \( t \) = time.

Higuchi kinetics

\[ Q = k_{H} t^{1/2} \]

Where \( K \) = release rate constant, \( t \) = time and \( Q \) = the drug release.

Hixon and Crowell cube root law

\[ Q^{1/3} = Q_0^{1/3} = k_{HC} t \]

Where \( Q_0 \) = initial amount of drug, \( Q_t \) = remaining amount of drug, \( t \) = time, \( k_{HC} \) = constant. The linear graph between cube root of the drug not released and time will be obtained only when the equilibrium is not achieved. \( k_{HC} \) shows the surface to volume relation of the pharmaceutical dosage form.

Korsemeyer and peppas model

\[ \frac{m_t}{m_{\infty}} = k t^n \]

Where \( m_t \) = fraction drug released at \( t \) = time, \( n \) = diffusional exponent, values of which \( n=0.5 \) for Fickian, \( 0.5<n<1 \) for anomalous, \( n=1 \) for case II or zero order and \( n>1 \) for super case II transport. This model is used for polymer based formulations involving multiple phenomenon with unknown mechanism of drug release [12].

Baker and Lonsdale model

\[ \frac{3}{2} \left( 1 - \left( 1 - F \right)^{2/3} \right) - F = k_{BL} t \]

Where \( F \) = the fraction of drug release at \( t \) = time and \( k_{BL} \) = release rate constant. A modification of Higuchi Kinetics for the drug release from spherical matrix [13].

Weibull model

\[ m = 1 - \exp \left[ -\left( \frac{t - T_i}{\alpha} \right)^p \right] \]

The equation 17 can be rearranged as follows

\[ \log [ -\ln (1 - m) ] = b \log (t - T_i) - \log \alpha \]

A linear relation can be obtained by the log-log plot of – \( \ln(1-m) \) versus time \( t \), the slope of which is the shape parameter (\( \beta \)) obtained from slope. This equation can be used to illustrate different types of dissolution curves.

Hopfenberg Model

\[ F = 100 [1 - (1 - k_{HB} t)^n] \]

Where \( F \) is the fraction of the drug released and \( t \) is time. \( “n” \) values 1, 2 and 3 for slab, cylinder and sphere respectively [14]. The basis of this model is on an assumption that the erosion of matrix is the only rate limiting step of drug release and other factors don’t affect that.

Stability Studies

The accelerated stability studies were carried out for a period of 6 months by following ICH guidelines. Three optimized intermediate release formulations were selected. The conditions were 40 °C ± 2 °C/70 % ± 5% RH. The dissolution and drug concentration were determined monthly. R Gui software was used to determine the shelf lives of optimized formulations (ICH QIA (R2), 2003).

III. RESULTS

Micromeritic properties of placebo and metoclopramide containing powder blends were found to be within pharmacopoeial limits. The selection of equal amounts of excipients in both powder blends was done using central composite design (Table 3). Blending rate constant was 12 minutes. Placebo and metoclopramide containing powders are compared in table 4. Table 5 shows the details of all physicochemical properties. The selected optimized intermediate release formulations showed first order release pattern (Table 6). Figure 1(a, b, c) shows the response surface methodological graphs while figure 2(a, b, c, d) show the metoclopramide HCI release rate in different buffer media.

IV. DISCUSSION

The presence of crystalline metoclopramide HCl in the powder blends caused to alter the micromeritic properties as indicated by results. Michel et al reported similar findings in 2008 while studying the effect of active pharmaceutical ingredient on physicochemical properties of tablets [15]. In case of metoclopramide containing blend, the decreased void spaces resulted in increase in bulk density and tapped density was increased due to crystalline nature of metoclopramide HCl. The crystalline nature caused the compression of excipients in a structured manner and increased flow properties due to metoclopramide HCl affinity with magnesium stearate while its affinity with excipients resulted in decrease in angle of repose. The differences in physicochemical properties of both placebo and metoclopramide HCl containing blends are shown in table 5 [16, 17]. Blending rate constant through assay method was applied to overcome the problem of exact amount of API in metoclopramide HCl formulations. 12 minutes blending time was the best time for the analysis of accurate amount of metoclopramide HCl. The relative standard deviation was found to be less than 6% which meets the basic criteria for tablets and capsules dosage form [18, 19]. Further process was carried out using fixed 12 minutes blending time.
The physical parameters i.e. hardness, friability, weight variation and release patterns in different buffer media i.e. buffers of pH 1.2, 4.5 and 6.8 are greatly influenced by the different concentrations of water soluble HPMC. Best release patterns were shown by the formulations F-10, figure 1(a) shows the response surface methodology graphs having cleared the effect of excipients on disintegration time. The formulation having the Avicel PH-102 shows altered disintegration time due to its direct effect on disintegration as shown in figure 1(a). A comparative analysis of the physical properties (hardness, weight variation, thickness, relative density and disintegration) of placebo and metoclopramide HCl containing tablets was done. Different properties showed different behavior. There was an increase in hardness and disintegration time while the crystalline nature of metoclopramide HCl caused a decrease in friability. Effect of HPMC and lactose DC on hardness and friability are shown in figures 1(b) and 1(c) respectively. The remaining physical properties showed negligible change. The physicochemical parameters are shown in table 5. They were within acceptable limits. Table 5 shows the tablet tensile strength, porosity and relative density. All were within acceptable limits. Dissolution studies were used to analyze and compare the release patterns of optimized formulations and reference brand (Maxolon®). Release of metoclopramide HCl from the formulated tablet decreases due to HPMC because of the increased complexity and formation of matrix as shown in figures 2 (a, b, c, d) [18]. It was observed that F10 was found to show the best results due to the adoption of all the parameters of physicochemical, stability studies and quality control. The results also showed that the kinetic studies using model independent approaches were comparatively more effective than model dependent approaches. The values of various kinetic models to study in vitro release pattern using different buffer media for intermediate release formulations are given in the table 6. The results for zero and first order regression values of intermediate release formulations F1, F7 and F10 in dissolution media of pH 1.2 were 0.740 to 0.749 and 0.809 to 0.812, buffer media of pH 4.5 were 0.777 to 0.781 and 0.802 to 0.899, buffer media of pH 6.8 were 0.746 to 0.789 and 0.870 to 0.898, and distilled water were 0.651 to 0.681 and 0.859 to 0.878. The relationship between models and geometry of dosage form from the calculation of regression values was established by Dash et al. in 2010. The Higuchi r² values for optimized intermediate release formulations in different buffer media of pH 1.2, 4.5, 6.8 and distilled water were 0.948 to 0.999, 0.961 to 0.984, 0.954 to 0.989 and 0.874 to 0.980 respectively. The data from the results in table 6 indicated that the regression values for zero order, first order and Higuchi kinetic model were near to standard value. The drug release can be controlled by using hydrophilic drug delivery systems as they have tendency to influence the release profiles, cost effective products and wide Food and Drug Administration (FDA) acceptance [20]. Type and level of excipient greatly influences the rate and extent of drug release from controlled release tablets containing HPMC [21]. Release rate can be modified by changing the polymer type, excipient and manufacturing process [22]. Roszdy and coworkers investigated the impact of controlled release formulations containing various gel forming excipients i.e. HPMC, HPC and carbomer on in-vivo tablet performance and IVIVC of the formulations [23]. HPMC is relatively stable at pH 1-13 as long as other excipients in the formulation are unaltered. Drug dissolution profiles of formulations containing HPMC are independent of pH [24]. The intermediate release metoclopramide HCl showed zero order release pattern at higher pH 6.8 and first order release at lower pH 1.2. The value of n less than 0.45 in Korsemeyer and Peppas model showed Fickian diffusion due to the presence of matrix forming hydrophilic polymer (HPMC) in the formulations. Sigmoid shape was observed in Weibull model and value of β was less than 1. Table 7 shows the values of similarity and dissimilarity factors of intermediate release formulations. According to FDA standard, the similarity values between 50 and 100 indicates the similarity between two dissolution profiles [25]. Similarity factor values for intermediate release formulations F1, F7 and F10 were 31.62, 34.64 and 27.24 in pH 1.2, 33.90, 35.27 and 29.20 in pH 4.5, 27.11, 29.96 and 25.18 in pH 6.8, and 30.87, 30.96 and 27.37 in distilled water respectively after comparing them with reference brand Maxolon® having the excellent physicochemical properties. The dissimilarity or difference factor values for F1, F7 AND F10 were 55.45, 58.34 and 60.76 in pH 1.2, 55.11, 55.22 and 57.33 in pH 4.5, 62.31, 65.32 and 66.89 in pH 6.8, and 56.40, 58.78 and 59.12 in distilled water respectively when compared with Maxolon®. The Similarity and dissimilarity comparison of dissolution profiles was reported by Liu et. al in 1997. Three intermediate release tablets were subjected to accelerated stability studies for a period of 24 months. All the physicochemical test results like hardness, disintegration time, weight variation, friability, dissolution studies and assay were within acceptable limits. R Gui software was used to estimate the shelf lives of selected intermediate release formulations. The shelf life for the optimized intermediate release formulation F-10 was found to be 64 months.

V. CONCLUSIONS

The optimization of intermediate release metoclopramide HCl tablets was successfully done using central composite rotatable design. The study of micromeritic properties of planned formulations helped in the selection of the formulations to be compressed by single punch machine. A comparative analysis of placebo and metoclopramide HCl containing formulations was done. Results were optimized by model dependent and model independent approaches after performing physicochemical and quality control studies. The formulation F10 was optimized for further studies.

VI. ACKNOWLEDGEMENTS

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REFERENCES


Figure 1(a) – RSM Plots showing the effect of HPMC K4M (A) and MCC (B) on the Disintegration (R)
Figure 1(b) – RSM Plots showing the effect of HPMC K4M (A) and Lactose DC (C) on the Hardness (R)

![RSM Plots showing the effect of Lactose DC (C) and MCC (B) on the Friability (R)](image-url)
Figures 2(a, b, c, d) - Combine Dissolution profile of the three optimized formulations of metoclopramide (n=6).
Table 1 - Relationship between coded and actual values of a Variable (Box and Wilson, 1951, Hanif et al. 2014)

<table>
<thead>
<tr>
<th>Code</th>
<th>Actual value of Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>-β</td>
<td>( X_{\text{min}} )</td>
</tr>
<tr>
<td>-1</td>
<td>( [(X_{\text{max}} + X_{\text{min}})/2] - [(X_{\text{max}} + X_{\text{min}})/2\alpha] )</td>
</tr>
<tr>
<td>0</td>
<td>( [(X_{\text{max}} + X_{\text{min}})/2] )</td>
</tr>
<tr>
<td>+1</td>
<td>( [(X_{\text{max}} + X_{\text{min}})/2] + [(X_{\text{max}} + X_{\text{min}})/2\alpha] )</td>
</tr>
<tr>
<td>+β</td>
<td>( X_{\text{max}} )</td>
</tr>
</tbody>
</table>

\( X_{\text{max}} \) = Maximum value of “x”

\( X_{\text{min}} \) = Minimum Value of “x”

\( \alpha = 2^{k/4} \)

\( k \) = Number of variables (In present study, \( \alpha=1.682 \))

Table 2 - Factors levels applied in the optimizations of Immediate, Intermediate and Slow Release Formulations (12)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Factor level X</th>
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<td>(-\beta (X_{\text{min}}))</td>
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</tr>
<tr>
<td>(X_1) HPMC (%)</td>
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</tr>
<tr>
<td>(X_2) Avicel PH 102(%)</td>
<td>5</td>
</tr>
<tr>
<td>(X_3) Lactose DC (%)</td>
<td>13</td>
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</table>

Table 3 - Formulations according to CCRD and release pattern of Metoclopramide HCl intermediate release tablets

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Factor 1 (XI) HPMC</th>
<th>Factor 2 (X2) Avicel PH-102</th>
<th>Factor 3 (X3) Lactose DC</th>
<th>Factor 1 (XI) HPMC</th>
<th>Factor 2 (X2) Avicel PH-102</th>
<th>Factor 3 (X3) Lactose DC</th>
<th>Magnesium Stearate</th>
<th>Meto.HCl</th>
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<td>36</td>
<td>5</td>
<td>10</td>
<td>178</td>
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Table 4 - Preformulation evaluation of the blended powder (n=5)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Formulations</th>
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</thead>
<tbody>
<tr>
<td>Angle of Repose (Degrees)</td>
<td>( 22.5\pm0.01 )</td>
</tr>
<tr>
<td>Loose Bulk Density (g/ml)</td>
<td>( 0.545\pm0.03 )</td>
</tr>
<tr>
<td>Tapped Bulk Density (g/ml)</td>
<td>( 0.569\pm0.050 )</td>
</tr>
<tr>
<td>Compressibility Index (%)</td>
<td>( 4.21\pm0.02 )</td>
</tr>
<tr>
<td>Calculated Drug Content after 12min (%)</td>
<td>( 99.65\pm0.02 )</td>
</tr>
</tbody>
</table>
Table 5 - Physicochemical properties of intermediate release metoclopramide HCl tablets

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Friability (%)</th>
<th>Weight Variation (mg)</th>
<th>Hardness (kg)</th>
<th>Disintegration time (min)</th>
<th>Thickness (mm)</th>
<th>Tensile Strength (N)</th>
<th>Porosity of the tablet (%)</th>
<th>Shelf Life (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
<td>+5%</td>
<td>5-10</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F1</td>
<td>0.90±0.091</td>
<td>115±3.55</td>
<td>5.21±0.98</td>
<td>8.60±9.76</td>
<td>3.41±0.503</td>
<td>55.43±30</td>
<td>4.00±0.57</td>
<td>52</td>
</tr>
<tr>
<td>F7</td>
<td>0.71±0.095</td>
<td>116±2.50</td>
<td>5.75±0.54</td>
<td>10.32±9.23</td>
<td>3.32±0.420</td>
<td>58.62±39</td>
<td>4.21±0.61</td>
<td>60</td>
</tr>
<tr>
<td>F10</td>
<td>0.56±0.081</td>
<td>117±2.78</td>
<td>6.450±0.11</td>
<td>15.67±8.73</td>
<td>3.010±0.061</td>
<td>58.3±10</td>
<td>3.98±0.22</td>
<td>64</td>
</tr>
</tbody>
</table>

* All values based on (Mean ± SE), n = 20

Table 7 - Model independent approaches

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero Order</th>
<th>First Orders</th>
<th>Higuchi</th>
<th>Korsmeyer–Peppas</th>
<th>Hixson-Crowell</th>
<th>Weibull Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R^2 adj</td>
<td>K_a</td>
<td>R^2 adj</td>
<td>K_r</td>
<td>R^2 adj</td>
<td>n</td>
</tr>
<tr>
<td></td>
<td>h^1</td>
<td>h^1</td>
<td>h^12</td>
<td>h^a</td>
<td>h^13</td>
<td></td>
</tr>
<tr>
<td>pH (1.2)</td>
<td>F1 0.749  7.23</td>
<td>0.810 0.72 0.987</td>
<td>21.73</td>
<td>0.9701</td>
<td>0.443</td>
<td>53.5</td>
</tr>
<tr>
<td>F7 0.741  6.58</td>
<td>0.809 0.78 0.948</td>
<td>10.27</td>
<td>0.9672</td>
<td>0.447</td>
<td>37.87</td>
<td>0.967 0.063 0.934 5.142</td>
</tr>
<tr>
<td>F10 0.740  7.85</td>
<td>0.812 0.79 0.999</td>
<td>28.08</td>
<td>0.9734</td>
<td>0.435</td>
<td>55.67</td>
<td>0.971 0.087 0.974 5.231</td>
</tr>
<tr>
<td>pH (4.5)</td>
<td>F1 0.799  4.68</td>
<td>0.827 0.23 0.961</td>
<td>10.03</td>
<td>0.987</td>
<td>0.312</td>
<td>53.5</td>
</tr>
<tr>
<td>F7 0.777  4.39</td>
<td>0.899 0.78 0.968</td>
<td>10.12</td>
<td>0.975</td>
<td>0.317</td>
<td>55.06</td>
<td>0.913 0.030 0.953 7.011</td>
</tr>
<tr>
<td>F10 0.781  5.35</td>
<td>0.802 0.79 0.984</td>
<td>10.11</td>
<td>0.976</td>
<td>0.265</td>
<td>53.59</td>
<td>0.942 0.041 0.975 7.214</td>
</tr>
<tr>
<td>pH (6.8)</td>
<td>F1 0.746  7.40</td>
<td>0.893 0.130 0.986</td>
<td>26.50</td>
<td>0.913</td>
<td>0.277</td>
<td>33.5</td>
</tr>
<tr>
<td>F7 0.785  8.01</td>
<td>0.870 0.164 0.954</td>
<td>29.54</td>
<td>0.925</td>
<td>0.298</td>
<td>23.20</td>
<td>0.939 0.076 0.998 10.114</td>
</tr>
<tr>
<td>F10 0.789  7.00</td>
<td>0.890 0.179 0.989</td>
<td>26.19</td>
<td>0.941</td>
<td>0.240</td>
<td>34.00</td>
<td>0.976 0.044 0.994 10.121</td>
</tr>
<tr>
<td>Distilled Water</td>
<td>F1 0.651  5.774</td>
<td>0.871 0.108 0.875</td>
<td>24.616</td>
<td>0.950</td>
<td>0.352</td>
<td>50.785</td>
</tr>
<tr>
<td>F7 0.671  6.021</td>
<td>0.859 0.167 0.874</td>
<td>29.54</td>
<td>0.940</td>
<td>0.280</td>
<td>56.014</td>
<td>0.904 0.103 0.983 10.132</td>
</tr>
<tr>
<td>F10 0.681  6.222</td>
<td>0.878 0.120 0.980</td>
<td>26.19</td>
<td>0.968</td>
<td>0.266</td>
<td>54.520</td>
<td>0.918 0.078 0.981 11.223</td>
</tr>
</tbody>
</table>
The dissolution profiles of dissolution data at 0.05, 0.1, 1, 1.5 and 2 hrs were compared only, each test formulation (Intermediate) were compared with IR brand Maxolon®.