FORMULATION AND EVALUATION OF OSMOTICALLY CONTROLLED RELEASE TABLETS OF TRAMADOL HYDROCHLORIDE

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ABSTRACT
In the present study elementary osmotic pumps (EOP) of tramadol hydrochloride were formulated and evaluated. The control release profile was selected and different variables were optimized to achieve the same. Formulation variables like type of osmogen, concentration of osmogen and aperture diameter and were found to affect the drug release from the developed formulations. The tablets prepared with potassium chloride as osmogen has shown good release and the release rate was more with an increase in orifice size. The correlation coefficient R² value obtained for zero order was found to be superior on comparison with first order kinetics. R² value for higuchi plot was 0.928, it indicates diffusion controlled release.

KEYWORDS: Elementary osmotic pumps, tramadol hydrochloride, osmogen.

INTRODUCTION
Oral drug delivery is the most widely utilized route of administration, among all the routes of administration that has been explored for the systemic drug delivery through different pharmaceutical dosage forms. It can be said that at least 90% of all drugs used to produce systemic effect is by oral route. Conventional oral drug delivery systems are known to provide an immediate release of drug, in which one cannot control the release of the drug and effective concentration at the target site. Tramadol hydrochloride, a centrally acting opioid analgesic, is used in severe acute or chronic pains. It offers several therapeutic advantages.
over other analgesics, such as good oral bioavailability and elimination half-life (5–7 h). Despite of this elimination half-life, Tramadol hydrochloride is prescribed 3–4 times a day. Frequent dosing schedule often leads to decreased patient compliance, increased incidence of side effects and tolerance development, especially, in long-term use in conditions like Arthritis, Osteoarthritis, Arthralgia, Postoperative Surgical Pains, etc. It seems that there is a strong clinical need and market potential for a delivery system that can deliver Tramadol hydrochloride in a controlled manner\(^{[1]}\). Present investigation is to develop controlled osmotic tablet of Tramadol hydrochloride with an aim of increasing its therapeutic effectiveness for extended period of time thus reducing dose frequency and side effects. As new innovation in oral controlled plasma drug delivery it avoids fluctuation in drug concentration and offers better drug utilization and patient compliance. So in the present study attempt has been made to control the release of Tramadol hydrochloride by two different approaches i.e. one using osmotic agents and other by changing the orifice size\(^{[2-10]}\). A semi permeable micro porous membrane that regulates the drug release surrounds the system. The developed formulations were evaluated for physico-chemical parameters and effect of various formulation variables on in vitro drug release was studied.

**MATERIALS AND METHODS**

Tramadol gift sample from Chandra labs hyd, Potassium chloride, Sodium chloride, Mannitol Sucrose, Triethyl citrate, Micro Crystalline Cellulose, Magnesium Stearate from MYL CHEM Mumbai PVP K-30, Cellulose acetate S.D Fine chem. LTD Mumbai.

**FORMULATION OF CORE TABLET**

Osmotic tablets of were prepared by direct compression method. Micro crystalline cellulose, osmotic agents, PVP K30 were weighed according to the given table and sifted through 40 mesh. To the above blend Tramadol was added and sifted through 18 mesh. The sifted materials were mixed for 10 min. Magnesium Stearate and talc was weighed and sifted through 40 mesh. To the powdered blend, lubricated blend was added and mixed properly. Then the total blend was compressed using 8mm round punches\(^{[11-13]}\).

**TABLE NO: 1**

<table>
<thead>
<tr>
<th>Ingredients (mg)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
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<td>100</td>
<td>100</td>
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<td>100</td>
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<td>Sodium chloride</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>50</td>
<td>--</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td></td>
<td>Mannitol</td>
<td>Potassium chloride</td>
<td>Lactose</td>
<td>Fructose</td>
<td>PVP K-30</td>
<td>Magnesium Stearate</td>
<td>MCC</td>
<td>Talc</td>
<td>Total wt</td>
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<td>6.25</td>
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<td>250</td>
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<td>5</td>
<td>33.5</td>
<td>5</td>
<td>250</td>
<td></td>
</tr>
</tbody>
</table>

**Coating with semi-permeable polymer**

Optimized Core tablets were coated by using a coating machine with a perforated pan. A solution of EC in Acetone at a concentration of (4%w/v), containing HPMC pthalate at concentration of 1% of w/w of, level of plasticizer was used as the coating solution. To the acetone, slowly ethyl cellulose was added with proper mixing. In between, plasticizer was added drop wise and through mixing was done to dissolve the ethyl cellulose. Addition of plasticizer in the coating solution improves film properties like film flexibility. The final coating solution was filtered through # 80 sieve. The coating solution contains ethylcellulose 4%, Ferric Oxide0.01%, HPMC Pthalate1%, Acetone25ml.

Core tablets of Tramadol were placed in coating pan and tablets were coated using the following parameters:

- Pan rpm: 10-11
- Coating solution spray rate: 4-5ml/min
- Inlet temperature: 38°C
- Outlet temperature: 28°C
- Atomizer pressure: 1.0 kg/cm²
- Fan pressure: 1-0.75 kg/cm²
- Inlet air blower: 900 cpm
- Outlet air blower: 1600 cpm

The coating solution was sprayed over the tablet bed by a spray gun till a desired weight gain was obtained on the active core tablets. Later the osmotic pump tablets were dried at 50°C for 1 Hr to remove the residual organic solvent[^14-20].
Evaluation of powder blend: The bulk and tap density of the powdered blend was determined using USP method I and Compressibility index, angle of repose and Hausner ratio were calculated. The results were presented in table 6.

EVALUATION OF COMPRESSED TABLETS

a) Hardness
This is the force required to break a tablet in diametric compression. Hardness of the tablets is determined by Monsanto hardness tester which consists of a barrel with a compressible spring. The pointer moving along the gauge in the barrel at which the tablet fractures.

b) Weight variation
Ten tablets were selected at random and average weight was determined. Then individual tablets were weighted and the individual weight was compared with an average weight. Not more than two of the individual weights deviate from the official standard.

c) Tablet size and Thickness
The size and thickness of the tablets were measured by using Vernier Calipers scale.

d) Drug content analysis
Five tablets weighed and crushed in a mortar then the powder equivalent to 100 mg of drug was transferred into 100ml of phosphate buffer. Absorbance of this solution was measured at 271 nm using UV-visible spectrophotometer.

e) Dissolution studies
i) In vitro dissolution studies for core tablets
Dissolution rate of core tablets from all formulations were performed using LAB INDIA dissolution apparatus (USP II) with paddle. The dissolution fluid was 900 ml phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature of 37° C were used in each test. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected up to 1 hr and were replaced with equal volume of phosphate buffer pH 6.8. The samples were analyzed at 271 nm using a UV spectrophotometer.

ii) In vitro dissolution studies for coated tablets
Dissolution rate of osmotic tablets from all formulations were performed using LAB INDIA dissolution apparatus (USP II) with paddle. The dissolution fluid was 900 ml 0.1N HCL for first 2 hrs then replaced with phosphate buffer pH 6.8 at a speed of 50 rpm and a temperature
of 37° C were used in each test. The dissolution experiments were conducted in triplicate. For all tests 5ml samples of the test medium were collected at set intervals (1, 2, 4, 6, 8, 12, 18 and 24hrs) and were replaced with equal volume of phosphate buffer pH 6.8. The samples were analyzed at 271nm using a UV spectrophotometer.

**FTIR STUDIES**

Infrared spectroscopy is a useful analytical technique utilized to check the chemical interaction between the drug and excipients used in the formulation. 1-2 mg of solid fine powder of drug and 200-300 mg of dry powder of KBr (IR grade) were taken in a mortar and mixed well with the help of a spatula. Spectrum measurement was carried out using KBr disk method in the wavelength region of 4000-400cm⁻¹ by FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with that of the pure drug to check any possible drug-excipient interaction.

**6.8 Kinetic Analysis of Dissolution Data**

The dissolution profile of optimized formulation was fitted into various models like zero order, first order, higuchi and peppa’s model to know the mechanism of drug release.

**RESULTS AND DISCUSSION**

**Pre compression parameters**

The prepared blend for all the formulations were evaluated.

The results were shown in the table no:2.

**TABLE NO: 2**

<table>
<thead>
<tr>
<th>S.no</th>
<th>Formulations</th>
<th>Bulk Density (gm/ml)</th>
<th>Tapped Density (gm/ml)</th>
<th>Compressibility index (%)</th>
<th>Angle of repose (°)</th>
<th>Haunser ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F1</td>
<td>0.43</td>
<td>0.49</td>
<td>12.24</td>
<td>22.7</td>
<td>1.14</td>
</tr>
<tr>
<td>2</td>
<td>F2</td>
<td>0.41</td>
<td>0.47</td>
<td>12.77</td>
<td>25.7</td>
<td>1.15</td>
</tr>
<tr>
<td>3</td>
<td>F3</td>
<td>0.46</td>
<td>0.53</td>
<td>13.21</td>
<td>26.1</td>
<td>1.15</td>
</tr>
<tr>
<td>4</td>
<td>F4</td>
<td>0.44</td>
<td>0.51</td>
<td>13.73</td>
<td>25.9</td>
<td>1.16</td>
</tr>
<tr>
<td>5</td>
<td>F5</td>
<td>0.40</td>
<td>0.47</td>
<td>14.89</td>
<td>24.3</td>
<td>1.18</td>
</tr>
<tr>
<td>6</td>
<td>F6</td>
<td>0.37</td>
<td>0.43</td>
<td>13.95</td>
<td>26.6</td>
<td>1.16</td>
</tr>
<tr>
<td>7</td>
<td>F7</td>
<td>0.41</td>
<td>0.48</td>
<td>14.58</td>
<td>25.5</td>
<td>1.17</td>
</tr>
<tr>
<td>8</td>
<td>F8</td>
<td>0.34</td>
<td>0.39</td>
<td>12.82</td>
<td>24.9</td>
<td>1.15</td>
</tr>
<tr>
<td>9</td>
<td>F9</td>
<td>0.38</td>
<td>0.44</td>
<td>13.64</td>
<td>26.6</td>
<td>1.16</td>
</tr>
<tr>
<td>10</td>
<td>F10</td>
<td>0.33</td>
<td>0.38</td>
<td>13.16</td>
<td>28.5</td>
<td>1.15</td>
</tr>
</tbody>
</table>
Bulk density and tapped density of powder blend was evaluated. The angle of repose for the entire formulations blend was evaluated i.e; from F1-F10 and it was found to be in the range of 22-29 thus it was found that it possess good flow properties. Compressibility index for the entire formulations blend was evaluated i.e :from F1-F10 it was found in the range of 12-13 ,thus it was found that it possess good flow properties. The Hausner’s ratio for the entire formulations blend was evaluated and the results were in the range from 1.14-1.18. All these formulations are within the limit.

EVALUATION OF THE TABLETS
The formulated tablets were evaluated and the results were shown in table3.

Table no: 3 Post formulation parameters of tablets

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Hardness (Kg/cm²)</th>
<th>Avg Weight mg</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>6.0</td>
<td>251</td>
<td>2.22</td>
<td>0.35</td>
<td>99.7</td>
</tr>
<tr>
<td>F2</td>
<td>6.6</td>
<td>249</td>
<td>2.12</td>
<td>0.32</td>
<td>98.8</td>
</tr>
<tr>
<td>F3</td>
<td>6.1</td>
<td>250</td>
<td>2.20</td>
<td>0.34</td>
<td>99.4</td>
</tr>
<tr>
<td>F4</td>
<td>6.2</td>
<td>248</td>
<td>2.19</td>
<td>0.37</td>
<td>99.1</td>
</tr>
<tr>
<td>F5</td>
<td>6.4</td>
<td>251</td>
<td>2.15</td>
<td>0.33</td>
<td>98.6</td>
</tr>
<tr>
<td>F6</td>
<td>6.3</td>
<td>250</td>
<td>2.17</td>
<td>0.42</td>
<td>98.3</td>
</tr>
<tr>
<td>F7</td>
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<td>0.39</td>
<td>99.5</td>
</tr>
<tr>
<td>F8</td>
<td>6.7</td>
<td>251</td>
<td>2.11</td>
<td>0.34</td>
<td>98.2</td>
</tr>
<tr>
<td>F9</td>
<td>6.4</td>
<td>250</td>
<td>2.16</td>
<td>0.42</td>
<td>99.0</td>
</tr>
<tr>
<td>F10</td>
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<td>249</td>
<td>2.13</td>
<td>0.38</td>
<td>99.3</td>
</tr>
</tbody>
</table>

The prepared tablets in all the formulations possessed good mechanical strength with sufficient hardness in the range of 6.0 to 6.7 kg/sq cm. Friability values for all the formulations were below 1%, was an indication of good mechanical resistance of the tablets. All the formulations passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The weight variation in all the Nine formulations was found to be 248 to 251 mg, which was in pharmacopoeial limits of ±5% of the average weight. The percentage drug content of all the tablets was found to be between 98.2 to 99.7 % of Tramadol which was within the acceptable limits.

DISSOLUTION DATA FOR CORE TABLET
Table no: 4

<table>
<thead>
<tr>
<th>Time(mins)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
<th>F10</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>5</td>
<td>26.6</td>
<td>25.1</td>
<td>33.9</td>
<td>37.2</td>
<td>29.6</td>
<td>24.1</td>
<td>28.1</td>
<td>26.4</td>
<td>28.5</td>
<td>29.1</td>
</tr>
</tbody>
</table>
Dissolution studies were performed for all formulations and the results for all the formulations from F1-F10 were shown in the table 4.

The studies performed at different concentrations of osmogen results that the release of drug is 98.4% in F8. Thus F8 was optimized, whereas in the remaining formulation the drug release was not as in F8.

*Since KCl produced good results further formulations were carried out by using KCl.

**Evaluation of coated formulation**

From the different osmogens used, the formulation done using KCl as osmogen has been optimized because of its better yield and coating is done with cellulose acetate. The data is depicted in the table no.20.

**Table no: 5 Evaluation of coated formulation**

<table>
<thead>
<tr>
<th>Physical Parameter</th>
<th>F8 before coating</th>
<th>F8 after coating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratio(P:osmotic )</td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Average weight(mg)</td>
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<td>258</td>
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</table>
DISSOLUTION STUDIES FOR OSMOTIC TABLETS

Table no: 6 Influence of orifice diameter on the dissolution profile of the Tramadol

<table>
<thead>
<tr>
<th>Time(hrs)</th>
<th>400µm</th>
<th>800µm</th>
<th>1200µm</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>5.1</td>
<td>25.4</td>
</tr>
<tr>
<td>2</td>
<td>5.9</td>
<td>7.3</td>
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<tr>
<td>4</td>
<td>10.4</td>
<td>14.7</td>
<td>57.5</td>
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<td>6</td>
<td>17.2</td>
<td>26.8</td>
<td>79.3</td>
</tr>
<tr>
<td>8</td>
<td>21.5</td>
<td>38.6</td>
<td>84.6</td>
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<td>29.8</td>
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<td>54.4</td>
<td>79.4</td>
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<tr>
<td>24</td>
<td>83.5</td>
<td>98.2</td>
<td>-</td>
</tr>
</tbody>
</table>

Effect of osmogen

To investigate the effect of orifice size on the release of active material from the tablets, the final coated tablets were drilled tablets to a known orifice of size 400 µm, 800µm, 1200 µm respectively manually with a pre-calibrated microdrill. All the batches of tablets with different orifice sizes were subjected to release studies.

It is observed that in all the formulations that contain KCl as osmogen at an orifice of 400µm, there is no onset of release of drug from tablet up to one hour (lag time) and also a very little amount was released even after 2 hours. This may be due to the insufficient development of enough osmotic pressure inside the core tablet.
It is evident that after coating with semipermeable membrane of Cellulose acetate, the increase in concentration of osmogen, KCl leads to increase in drug release from the tablet due to the osmotic effect.

The release of drug from the tablet takes place only after sufficient osmotic pressure builds up in the core. The difference in the osmotic pressure between inside and outside of the tablet causes water penetration into the core, the leading to the drug to be solubilized and released from the tablets orifice due to increased hydrostatic pressure. This process continues until the osmogen concentration remains sufficiently in the core to generate osmotic pressure. The imbibition of water will be continued until the osmotic pressure inside and outside environments become equal. This pressure causes the expulsion of drug along with the osmogens from the core to the outside of tablet.

As amount of KCl increased in the formulation, there is an enhancement in the release rate of drug from the tablets.

**Effect of orifice size on drug release**

The release profiles from tablets containing different orifice sizes. From the release studies it was clear that at 400µm the delivery rate was low when compared to that of 800µm and 1200µm orifice. There was comparatively rapid release from the orifice size of 1200µm than the 800µm; this may be due to little diffusion from the bigger orifice than small orifice. On the other hand a low release rate was observed for an orifice size of 400µm. In case of smaller orifices the drug release granules may block the orifice, there leading to a low drug release rate. As of large orifice size in 1200 µm, leading to a high drug release rate it is not considered.

The controlled zero order drug release profile was observed with 800µm orifice size, thus giving an optimized release rate. The formulation F8 was considered to be best formulation at 800µm orifice size.

**FT-IR STUDIES**

The IR spectrum of pure drug in fig no:22 was found to be similar to the standard spectrum of Tramadol HCl. The characteristics absorption peaks of Tramadol were obtained at 3400-3250 cm\(^{-1}\) indicating NH stretching of NH2, 3080 cm\(^{-1}\) indicating aromatic CH stretching, and 1550-1750 indicating C=C ring stretching.
I.R spectra of pure drug and optimized formulation were shown Figure no :21,22. All the characteristic peaks of Tramadol HCl were present in Spectra of optimized formulation thus indicating compatibility between drug and excipients. It shows that there was no significant change in the chemical integrity of the drug.

FIG NO: 3 FTIR Studies Of Pure Drug

FIG NO: 4 FTIR Spectra Of Optimized Formulation

KINETIC STUDIES FOR OPTIMIZED FORMULATION

Table no: 7 Release kinetics for the optimized formulation F8

<table>
<thead>
<tr>
<th></th>
<th>ZERO</th>
<th>FIRST</th>
<th>HIGUCHI</th>
<th>PEPPAS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% CDR Vs T</td>
<td>Log % Remain Vs T</td>
<td>%CDR Vs √T</td>
<td>Log C Vs Log T</td>
</tr>
</tbody>
</table>
Slope | 4.227962963 | -0.063258255 | 21.3693521 | 1.207730615
---|---|---|---|---
Intercept | 0.833641975 | 2.166610516 | -16.87673946 | 0.419307821
Correlation | 0.996837882 | -0.923901295 | 0.963694821 | 0.956451967
R² | 0.993685763 | 0.85393602 | -16.87673946 | 0.419307821

**Fig no: 5** Zero order plot for optimized formulation F8

**Fig no: 6** First order plot for optimized formulation F8

\[ y = 4.228x + 0.8336 \]
\[ R^2 = 0.9937 \]

\[ y = -0.0633x + 2.1666 \]
\[ R^2 = 0.8536 \]
In the graph of cumulative % drug released vs time (fig no: 23) Zero order resulted in straight line with $R^2$ value of 0.993 whereas (fig no: 24)of % drug remained vs time showed linear relation ship with $R^2$ value of 0.853and in (fig no: 25) of higuchi plot i.e; cumulative % drug release vs square root of time showed $R^2$ value of 0.93.

The correlation coefficient $R^2$ value obtained for zero order was found to be superior on comparision with first order kinetics. $R^2$ value for higuchi plot was 0.928, it indicates diffusion controlled release.
From Korsemeyer-Peppas equation the n-values were found to be n> 0.89 for the optimized formulation. Therefore it shows that the release mechanism was Non- Fickian diffusion (Anomalous transtport). It refers to a combination of both diffusion and erosion controlled-drug release.

CONCLUSION
Osmotic tablets for Tramadol could be successfully prepared with different osmogens in different concentration and could be coated with semipermeable polymer like cellulose acetate and an orifice of known diameter could be drilled on the tablet for the release of the drug. In vitro release studies were carried out for all formulations to quantify percentage cumulative release of drug. Based on the drug release profile suitable formulation was selected. The Formulation no-8 containing drug and Potassium Chloride in the ratio of 1:1 has shown 98.2% of drug release in 24 hours and the drug release followed in zero order kinetics. This formulation no-8 (1:1) was studied for various effects like influence of orifice size on release. The results have revealed that the release rate was more with an increase in orifice size. The effect of orifice size on cumulative release from Formulation no – 8 (1:1) formulation was studied with different pore size 0.4 mm, 0.8 mm, 1.2 mm. The release rate was low at 0.4 mm and high at 1.2 mm but desired release rate was obtained with 0.8mm. Formulations of core tablets shown increased drug release rate with an increase in osmogen concentration. There is a good scope for the development of elementary osmotic pump system for this drug.

REFERENCES


