Influence of electrolytes on the release of tramadol hydrochloride from controlled release matrix tablets

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ABSTRACT

The main aim of the present investigation was to study the effect of electrolytes dried aluminum hydroxide and calcium carbonate on the release of Tramadol hydrochloride (THL) form HPMC K4M controlled release matrix tablets. Totally 9 formulations were prepared with varying concentration of electrolytes. All the formulations fulfilled the pre compression parameters like angle of repose and compressibility index. The blends were compressed in to CR tablets by direct compression method. In-vitro dissolution studies were performed in 1.2N HCl for 2hrs and pH 7.4 phosphate buffer over 12hrs. Among all the formulations, F2 (containing 6.66% w/w of dried aluminum hydroxide) and F6 (6.66% w/w of calcium carbonate) showed the controlled drug release of 94.98% and 94.87% over 12hrs. To ascertain the mechanism of Tramadol Hydrochloride release data was fitted into various release kinetic models. All the formulations results showed prolonged and controlled release and compliance with Higuchi plot which reveals that the drug reveals follows Non-Fickian diffusion mechanism. The FTIR spectral analysis also reveals that there was no interaction between the drug and polymers used.

KEY WORDS: Tramadol Hydrochloride, Dried aluminum hydroxide, Calcium carbonate, HPMC K4M.

1. INTRODUCTION

Tramadol Hydrochloride (THC) is a non-steroidal anti-inflammatory drug, which is used in the treatment of osteoarthritis when NSAIDs like acetaminophen, or COX-2 inhibitors alone produce inadequate pain relief. Tramadol Hydrochloride is rapidly and completely absorbed following oral administration with absolute bioavailability of 75% (approx). The half-life is approximately 6-7hrs and requires dosing for every 6 hrs in order to maintain optimal relief of chronic pain (Birkett, 1996). Long term treatment with Controlled-release Tramadol once daily is generally safe in patients with osteoarthritis or refractory low back pain and is well tolerated (James Swarbrick., 2007). It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep, and improved compliance. To reduce the frequency of administration and to improve patient compliance. Present the oral controlled release matrix tablets of Tramadol hydrochloride using different electrolytes like Dried aluminum hydroxide and Calcium carbonate.

2. MATERIALS AND METHODS

Tramadol Hydrochloride was obtained as a gift sample from Darwin Laboratories, Vijayawada, HPMC K4M obtained from Colorcon Asia Pvt. Ltd, Goa, Microcrystalline cellulose obtained from Lubrizol Pvt. Ltd, Mumbai, Dried aluminum hydroxide and calcium carbonate obtained from Colorcon Asia Pvt. Ltd, Goa, Talc obtained from Otto chem-biochem, Mumbai, Magnesium Stearate obtained from SD- fine chemicals Ltd, Mumbai.

2.1. Drug and excipient compatibility studies:

2.1.1. Fourier Transform Infrared Spectroscopy (FTIR): (Gandla Swetha, 2014): IR spectra were recorded between 400 and 4000 cm−1 by a Perkin Elmer 1600 Series FTIR (Norwalk, USA). Each sample was mixed with KBr (FT-IR grade, Aldrich, Steinhelm, Germany) and compressed at 70 kN with a Perkin-Elmer hydraulic press.

2.2. Preformulation studies:

2.2.1. Bulk density: (Martin A 2001): Bulk density is the ratio of given mass of powder to its bulk volume.

\[ \text{Bulk density} = \frac{M}{V_o} \]

Where M is the weight of the sample taken, \( V_o \) = apparent volume

2.2.2. Tapped density: Tapped density was determined by using graduated cylinder.

\[ Dt = \frac{\text{Mass of the powder blend (M)}}{\text{Tapped volume (Vt)}} \]

2.2.3. Angle of repose: The angle of repose has been used to characterize the flow properties of solids. Angle of repose is a characteristic related to inter particulate friction or resistance to movement between particles. This is the maximum angle possible between surface of pile of powder or granules and horizontal plane.

2.2.4. Carr’s index (compressibility): The compressibility and Hausner’s ratio are the measures of the propensity of a powder to be compressed.

\[ \%\text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100 \]

2.2.5. Hausner’s ratio: The ratio of tapped density to the bulk density of the powders is called the Hausner’s ratio.

\[ \text{Hausner’s ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \]
2.3. Formulation of matrix tablets by direct compression: (Jayadev Patil, 2011) Compressed tablets of Tramadol Hydrochloride using different electrolytes (dried aluminum hydroxide, calcium carbonate) were prepared by direct compression method as per formulae given in Table 2. Accurately weighed quantities of API, excipients were passed through sieve no #40 and remaining ingredients were added to the blend in a polybag and mixed for 10 minutes. The resulting powder blend was compressed on single punch tablet press (Cadmach, India) using 10mm round punches to round tablets weighing 300mg with a hardness of 4-5 kg/cm².

2.4. Post compressional parameters: (Leon lachman and Herbert Lieberman, 1987)

2.4.1. Hardness: Hardness of the tablets was tested using ‘Monsanto’ hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the tablet and a zero reading is taken. The upper plunger is then forced against a spring by turning a thread bolt until the tablet fractures. As the spring is compressed, a pointer rides along the guage in the barrel to indicate the force, which is a measure of hardness. The hardness of the tablet depends up on the weight of the material used, space between upper and lower punches at the time of compression and pressure applied during compression.

2.4.2. Friability (%F): The Roche friabilator was used for this test, this device subjects as number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm by dropping the tablets from a distance of six inches with each revolution.\[
\% F = 1 - \frac{\text{loss in weight/ initial weight}}{100}
\]

2.4.3. Weight variation: Weight variation was calculated as per method descried in USP. 20 tablets were weighed individually and the average weight is calculated.

2.4.4. In vitro drug release/ dissolution studies (Indian Pharmacopeia, 2010): The tablet samples were subjected to in-vitro dissolution studies using type II paddle type dissolution apparatus at 37±2°C and 50rpm speed. The dissolution rate was studied using 900ml of 0.1N HCl for 2 hrs and 7.4 pH phosphate buffer for 10 hrs. Samples were withdrawn at regular intervals up to 12 hrs and each sample was determined by Elico UV visible spectrophotometer at 271nm after suitable dilution of the samples. Necessary corrections were made for the loss of drug due to each sampling and the cumulative amount of drug released was determined.

2.4.5. Study of release kinetics and release mechanism: From the dissolution studies of various matrix tablets containing Tramadol Hydrochloride the following invitro kinetics were evaluated.

2.4.6. Zero – order release constant: (Brazel, 2000) Drug dissolution from dosage that do not disaggregate and release the drug slowly can be represented by the equation:

\[\text{Q}_t = \text{Q}_o + K_0 t \]  \hspace{1cm} (1)

Where,

- \(\text{Q}_t\) is the initial amount of drug dissolved at time \(t\),
- \(\text{Q}_o\) is the initial amount of drug in the solution, most of the times it is equal to zero,
- \(K_0\) is the zero order release constant

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product.

2.4.7. First order-release rate constant (Kalam, 2007): Release behavior generally follows the following first order release equation:

\[\ln \text{Q}_t = \ln \text{Q}_o + K_1 t \]  \hspace{1cm} (2)

Where, \(\text{Q}_t\) is the initial amount of drug dissolved at time \(t\),
- \(\text{Q}_o\) is the amount of drug in the solution,
- \(K_1\) is the first order release rate constant.

In this way a graphic of the decimal log of the released amount of drug vs time will be linear

2.4.8. Higuchi’s diffusion constant: (Higuchi, 1963)

\[\text{Q} = \text{K}_H t^{1/2} \]  \hspace{1cm} (3)

Where, \(\text{Q}\) is the amount of drug released at time \(t\) per unit area,
- \(\text{K}_H\) is the Higuchi diffusion rate constant.

2.4.9. Korsemeyer peppas constant: (Koresmeyer, 1983)

\[\frac{M_t}{M_{\infty}} = K t^n \]  \hspace{1cm} (4)

Where,

- \(M_t\) and \(M_{\infty}\) are the amounts of drug released at time \(t\) and infinite time,
- \(K\) is a constant incorporating structural and geometric characteristic of the device,
- \(N\) is the drug release exponent, indicative of the mechanism of drug release.

2.4.10. Similarity factor, \(f_2\) value: (Shah, 1998): The similarity factor \(f_2\) (I2>50) as defined by FDA and EMEA is a logarithmic reciprocal square root transformation of one plus the mean squared difference or drug %dissolved between the test and reference products.
\[ f_2 = 50 \times \log \left( 1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right)^{-0.5} \times 100 \]

Where, \( n \) is the number of dissolution time points. ‘\( R_t \)’ and ‘\( T_t \)’ are the reference and test dissolution values (mean of at least 12 dosage units) at time \( t \).

3. RESULTS AND DISCUSSIONS

Fourier Transform Infra-Red Spectrums

Drug Excipient Compatibility studies: Preformulation studies were carried out through Drug Excipient compatibility studies using FTIR spectral analysis.

![Figure.1.FTIR Spectrum of pure drug Tramadol Hydrochloride](image)

![Figure.2.FTIR Spectra for Formulation F2](image)

![Figure.3.FTIR Spectra for Formulation F6](image)

Table 1. Preformulation studies of powder blend of directly compressible formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Angle of repose</th>
<th>Bulk density (gm/cm(^2))</th>
<th>Tapped density (gm/cm(^2))</th>
<th>% Compressibility</th>
<th>Hauser’s ratio</th>
<th>Flowability</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>39±2</td>
<td>0.50 ± 0.03</td>
<td>0.61 ± 0.02</td>
<td>18 ± 1</td>
<td>1.22± 0.02</td>
<td>Good</td>
</tr>
<tr>
<td>F2</td>
<td>35±1</td>
<td>0.52 ± 0.01</td>
<td>0.63 ± 0.04</td>
<td>15 ± 3</td>
<td>1.15±0.06</td>
<td>Good</td>
</tr>
<tr>
<td>F3</td>
<td>34±3</td>
<td>0.54 ± 0.02</td>
<td>0.63 ± 0.01</td>
<td>15 ± 3</td>
<td>1.17±0.03</td>
<td>Good</td>
</tr>
<tr>
<td>F4</td>
<td>33±2</td>
<td>0.54 ± 0.03</td>
<td>0.62 ± 0.05</td>
<td>14 ± 4</td>
<td>1.15±0.02</td>
<td>Good</td>
</tr>
<tr>
<td>F5</td>
<td>32±4</td>
<td>0.58 ± 0.01</td>
<td>0.65 ± 0.02</td>
<td>12 ± 5</td>
<td>1.13±0.04</td>
<td>Good</td>
</tr>
<tr>
<td>F6</td>
<td>31±5</td>
<td>0.56 ± 0.02</td>
<td>0.64 ± 0.03</td>
<td>12 ± 5</td>
<td>1.15±0.06</td>
<td>Good</td>
</tr>
<tr>
<td>F7</td>
<td>30±2</td>
<td>0.56 ± 0.04</td>
<td>0.65 ± 0.01</td>
<td>13 ± 4</td>
<td>1.17±0.03</td>
<td>Good</td>
</tr>
<tr>
<td>F9</td>
<td>34±2</td>
<td>0.54 ± 0.02</td>
<td>0.62 ± 0.02</td>
<td>14 ± 2</td>
<td>1.15±0.06</td>
<td>Good</td>
</tr>
</tbody>
</table>

Table 2. Composition of Various Controlled Release Matrix Tablets of Tramadol hydrochloride

<table>
<thead>
<tr>
<th>Ingredients (mg/tab)</th>
<th>Formulations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Tramadol Hydrochloride</td>
<td>100</td>
</tr>
<tr>
<td>HPMC K4M</td>
<td>100</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>90</td>
</tr>
<tr>
<td>Dried aluminum hydroxide</td>
<td>--</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>--</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>5</td>
</tr>
<tr>
<td>Weight of each tablet(mg)</td>
<td>300</td>
</tr>
</tbody>
</table>
### Table 3. Post-Compressional studies of directly compressible matrix tablet formulations

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Weight uniformity (mg)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>5 ± 0.12</td>
<td>0.21 ± 0.01</td>
<td>300 ± 2.0</td>
<td>100 ± 1.25</td>
</tr>
<tr>
<td>F2</td>
<td>5 ± 0.34</td>
<td>0.11 ± 0.04</td>
<td>310 ± 2.1</td>
<td>101 ± 1.98</td>
</tr>
<tr>
<td>F3</td>
<td>5 ± 0.34</td>
<td>0.11 ± 0.04</td>
<td>300 ± 1.2</td>
<td>99 ± 1.67</td>
</tr>
<tr>
<td>F4</td>
<td>5 ± 0.22</td>
<td>0.14 ± 0.02</td>
<td>298 ± 3.0</td>
<td>97 ± 1.25</td>
</tr>
<tr>
<td>F5</td>
<td>5 ± 0.26</td>
<td>0.12 ± 0.03</td>
<td>299 ± 2.0</td>
<td>102 ± 0.98</td>
</tr>
<tr>
<td>F6</td>
<td>5 ± 0.25</td>
<td>0.13 ± 0.02</td>
<td>301 ± 3.0</td>
<td>98 ± 0.65</td>
</tr>
<tr>
<td>F7</td>
<td>5 ± 0.32</td>
<td>0.10 ± 0.05</td>
<td>298 ± 3.0</td>
<td>101 ± 0.54</td>
</tr>
<tr>
<td>F8</td>
<td>5 ± 0.32</td>
<td>0.10 ± 0.05</td>
<td>297 ± 2.0</td>
<td>102 ± 0.78</td>
</tr>
<tr>
<td>F9</td>
<td>5 ± 0.22</td>
<td>0.14 ± 0.02</td>
<td>299 ± 2.0</td>
<td>99 ± 0.85</td>
</tr>
</tbody>
</table>

### Table 4. *In vitro* kinetic data of the prepared Formulations

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Zero order</th>
<th>First order</th>
<th>Higuchi values</th>
<th>Korsmeyer Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>‘K’ (hrs⁻¹)</td>
<td>‘K’ (hrs⁻¹)</td>
<td>‘K’ (hrs⁻¹)</td>
<td>‘K’ (hrs⁻¹)</td>
</tr>
<tr>
<td></td>
<td>R²</td>
<td>R²</td>
<td>R²</td>
<td>R²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>6.942</td>
<td>0.773</td>
<td>0.237</td>
<td>0.973</td>
</tr>
<tr>
<td>F2</td>
<td>6.864</td>
<td>0.823</td>
<td>0.216</td>
<td>0.962</td>
</tr>
<tr>
<td>F3</td>
<td>5.966</td>
<td>0.700</td>
<td>0.165</td>
<td>0.921</td>
</tr>
<tr>
<td>F4</td>
<td>5.945</td>
<td>0.777</td>
<td>0.138</td>
<td>0.926</td>
</tr>
<tr>
<td>F5</td>
<td>5.859</td>
<td>0.758</td>
<td>0.131</td>
<td>0.909</td>
</tr>
<tr>
<td>F6</td>
<td>7.035</td>
<td>0.834</td>
<td>0.198</td>
<td>0.985</td>
</tr>
<tr>
<td>F7</td>
<td>6.378</td>
<td>0.785</td>
<td>0.163</td>
<td>0.951</td>
</tr>
<tr>
<td>F8</td>
<td>6.465</td>
<td>0.843</td>
<td>0.154</td>
<td>0.979</td>
</tr>
<tr>
<td>F9</td>
<td>6.942</td>
<td>0.773</td>
<td>0.237</td>
<td>0.973</td>
</tr>
<tr>
<td>Marketed</td>
<td>7.848</td>
<td>0.823</td>
<td>0.223</td>
<td>0.931</td>
</tr>
</tbody>
</table>

### Figures

- Figure 4. Comparative release profiles of Tramadol Hydrochloride Formulations F1-F5
- Figure 5. Comparative release profiles of Tramadol Hydrochloride Formulations F6-F9
- Figure 6. Comparative release plot of Tramadol Hydrochloride from F2 and Marketed product
- Figure 7. Comparative release plot of Tramadol Hydrochloride from F6 and Marketed product
**Discussion:** The present study was performed to evaluate the influence of certain inorganic electrolytes on the controlled release of freely soluble THC from controlled release matrix tablets of HPMC K4M. The electrolytes used were Dried Aluminium hydroxide and Calcium carbonate. HPMC K4M was used as polymer for matrix tablet formulations.

Literature survey revealed that THC was formulated as sustained release dosage forms as matrix tablets, bi-layer tablets, Gastro-retentive tablets, Oral-Disintegrating tablets by employing various methods. In the present study, formulations were developed with THC by employing pharmaceutically acceptable electrolytes in the matrix tablets with an objective to achieve linear controlled release over an extended period of time.

A simple sensitive UV-spectrophotometric method was used for the estimation of Tramadol Hydrochloride at a wavelength of 271nm. A good linear relationship was observed and the selected method was found to be sensitive, accurate, precise and reproducible.

FT-IR spectral studies were performed on selected matrix tablets of Tramadol Hydrochloride during the dissolution studies. The spectra of Tramadol hydrochloride exhibited principal peaks at a wave numbers of 4000-600cm$^{-1}$. The spectral studies of THC matrix tablet formulations exhibited weak (or) no changes in the principal peaks and all the peaks were observed at specific wave numbers as that of their pure drug. Thus these studies indicated that there were no interactions between the functional moieties of drug molecule with the polymer or with the electrolytes incorporated in the formulations.

Pre-compression parameters of various powder blends before direct compression were evaluated. Flow properties such as Carr’s index, angle of repose, tapped density, bulk density, compressibility and flowability were measured for all the powder blends and all the formulations were within the range indicating good or excellent flow characteristics and the values were depicted in Table 1. Controlled release matrix tablets of Tramadol hydrochloride were prepared by direct compression method. The composition of drug to polymer ratio in all tablet formulations was constant, while the electrolyte concentration was varied. The composition of matrix tablet formulations was given in Table 2. The direct compression process was found to be ideal for inclusion of electrolytes into matrix system.

Electrolytes may undergo dissociation if they were subjected to wet granulation process. Some electrolytes undergo precipitation, if solvents are used for granulation. Hence direct compression process was employed in the present work for the preparation of controlled release matrix tablets of THC. All batches of matrix tablets were compressed under identical conditions to minimize processing variables. Then post-compression parameters of the matrix tablets such as weight uniformity, hardness, friability, drug content uniformity and swelling index were measured and the values were depicted in Table 3.

**In-vitro** Tramadol Hydrochloride release from the matrix tablets were studied in 1.2pH acidic buffer for the first two hours followed by 7.4 pH phosphate buffer as medium over a period of 12hrs. THC release from the matrix tablets depends on drug-polymer-electrolytes (Dried aluminum hydroxide and calcium carbonate) ratio employed in preparation. The matrix tablet formulations of HPMC K4M was found to release the drug at a faster rate, where as drug release from the matrix tablets containing electrolytes where found to be slow and spread over long period of time. The results were shown in Figure: 1 – 2. The cumulative percent of drug release for F1, F2, F3, F4, F5, F6, F7, F8, F9 formulations were found to be 95.42 ± 2.4, 94.98 ± 1.89, 90.40 ± 3.54, 85.61 ± 2.56, 81.76 ± 2.19, 94.87 ± 3.74, 83.37 ± 2.45, 85.54 ± 3.15 and 82.02 ± 3.74 respectively at the end of 12 hrs.

Dried Aluminium hydroxide and Calcium Carbonate has high influence on drug release from matrix tablets of HPMC K4M. Good linear relationship was observed between concentration of electrolytes and THC release from the matrix tablets. As the concentration of electrolytes increases, the THC release from the matrix tablets was slow and extended for a prolonged period. It was observed that the optimal concentration of each electrolyte varied for ideal drug release of Tramadol Hydrochloride. The inclusion of electrolytes within the swollen matrix for controlling the release of THC due to fundamental structural changes in gel boundary and integral pH, thus induces the textural variations in the swollen matrix. It was observed that electrolytes solubility and formation of buffer threshold within the matrix plays an essential role in effective interaction with and textural changes. The solubility of electrolytes is playing an important role in maintaining a pH value inside the matrix. Calcium carbonate and Dried Aluminium hydroxide maintains pH greater than 10 in aqueous solutions which posses desired control on THC release from the matrix tablets.

To ascertain the mechanism of Tramadol Hydrochloride release, the **in vitro** Tramadol Hydrochloride release data was fitted into various release kinetic models such as Zero order, First order, Higuchi and Peppas models. When log$\%$ drug unreleased values were plotted against time, linearity was observed indicating that the drug releases from the matrix tablets followed first order kinetics. The first order plots and the corresponding release rate constants were calculated and given in Table 4 and the regression coefficients ($r^{2}$) obtained for the first order kinetics were found to be higher when compared with those of zero order kinetics, indicating that drug release from all the formulations followed first-order kinetics.
Release of the THC from matrix tablets containing hydrophilic polymer generally involves factors of diffusion. To evaluate the THC release mechanism from the tablets, plots of percent drug released vs. square root of time as per Higuchi’s equation were constructed and the plots were found to be linear in all cases with $r^2$ values in the range of 0.920-0.981 indicating that the THC release mechanism from the matrix tablets may be diffusion controlled for insoluble matrices. To confirm the anomalous transport mechanism, the in vitro dissolution data were fit into Peppas equation which resulted in “n” values greater than 0.45, indicating the mechanism of THC release from matrix tablets follows non-Fickian diffusion, signifying the mechanism of THC release follows fast erosion of polymeric matrix followed by diffusion of THC resulting in extending the drug release over a prolonged period of time. The Peppas “n” values were given in Table 4.

The swelling behaviors of selected matrix tablets were measured by percentage swelling index at various time intervals. The percentage of swelling in the formulations F2 and F6 were very high during the dissolution. The formulations F2 and F6 having electrolytes exhibited low swelling rate during the first 2-6 hrs followed by gradual increase in the swelling.

The similarity factor ($f_2$) was calculated in order to compare the release profiles of F2 and F6 with that of the reference formulation. The formulations F2 and F6 had a release profiles similar to that of the marketed formulation, with similarity factor $F_2 = 55$ & 56 respectively, hence these two formulations were comparable to the marketed formulation.

4. CONCLUSION

In the present investigation these studies clearly indicated that the incorporation of electrolytes in the matrix tablet formulations had greatly influenced the drug release properties. The electrolytes such as dried aluminum hydroxide and calcium carbonate were found to be ideal electrolytes for extending the drug release. These matrix tablets with the said electrolytes exhibited good controlled release characteristics by in-vitro studies. Thus, the present study was found to be suitable for preparation of matrix tablets employing the electrolytes for oral control release of Tramadol Hydrochloride along with HPMC K4M fulfilling the major objective by extending the drug release up to 12 hours.

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