Preparation and Characterization of Sustained Release Matrix Tablets of Tizanidine Hydrochloride for Spinal Injuries

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Abstract

Purpose: To formulate matrix type sustained-release (SR) tablets of tizanidine hydrochloride (TH) for prolonged drug release and improvement in motor activity after spinal injuries.

Methods: Matrix tablets were prepared by the wet granulation method using four polymers (hydroxyl propyl methyl cellulose [HPMC] K 100, ethyl cellulose [EC], guar gum, and polyvinylpyrrolidone (PVP K30) and characterized for hardness, friability, drug content, swelling, weight variation, in vitro drug release, and in vivo motor function activity using the spinal injury rat model.

Results: All tablets showed good drug content, hardness, and other physicochemical properties. The tablet formulations showed a percent drug release ranging from 92.54 ± 1.02 to 98.56 ± 1.26 % at the end of 12 h. Using the spinal injury rat model, negative control had a motor activity of only 12.75 %, while F4 (containing HPMC, EC, and PVP) and F5 (containing EC, guar gum, and PVP) had motor activities of 62.25% and 57.5%, respectively, compared with 68.0 % for normal controls.

Conclusion: SR matrix tablets of TH showed significant improvement in motor activity in post-traumatic spinal injury rat model.

Keywords: Sustained release tablet, Spinal injuries, Matrix tablet, Tizanidine hydrochloride

INTRODUCTION

Oral sustained-release (SR) drug delivery systems are designed to deliver therapeutically effective concentrations of drug to the systemic circulation over an extended period of time. In general, conventional dosage forms are associated with various limitations, such as drug plasma level fluctuations (leading to adverse effects or toxicity due to overdoses), high dosage frequency, high dosage requirements, and poor patient compliance. For effective treatment, the drug plasma concentration must be maintained within a therapeutic range. The SR form decreases side effects and increases patient compliance, due to reduction in frequency of dosing. The SR form also maintains constant blood levels, and avoids drug plasma level fluctuations associated with conventional immediate release formulations [1].

Spinal injury (SI), especially post-traumatic injury, can be devastating to the patient. To repair the initial tissue damage, SI leads to complex cellular and molecular interactions within the central nervous system, and is characterized by the shearing of cell membranes and axons, disruption of the blood-spinal cord barrier, cell death, immune cell transmigration, and myelin degradation [2-5].
Neuropathic pain and inflammation greatly affect the quality of life after SI, and chronic pain is a very common and significant problem. Nonsteroidal anti-inflammatory drugs (NSAIDs) and skeletal muscle relaxants are frequently used for alleviating the pain, inflammation, and spasticity [6,7]. The chronic pain associated with SI is effectively treated with muscle relaxants like tizanidine hydrochloride (TH).

TH, an imidazole derivative, is an α-2-adrenergic receptor agonist which regulates myotonolytic effects of skeletal muscle. It reduces pathologically increased painful spasticity, especially in patients with spinal cord injury. In animal studies, its mechanism of action involves depressing polysynaptic reflexes, probably by antagonizing the excitatory actions of spinal interneurons [6-8]. In addition, it is effective in reducing muscle tone in spastic patients. TH is an antispastic agent with similar efficacy to that of baclofen, with a more favorable tolerability profile [9,10]. Furthermore, the benefits of administering TH in a modified release formulation have been demonstrated in clinical studies, with symptoms of spasticity and disability improved by approximately 94 % and 79 %, respectively [10]. However, TH has a short half-life (2.5 h), and low bioavailability (40 %), so a frequent dosage regimen is required.

Matrix tablets prepared with suitable polymers provide an effective approach in designing SR dosage forms [11-14]. Based upon these previous studies, a SR matrix tablet formulation of TH could result in a reduction in the administered dose and in its frequency of intake, and result in better patient compliance.

In the present study, we formulated TH tablets using a wet granulation method, then characterized the SR matrix tablets using polymers [hydroxypropyl methyl cellulose (HPMC), ethyl cellulose (EC), guar gum, and polyvinylpyrrolidone K-30 (PVP K-30)]. The resulting tablets were characterized for their in vivo motor function activity using the spinal injury rat model.

**EXPERIMENTAL**

**Materials**

TH, hydroxypropylmethyl cellulose (HPMC K100), EC, guar gum, PVP K-30, lactose, microcrystallin cellulose (MCC), and magnesium stearate were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals were of analytical grade.

**Methods**

**Preparation of SR matrix tablets of TH**

TH matrix tablets were prepared by the wet granulation method (Table 1).

For the preparation of tablets, all the powders were passed through 80 mesh (177 µm) filter. Drug and polymers (including granulating agents such as MCC and lactose) were mixed thoroughly in PVP solution (2 %), and then the resulting mass of cohesive material was passed through a 701 µm size mesh. The prepared granules were dried at 45 °C for 1 h, then talc and magnesium stearate were added. Finally, the tablets were compressed using a tablet compression machine (single punch tablet press; TDP, Shanghai, China).

**Tablet properties**

Tablet thickness were determined using a Vernier caliper, in three different positions for each tablet, followed by averaging the values (n = 6). Tablet hardness was measured using a Monsanto hardness tester (n = 6).

A USP disintegration apparatus (BJ-1; Nade Lab Instrument Disintegration Testing Tablet Disintegration Tester, Zhejiang, China) was used.

### Table 1: Composition of SR matrix tablets of tizanidine hydrochloride (per tablet)

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>TH (mg)</th>
<th>HPMC K 100 (mg)</th>
<th>EC (mg)</th>
<th>Guar gum (mg)</th>
<th>PVP K 30 (mg)</th>
<th>MCC (mg)</th>
<th>Lactose (mg)</th>
<th>Magnesium stearate (mg)</th>
<th>Talc (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>8</td>
<td>70</td>
<td>-</td>
<td>-</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F2</td>
<td>8</td>
<td>-</td>
<td>70</td>
<td>-</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F3</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>70</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F4</td>
<td>8</td>
<td>35</td>
<td>35</td>
<td>-</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F5</td>
<td>8</td>
<td>-</td>
<td>35</td>
<td>35</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>F6</td>
<td>8</td>
<td>35</td>
<td>-</td>
<td>35</td>
<td>15</td>
<td>25</td>
<td>35</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

**Note:** TH: Tizanidine hydrochloride; HPMC: hydroxyl propyl methyl cellulose; PVP K30: polyvinylpyrrolidone K30; MCC micro crystalline cellulose
to determine the disintegration time. A weight variation (WV) test was performed for 20 tablets from each batch, and the average values were calculated (Table 2). The percent weight variation was determined using equation 1:

\[ \text{WV} \% = \left( \frac{\text{total weight of twenty tablets} - \text{sum of the individual weights of twenty tablets}}{\text{total weight of twenty tablets}} \right) \times 100 \]  

The friability test was performed using a Roche friabilator (CS2 Nade Lab Instrument Disintegration Testing Tablet Friability Tester, Zhejiang, China). Ten tablets were weighed and placed in the friabilator, rotating at 25 rpm. After 100 revolutions, the tablets were dusted and reweighed. The percentage friability was determined using equation 2:

\[ \text{Friability} \% = \left( \frac{\text{Wo}}{\text{Wt}} \right) \times 100 \]  

where Wo and Wt were the initial and final weights, respectively, before and after a hundred revolutions.

**Drug content**

Ten tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of TH was placed in a 100 mL volumetric flask and made up to the volume with phosphate buffer, pH 6.8. The contents were agitated on a magnetic stirrer at 37 °C for 24 h. At the end of 24 h, the contents were analyzed spectrophotometrically at 320 nm after suitable dilutions (Table 2).

**Swelling index**

Swelling studies were performed to assess the extent of swelling for different formulations. The percent swelling was determined using equation 3:

\[ S \% = \left( \frac{\text{Ws} - \text{Wd}}{\text{Wd}} \right) \times 100 \]  

where Ws and Wd were the dry and swollen weights, respectively, at immersion time t in the test liquid.

**In vitro release studies**

In vitro dissolution studies of prepared tablets were performed in triplicate in a USP XXIII 8 station dissolution test apparatus (ZRS-8L; Intelligent Dissolution Tester, Tianjin University Radio Factory, Tianjin, China) at 100 rpm and 37 ± 1 °C. Simulated gastric fluid (900 mL, without enzymes) was used as the media, and the study was performed for 12 h. In the first 2 h, 0.1 N HCl was used, which was changed to phosphate buffer pH 6.8 after 2 h. The medium was changed by vacuum filtration, and the undissolved particles were washed with pH 6.8 phosphate buffer, then added again to the apparatus for further study. Aliquots of 5 mL were withdrawn at predetermined times and replaced with an equivalent amount of fresh dissolution media that was maintained at the same temperature. The withdrawn samples were filtered, diluted, and then recorded at 320 nm with a spectrophotometer.

**In vivo motor function activity of the spinal injury rat model**

Healthy male Wistar rats (200–250 g) were used for the study. The rats were kept in cages with standard environmental conditions of light and temperature. The rats were provided food and water *ad libitum*. Protocols of the animal studies were approved by the local Institutional Animal Care and Use Committee and performed in compliance with Directive 2010/63/EU on the handling of animals used for scientific purposes. Rats were divided into four groups (normal control, negative control, standard, and test groups) with six rats in each group. After administration of thiopental sodium (40 mg/kg), all animals were subjected to laminectomy (except the normal control group) to produce acute spinal injury by using an extradural 40 g force clip compression for 10 s at the T7 vertebrae, until the motor nerve activity was most affected. One group of normal control animals did not undergo the laminectomy. After 10 h, the experiment was initiated. Control groups were fed a suspension of 2 % Tween 80. The standard group received methyl prednisolone (MP) (30 mg/kg) intravenously at 30 min post injury. The test groups received an aqueous suspension of the TH SR tablets F4 and F5 per oral (p.o.) (1,000 µg/kg). At the end of 24 h, the motor nerve activity was determined by observing the performance of rats in the horizontal bar test. In this test, the rats were mounted on an assembly of a horizontal bar (2 mm diameter; 40 cm long) mounted on two supports, 50 cm in height. The rat was held by the tail, and allowed to touch the middle of the bar with only its forepaws. Its tail was released, and the stopwatch was simultaneously started. The time spent by rats on the horizontal bar was recorded, and scored as 1–5 seconds = 1; 6–10 seconds = 2; 11–20 seconds = 3; 21–30 seconds = 4; > 30 seconds = 5; and touching of the bar support with a forepaw = 5. If 5 points were achieved, then a 4 mm diameter bar was used again for the same rat, with the addition of 2 in scoring for the respective timings.
Statistical analysis

Results were expressed as mean values and standard deviations (± SD), and the significance of the difference was analyzed by the Student’s t-test, using Origin® 9 software, LA, US. A P-value less than 0.05 (p < 0.05) was considered significant.

RESULTS

The prepared SR matrix tablets of TH were evaluated for various physicochemical parameters (Table 2).

The weight variations of all the formulations were not significant and were within the pharmacopoeia limits of ± 7.5%. The tablets also showed hardness in the range of 3.5 ± 0.75 kg/cm² to 5.5 ± 0.88 kg/cm². The percentage friability was less than 1 % for all the formulations, indicating mechanical stability of the formulated tablets. Content uniformity for all formulations ranged from 94.72 ± 0.05 % to 98.80 ± 0.03 %, and the contents were in compliance with pharmacopoeia limits. The highest swelling was found for formulation F6, which contained HPMC and guar gum.

The percent cumulative drug release for all the formulations were in the following order: F5 > F4 > F1 > F6 > F2 > F3 (Fig 1).

Formulation F5 showed the higher drug content and highest cumulative drug release percentage. The best fit models for TH were the Higuchi models for F3 and F5, while the other models showed first-order release kinetics. The n values were greater than 0.6, suggesting non-Fickian diffusion (Table 3).

Table 2: Evaluation of SR matrix tablets of tizanidine hydrochloride

<table>
<thead>
<tr>
<th>Code</th>
<th>Weight variation* (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Content uniformity (%)</th>
<th>% Swelling (4 hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>150 ± 0.35</td>
<td>5.0 ± 0.59</td>
<td>0.42 ± 0.6</td>
<td>95.40 ± 0.05</td>
<td>39.4±0.101</td>
</tr>
<tr>
<td>F2</td>
<td>150 ± 0.76</td>
<td>5.5 ± 0.88</td>
<td>0.45 ± 0.09</td>
<td>98.80 ± 0.03</td>
<td>34.7±0.009</td>
</tr>
<tr>
<td>F3</td>
<td>150 ± 0.48</td>
<td>3.5 ± 0.75</td>
<td>0.72 ± 0.07</td>
<td>97.71 ± 0.02</td>
<td>42.2±0.023</td>
</tr>
<tr>
<td>F4</td>
<td>149 ± 0.33</td>
<td>5.5 ± 0.38</td>
<td>0.21 ± 0.02</td>
<td>94.72 ± 0.05</td>
<td>24.0±0.103</td>
</tr>
<tr>
<td>F5</td>
<td>150 ± 0.69</td>
<td>4.5 ± 0.75</td>
<td>0.68 ± 0.04</td>
<td>89.11 ± 0.01</td>
<td>49.0±0.03</td>
</tr>
<tr>
<td>F6</td>
<td>149 ± 0.93</td>
<td>4.0 ± 0.23</td>
<td>0.77 ± 0.03</td>
<td>92.24 ± 0.20</td>
<td>52.02±0.02</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation; F: formulation

Fig. 1: In vitro drug release of SR matrix tablet formulations of tizanidine hydrochloride
Table 3: Drug release mechanism of all the sustained-release tablet formulations of tizanidine hydrochloride

<table>
<thead>
<tr>
<th>Code</th>
<th>Zero order release</th>
<th>First order release</th>
<th>Higuchi release kinetics</th>
<th>Korsmeyer-Peppas release</th>
<th>Best fit model</th>
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<tr>
<td></td>
<td>( r^2 )</td>
<td>( r^2 )</td>
<td>( r^2 )</td>
<td>( r^2 )</td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>0.565</td>
<td>0.819</td>
<td>0.796</td>
<td>0.776</td>
<td>First order</td>
</tr>
<tr>
<td>F2</td>
<td>0.740</td>
<td>0.921</td>
<td>0.918</td>
<td>0.825</td>
<td>First order</td>
</tr>
<tr>
<td>F3</td>
<td>0.786</td>
<td>0.923</td>
<td>0.940</td>
<td>0.839</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F4</td>
<td>0.756</td>
<td>0.924</td>
<td>0.921</td>
<td>0.822</td>
<td>First order</td>
</tr>
<tr>
<td>F5</td>
<td>0.752</td>
<td>0.920</td>
<td>0.921</td>
<td>0.822</td>
<td>Higuchi</td>
</tr>
<tr>
<td>F6</td>
<td>0.772</td>
<td>0.948</td>
<td>0.930</td>
<td>0.825</td>
<td>First order</td>
</tr>
</tbody>
</table>

\( F \): formulation; \( r^2 \): regression coefficient

Table 4: In vivo motor function activity of SR matrix tablets of tizanidine hydrochloride in the spinal injury rat model

<table>
<thead>
<tr>
<th>Group</th>
<th>Total activity score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (normal)</td>
<td>8.70 ± 1.50</td>
</tr>
<tr>
<td>Control (negative)</td>
<td>1.02 ± 1.20</td>
</tr>
<tr>
<td>Standard (MP given i.v.)</td>
<td>5.44 ± 0.50</td>
</tr>
<tr>
<td>Test (F4)</td>
<td>4.98 ± 0.10*</td>
</tr>
<tr>
<td>Test (F5)</td>
<td>4.60 ± 0.24*</td>
</tr>
</tbody>
</table>

*Experimental section describes the scoring system; \( ^* p < 0.05 \) was considered significant; i.v. = intravenous; \( F \) = formulation; MP = methyl prednisolone

On the basis of the in vitro drug release results, tablet formulation F4 (containing HPMC and EC) and F5 (containing EC and guar gum) were selected for in vivo studies to assess the effectiveness of treating motor nerve activity in the post-traumatic spinal injury rat model. The results showed that the F4 formulation showed the best recovery from spinal injury, with F4 (containing HPMC, EC, and PVP) and F5 (containing EC, guar gum, and PVP) showing activity scores of 4.98 ± 0.10 and 4.60 ± 0.24, respectively, compared to a score of 5.44 ± 0.50 for the standard group (Table 4).

DISCUSSION

TH, which is an imidazoline that acts as an agonist at \( \alpha-2 \)-adrenergic receptors, has been shown to be effective in reducing spasticity, and is an effective drug for spasticity induced by spinal injuries. Because of its swelling properties, previous studies reported that the matrix tablet showed prolonged durations of action [11-14], consistent with the observation that swelling is one of the most critical factors in sustaining drug release. In the present study, hydrophilic polymers like HPMC with guar gum (F6) showed good swelling, due to better imbibition of water or simulated gastric fluid.

When significant swelling occurs, the diffusional path length is increased, and drug release is retarded or sustained. The results of drug release in the present study were consistent with previous studies, which also reported that the amount of drug release was inversely proportional to the polymer concentration in prepared matrix tablets [11-12,17-22].

Swelling increased with time, and weight gain by prepared tablets increased in direct proportion with the rate of hydration, for up to 4 h. Later, it gradually decreased due to dissolution of the outermost tablet gel layer into the dissolution medium. In addition, the swelling was directly proportional to the polymer concentration. A matrix, upon contact with an aqueous solution, undergoes wetting, which starts from the surface, followed by the progression via microscopic pores into the inner core. The nature of the polymer therefore plays an important role in this swelling process. The presence of water in the polymer causes a stress, resulting in hydration of the polymer, which swells to yield a gelatinous viscous layer [15,16].

The use of HPMC, EC, guar gum, and PVP in the polymeric granules not only provided sustained release, but also provided complete release from the SR tablets. Furthermore, the combination of HPMC and EC with PVP (F4) and EC and guar gum with PVP (F5) showed good in vitro, as well as in vivo, properties.

After treatment, the negative controls had a motor activity of only 12.75 %, while the F4- and F5-treated animals had motor activities of 62.25 and 57.5 %, respectively, compared with a motor activity of 68 % for the standard group. The increased motor activity was an indication of reduced spasticity. The rat model of spinal injury demonstrated the efficacy of TH SR tablets, as compared to that of the standard. The prolonged and sustained release profile may therefore be
suitable for patients with traumatic spinal injuries, to improve their quality of life.

CONCLUSION

Sustained release matrix tablets of TH prolong the time of drug release, and thus might be helpful in improving patient compliance and motor function activity in patients with post-traumatic spinal injuries. The prepared formulations showed remarkable improvement in motor function activity in the traumatic spinal injury rat model. The formulations should therefore be further tested in patients with spinal injuries, to assess their possible neuroprotective effects in reducing painful spasticity.

REFERENCES