Abstract:

**Purpose:** The aim of the present work was to develop an extended-release dosage form of Tapentadol Hydrochloride (HCl) with various types of polymers and to compare them. Tapentadol is a centrally-acting opioid analgesic indicated for the management of moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy in adults. Tapentadol is a BCS class-I drug having biological half-life of 4-5 hours, its systemic bioavailability is 32%, is a suitable candidate for extended release dosage form.

**Method:** Matrix tablets were prepared using different types of hydrophilic and hydrophobic polymers like PEG 6000, Xanthum gum, Guar gum, HPMC K100M, HPMC 15 cps, Carbapol 974, Carbapol 971, Eudragit EPO, Eudragit S-100, CAP, Ethyl Cellulose, Polyox WSR 303, Compritol ATO 888, Gelucire 43/02, 50/1, Geleol and Kollidon SR, by direct compression method and evaluated for various physical and chemical parameters.

**Results and Discussion:** Most hydrophilic polymers failed to prolong the drug release in comparison to hydrophobic polymers based matrix tablets. Among all the polymers HPMC K100M (hydrophilic synthetic cellulose derivative), Carbopol 971NF (hydrophilic synthetic hydrogel), Polyox WSR 303 (water soluble resin) and Gelucire 43/01 (hydrophobic waxy polymer) were found to give optimum and consistent sustained release of drug. All the four formulations showed first order kinetics with non-fickian diffusion controlled release mechanism.

**Key words:** BCS class-I, neuropathic pain, extended release, PEG, hydrophilic, waxy polymer, non-fickian.

**Introduction:**

Tapentadol, 3-[(1R, 2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol hydrochloride is a novel analgesic agent with two mechanisms of action within the same molecule: agonist activity at the µ opioid receptor and norepinephrine...
reuptake inhibition\textsuperscript{[1-3]}. Both immediate release and extended release formulations of tapentadol are available and appear to provide analgesia in acute and chronic pain states similar to oxycodone or morphine\textsuperscript{[4,5]}. Tapentadol demonstrates improved gastrointestinal tolerability (specifically in the incidence of nausea, vomiting, and constipation) compared with strong opioids at doses providing similar analgesia\textsuperscript{[5]}. Tapentadol is available in market as Nucynta ER, Nucynta\textsuperscript{TM} CR, Palexia, Palexia Depot, Palexia Retard, Palexia SR. Tapentadol HCl is a “Class-I” drug according to Biopharmaceutics Classification System (BCS), possessing both high solubility and high permeability absorption characteristics\textsuperscript{[6]}. Tapentadol HCl is rapidly and completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached 2 hours after oral dosing and its elimination half-life ranges from 4.5-5 hrs. and requires dosing every 5 hours in order to maintain optimal relief of chronic pain\textsuperscript{[4]}. Consequently once daily extended release tablets have been formulated. Long term treatment with sustained release Tapentadol once daily is generally safe in patients with painful diabetic peripheral neuropathy or osteoarthritis and low back pain\textsuperscript{[7,8]}. It has the potential to provide patients increased control over the management of their pain, fewer interruptions in sleep and improved compliance\textsuperscript{[8,9]}. Tapentadol HCl has a short elimination half-life and rapidly absorbed in gastrointestinal tract. If it is formulated by conventional tablets, it will require multiple daily administrations (2-3 times daily) which ultimately results into inconveniency to the patients and possibility of reduced compliance with prescribed therapy\textsuperscript{[10,11]}. Also fluctuation in plasma drug concentration leads to exaggerated side effects, this all limitations can be minimized by adopting extended release formulation\textsuperscript{[12]}. They minimize the local and systemic side effects, improving treatment efficacy. The extended release formulations minimize drug accumulation with chronic dosing. Improve the bioavailability of many drugs which helps in less usage of total dose of drug. Improve the ability to provide special effects. For example, morning relief of many pain condition (arthritis) through bed time dosing\textsuperscript{[13]}. Various type of polymers have been used in the present work to achieve extended release of drug, starting from natural gums, to synthetic polymers, swellable to erodible polymers, Hydrophillic to Hydrophobic polymers, Hydrogels, etc. **Materials:**

Tapentadol hydrochloride was procured from MSN labs Hyd. Povidone sample was procured from ISP technologies. Other chemicals were purchased from Himedia, Mumbai and were of analytical grade. Gelucire 43/01, Gelucire 50/02, Compritol ATO 888, Geleol pellets were received as gift samples from Gattefosse, Mumbai.
Methods:

Matrix tablets were prepared by either direct compression method or melt granulation technique\textsuperscript{[14,15]}. The matrix tablets were composed as shown in Table 1.

Table 1: Precompression Parameters:

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Flow Rate (g/sec\textsuperscript{-1})</th>
<th>Carr's Index (%)</th>
<th>Hausner's ratio</th>
<th>(\rho_T) (g/ml)</th>
<th>% porosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.14</td>
<td>14.63±0.2</td>
<td>1.17±0.03</td>
<td>1.41</td>
<td>79.1</td>
</tr>
<tr>
<td>F2</td>
<td>3.83</td>
<td>13.02±0.31</td>
<td>1.15±0.03</td>
<td>1.57</td>
<td>54.0</td>
</tr>
<tr>
<td>F3</td>
<td>2.98</td>
<td>12.70±0.14</td>
<td>1.14±0.12</td>
<td>1.98</td>
<td>34.5</td>
</tr>
<tr>
<td>F4</td>
<td>2.17</td>
<td>17.25±0.6</td>
<td>1.21±0.06</td>
<td>2.65</td>
<td>44.6</td>
</tr>
<tr>
<td>F5</td>
<td>2.16</td>
<td>19.06±0.12</td>
<td>1.26±0.05</td>
<td>1.94</td>
<td>56.4</td>
</tr>
<tr>
<td>F6</td>
<td>3.05</td>
<td>22.67±0.37</td>
<td>1.26±0.02</td>
<td>1.52</td>
<td>32.8</td>
</tr>
<tr>
<td>F7</td>
<td>3.93</td>
<td>24.21±0.34</td>
<td>1.33±0.04</td>
<td>2.65</td>
<td>42.5</td>
</tr>
<tr>
<td>F8</td>
<td>3.06</td>
<td>11.05±0.72</td>
<td>1.12±0.01</td>
<td>1.53</td>
<td>46.7</td>
</tr>
<tr>
<td>F9</td>
<td>2.01</td>
<td>12.79±0.2</td>
<td>1.13±0.03</td>
<td>1.64</td>
<td>37.8</td>
</tr>
<tr>
<td>F10</td>
<td>1.98</td>
<td>11.04±0.34</td>
<td>1.11±0.01</td>
<td>1.97</td>
<td>39.6</td>
</tr>
<tr>
<td>F11</td>
<td>2.06</td>
<td>10.94±0.21</td>
<td>1.10±0.15</td>
<td>1.86</td>
<td>58.2</td>
</tr>
<tr>
<td>F12</td>
<td>1.80</td>
<td>14.09±0.3</td>
<td>1.17±0.08</td>
<td>2.01</td>
<td>69.7</td>
</tr>
<tr>
<td>F13</td>
<td>1.63</td>
<td>11.92±0.21</td>
<td>1.11±0.01</td>
<td>1.90</td>
<td>54.4</td>
</tr>
<tr>
<td>F14</td>
<td>5.04</td>
<td>20.48±0.53</td>
<td>1.24±0.04</td>
<td>2.53</td>
<td>32.5</td>
</tr>
<tr>
<td>F15</td>
<td>5.25</td>
<td>24.82±0.34</td>
<td>1.33±0.15</td>
<td>2.13</td>
<td>28.6</td>
</tr>
<tr>
<td>F16</td>
<td>4.56</td>
<td>19.94±0.57</td>
<td>1.24±0.07</td>
<td>1.24</td>
<td>36.9</td>
</tr>
</tbody>
</table>

n=3; mean±s.d

The waxy polymers were melted in a porcelain dish over a water bath maintained at 75 °C for 3 min and Tapentadol hydrochloride (TH- 50mg) was added with continuous stirring until uniformly mixed. Drug to polymer ratio taken, was 1:2. The molten mixture was allowed to cool and solidify at room temperature crushed in a mortar and passed through a sieve # 40. The granules were mixed with Lactose (60 mg), PVP K30 (10mg), Sodium bicarbonate (20 mg), Aerosil 200 (3mg), Talc (3mg), Magnesium stearate (3 mg). The powder was compressed into 8 mm diameter flat–faced tablets using a press.

The drug (TH) and other polymers were mixed together in the ratio of 1:2, in a zipped poly-bag for 10 min, and mixed with same quantities of other ingredients. The mixtures were compressed into flat-faced tablets by direct compression.
Blend uniformity for the chosen zipped poly bag mixing method, was confirmed by UV spectroscopy at lambda max of 272nm.

F1(PEG 6000), F2 (Xanthum gum), F3 (Guar gum), F4 (HPMC K100M), F5 (HPMC 15 cps), F6 (Carbapol 974), F7 (Carbapol 971), F8 (Polyox WSR 303), F9 (Compritol ATO 888), F10 (Eudragit EPO), F11 (Eudragit S-100), F12 (CAP), F13 (Ethyl Cellulose), F14 (Gelucire 43/02), F15 (Gelucire 50/1), and F16 (Geleol).

**Evaluation of drug - polymer interaction:**

The pure drug, wax and the matrix tablet formulation were subjected to IR spectroscopy using FT-IR spectrophotometer (IR Affinity-1, Shimadzu). Their spectra were obtained over the wave number range of 4000 – 400 cm\(^{-1}\).

**Evaluation of Flowability of powder mass:**

1. **Flow rate:**

The flow rate of the precompressed powder formulations were determined as the ratio of mass (g) to time (seconds) using a steel funnel with an orifice diameter of 10 mm (n = 3).

2. **Carr’s compressibility index and Hausner’s ratio:**

30g quantity of powder mix of each formulation was carefully poured through a short stem glass funnel in a 100ml measuring cylinder and the volume, \(V_0\), occupied by the powder mix without tapping was noted. After 100 taps on the table, the occupied volume \(V_{100}\) was read.

The bulk and tap densities were calculated as the ratio of weight to volume (\(V_0\) and \(V_{100}\) respectively). Carr’s Index is a measure of powder bridge strength and stability, and Hausner’s ratio is a measure of the interparticulate friction and consolidation. Carr’s index and Hausner’s ratio were calculated using the following equations:-

\[
\text{Carr’s index} = \frac{(\text{Tapped density} – \text{Bulk density})}{\text{Tapped density}} \times 100
\]

\[
\text{Hausner’s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}.
\]

3. **True Particle density (\(\rho_T\))** of the powder blends were measured using a 25ml glass pycnometer with n-decane as non-solvent. Percentage porosity was calculated using the bulk and particle densities.
The compressibility studies:

1. Kawakita Analysis: The reduction in volume of bed with tappings was noted using bulk density apparatus. The plot of number of tappings \(n\) versus the degree of volume reduction \((n/C)\) was obtained, and the value of constants \(a\) and \(b\) was calculated by using the following equation \[^{16-18}\]:

\[
(n/C) = (n/a) + (1/ab)
\]

where \(n\) is the number of taps; \(a\) and \(b\) are constants, ‘\(a\)’ describe the degree of volume reduction at the time of tapping and is called tabletibility; ‘\(1/b\)’ is considered as constant of cohesion, and \(C\) is the degree of volume reduction and is given by equation as follows

\[
C = (V_0 - V_\infty) / V_0
\]

where \(V_0\) is the initial volume before tapping and \(V_\infty\) is volume after tapping.

2. Heckel compaction study:

The compaction characteristics of the powder blends were studied by means of the Heckel equation \[^{17,18}\].

\[
\ln \left[1/(1-\rho_r)\right] = KP + A
\]

Where, \(K\) and \(A\) are constants obtained from the slope and intercept of the plot \(\ln[1/(1-\rho_r)]\) versus \(P\), \(\rho_r\) is the relative density of a powder compact at pressure \(P\). Constant \(K\) (slope) give a measure of the plasticity of a compressed material. Greater slope indicated a greater degree of plasticity of materials, reflecting low resistance to pressure, good densification, higher plastic deformation ability, and easy compression. The reciprocal of the slope value represents the yield stress or yield pressure \((Py=1/K)\) for the particles. \(Py\) is defined as the stress at which plastic deformation of a particle is initiated. Constant \(A\) (intercept) which is extrapolated from the linear part of the Heckel plot. It represents the die filling and particle rearrangement before deformation and bonding of the discrete particles.

The compressibility studies were performed by using 10mm flat face punch and hand operated KBr hydraulic press. The appropriate amounts of powder mixtures were pressed at 320 MPa. At
the desired pressure, it was kept still for 20 sec. The height of the compact was measured and the volume was calculated. The compressibility data of each formulation were evaluated by fitting to the Heckel equation where, \( \rho_r \) is relative density of the tablet and \( P \) is the applied pressure (MPa), \( K \) is a constant determined from the slope and \( A \) from the intercept of a plot of \( \ln(1/1-\rho_r) \) vs. \( P \).

The data was also analyzed by Kawakita equation, in which \( P \) is the applied pressure (MPa), \( C \) is the degree of volume reduction, \( 1/ab \) is determined from intercept and \( 1/a \) from the slope a plot of \( P/C \) vs \( P \).

**Evaluation of Hardness and Thickness:**

The hardness of the tablet was determined by using a Monsanto hardness tester, expressed in kg/cm. The thickness of the tablets was measured by Digital Vernier Caliper, expressed in mm.

**Swelling index:**

Three tablets from each batch were weighed individually and placed separately in a thoroughly cleaned Petri dish containing 5 ml of 0.1 N HCl. At regular intervals the tablets were removed and weight was noted. The swollen tablets were reweighed and swelling index was calculated by using the formula [17]:

\[
S.I = \left( \frac{W_2 - W_1}{W_1} \right) \times 100
\]

Where, S.I–swelling index, \( W_1 \)-initial weight of Tablet, \( W_2 \)-weight of swollen tablet at time \( t \)

**Evaluation of in vitro drug release:**

In vitro dissolution assessment of the tablets was carried out in a USP II dissolution apparatus (Electrolab, TDT-08L). Nine hundred millilitres of 0.1 M HCl was used as the dissolution medium for 2 hrs and then replaced with phosphate buffer (pH 6.8) as the dissolution medium for another 8 hrs. Test temperature was 37±0.5°C while paddle rotation speed was kept at 75 rpm. At predetermined time intervals, 5 ml samples were withdrawn over a period of 12 hrs, filtered, suitably diluted and assayed at 272 nm spectrophotometrically (Shimadzu 1800). Sink condition was maintained by replenishing the dissolution medium with 5 ml fresh dissolution fluid on each occasion. All tests were carried out in triplicate. The regression equation of the calibration curve was:

\[
y = 0.008x - 0.001.
\]
Kinetic Modeling of Drug Release:

The dissolution profile of all the batches were fitted to zero order, first-order, Higuchi, Korsemeyer-Peppas to ascertain the kinetic modeling of drug release.

Results and Discussion:

Blend uniformity was consistent for all the formulations (95-105% recovery). The FTIR scan shows prominent peaks for the various active groups such as 3554 cm\(^{-1}\) corresponding to the N-H stretch in the tertiary amino group, 1457 cm\(^{-1}\) corresponding the C-O stretch between phenolic C and O group. The FTIR spectroscopic studies showed no significant changes in the intensity of principal peaks of the drug in any of the formulations. It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

All the formulations showed good flow rate indicating the correct concentrations of lubricant and glidant was used in the formulations, adequate for the necessary tableting technological parameters. The compressibility index and hauser’s ratio varied among the formulations, with highest for formulation with Carbapol 971NF whereas lowest for formulation with Gelucire 50/01. High values for Carr’s and Hausner ratios, denoted high cohesiveness of the powder blend. Different evaluated precompression parameters are shown in the table no. 1.

Highly porous formulations were found to be with PEG 6000 and CAP. The hardness of all formulations ranged from 2.4 to 5.2 kg/cm\(^2\), acceptable for the tablets.

Table 2: The compressibility studies:

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Kawakita parameters</th>
<th>Heckel parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>a</td>
<td>I/b</td>
</tr>
<tr>
<td>F1</td>
<td>0.752</td>
<td>0.097</td>
</tr>
<tr>
<td>F2</td>
<td>0.697</td>
<td>0.246</td>
</tr>
<tr>
<td>F3</td>
<td>0.621</td>
<td>0.198</td>
</tr>
<tr>
<td>F4</td>
<td>0.680</td>
<td>0.410</td>
</tr>
<tr>
<td>F5</td>
<td>0.703</td>
<td>0.398</td>
</tr>
<tr>
<td>F6</td>
<td>0.745</td>
<td>0.432</td>
</tr>
<tr>
<td>F7</td>
<td>0.731</td>
<td>0.402</td>
</tr>
<tr>
<td>F8</td>
<td>0.636</td>
<td>0.110</td>
</tr>
<tr>
<td>F9</td>
<td>0.539</td>
<td>0.091</td>
</tr>
<tr>
<td>F10</td>
<td>0.723</td>
<td>0.210</td>
</tr>
<tr>
<td>F11</td>
<td>0.716</td>
<td>0.189</td>
</tr>
<tr>
<td>F12</td>
<td>0.774</td>
<td>0.379</td>
</tr>
</tbody>
</table>
The parameters calculated from Kawakita equation for the formulations prepared with different polymers are given in Table no. 2. Kawakita equation was used to study powder compression using the degree of volume reduction ‘a’ of the powder mass \(^{[19, 20]}\). The highest ‘a’ value which was observed for F12 formulation, indicated the highest porosity and volume reduction. The higher values of 1/b have been reported to be related to the higher force required to reduce the volume to one half of the powder’s original volume and resulted from the particle fragmentation during compression. Low Py values indicates low resistance to pressure and high plastic deformation of the powder formulations. The smaller K values and highest Py value were calculated for F1 and F3, might be caused by its moisture content impairing the compressibilty. Higher values of A indicates high degree of rearrangement and easy compressibility, observed in F1, F2, F3 and F6. In the plots of F2, F9, F14, F15 and F16 initial linear part following prominant plateau were observed indicating hardening and change of crystal density and also elastic deformation of the powder \(^{[19, 21-22]}\). The formulations with HPMC K100M (F4), HPMC 15 cps (F5), Carbapol 974 (F6), Carbapol 971 (F7), Polyox WSR 303 (F8) were found to show maximum swellability. Swellability influences the drug release profile as, it crucially controls both the diffusion of the medium into the matrix and the drug dissolution and diffusion throughout the gel layer of the swollen matrix \(^{[23,24]}\).

<table>
<thead>
<tr>
<th></th>
<th>F13</th>
<th>F14</th>
<th>F15</th>
<th>F16</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>0.707</td>
<td>0.254</td>
<td>0.999</td>
<td>0.0100</td>
</tr>
<tr>
<td>b</td>
<td>1.02</td>
<td>1.24</td>
<td>1.26</td>
<td>1.01</td>
</tr>
<tr>
<td>K</td>
<td>0.9361</td>
<td>0.8152</td>
<td>0.8090</td>
<td>0.7291</td>
</tr>
<tr>
<td>Py</td>
<td>99</td>
<td>1.24</td>
<td>1.26</td>
<td>97</td>
</tr>
</tbody>
</table>

Figure 1: Swelling Index.
All formulations showed extended release profile for nearly 12 hours except F1 and F12. The more optimum, prolonged and consistent sustained drug release was observed in case of formulations with HPMC K100M (F4), Carbopol 971NF (F7), Polyox WSR 303 (F8), Gelucire 43/02 (F14) in comparison to other formulations. As shown in the table 5.

Where HPMC K100M, Carbopol 971NF, Polyox WSR 303 are the hydrophilic polymers and Gelucire 43/02 is hydrophobic waxy polymer. The three hydrophilic polymers were found show bioadhesion and maximum swellability. Swellability was observed to be increasing in the order of F8, F4 and F7. Figure no. 1 shows the comparative swellability index of all formulations F1 to F16.

**Table 3: Drug Release Kinetics of the best selected formulations:**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero order Kinetics</th>
<th>First order Kinetics</th>
<th>Higuchi</th>
<th>Korsmeyer-peppas</th>
<th>Drug release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>$R^2$</td>
<td>n</td>
</tr>
<tr>
<td>F4</td>
<td>0.8207</td>
<td>0.9553</td>
<td>0.9803</td>
<td>0.9550</td>
<td>0.4872</td>
</tr>
<tr>
<td>F7</td>
<td>0.9501</td>
<td>0.9825</td>
<td>0.9851</td>
<td>0.9800</td>
<td>0.4632</td>
</tr>
<tr>
<td>F8</td>
<td>0.9124</td>
<td>0.9721</td>
<td>0.9808</td>
<td>0.9798</td>
<td>0.5245</td>
</tr>
<tr>
<td>F14</td>
<td>0.8425</td>
<td>0.9572</td>
<td>0.9731</td>
<td>0.9760</td>
<td>0.765</td>
</tr>
</tbody>
</table>

The in-vitro dissolution plots are shown for all formulations from F1 to F16 in the Figure no. 2,3,4. The dissolution data of all the four formulations when fitted better into the first-order equation. It was evident from $R^2$ (correlation coefficient) value for first order kinetics higher than $R^2$ obtained from the zero-order equation for all formulations, showing that the release is an apparent first-order process. This indicates that the amount of drug released is dependent on the matrix drug load. On reduction of concentration for drug release, the diffusional path increases resulting in drug release at a comparatively slower rate in the later phase, thus fitting into Higuchi’s kinetics. Which was evident from the plot by Higuchi’s equation showing high linearity for all the four formulations indicating that the release process is diffusion-controlled. Accordingly the drug release from these matrix tablets involves penetration by dissolution fluid, dissolution of the drug in dissolution fluid and diffusion of the dissolved drug $^{[25, 26]}$. 

To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas equation \[^{[27]}\]. All of the four formulations showed fair linearity. This indicates that more than one type of release phenomena is involved. The release mechanism is shown in the table 3.

Figure 2: % Cumulative vs. Time plot for Hydrophilic polymers.

Figure 3: % Cumulative vs. Time plot for water insoluble polymers.

Figure 4: % Cumulative vs. Time plot for Hydrophobic waxy polymers.
Conclusion:

The hydrophobic polymers were better than hydrophilic polymers in prolonging the release of Tapentadol, which is a BCS class I drug. However, formulations with HPMC K100M (F4), Carbopol 971NF (F7), Polyox WSR 303 (F8), Gelucire 43/02 (F14) showed optimum and consistent sustained release among all formulations. Among these, first three are the hydrophilic polymers and Gelucire 43/01 is hydrophobic waxy polymer. Due to the Sol-Gel Behavior of the HPMC and Carbopol, served as good release extending polymers, exhibiting first order quasi fickian diffusion type of drug release mechanism. Whereas, Polyox WSR 303 and Gelucire 43/01 exhibited first order nonfickian anomalous diffusion mechanism of drug release. Swellability was observed to be increasing in the order of F8, F4 and F7. Which is supposed to influence the drug release kinetics. The higher degree of volume reduction was observed for F7 formulation among these selected formulations indicating the higher porosity and volume reduction. The low constant of cohesion was observed in case of F8 and F14, related to the lower force required to reduce the volume to one half of the powder’s original volume which is resulted from the particle fragmentation during compression. F4, F7, F8 exhibited low Py values indicating low resistance to pressure and high plastic deformation of the powder formulations. Initial linear part following prominent plateau were observed indicating hardening and change of crystal density and also elastic deformation of the powder blend in case of F14.
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