Title: SUSTAINED RELEASE FORMULATION COMPRISING TIZANIDINE

Abstract: The present invention relates to a sustained release multiparticulate formulation comprising Tizanidine or a pharmaceutically acceptable salt thereof. The multiparticulate form is used for the treatment of painful muscle spasms due to problems with spasticity and musculoskeletal system in the form of oral dosage forms such as capsules, sachets, tablets.
SUSTAINED RELEASE FORMULATION COMPRISING TIZANIDINE

Technical Field of the Invention

The present invention relates to a multiparticulate oral pharmaceutical formulation comprising tizanidine or a pharmaceutically acceptable salt thereof for use in the treatment of painful muscle spasms due to spasticity and musculoskeletal system.

Background of the Invention

Tizanidine is a central acting muscle relaxant medicine that primarily affects the central nervous system, especially the spinal cord. Its antispasmodic activity is due to the agonist effect on central presynaptic alpha 2 - adrenergic receptors. It mainly acts at the level of the spinal cord. It reduces resistance to passive movements, alleviates spasm and muscle contraction, relaxes voluntary muscle strength. It is used to assist in the treatment of spasticity and against painful muscle spasms due to problems in the musculoskeletal system.

The chemical name of tizanidine is 5-chloro-N-(2-imidazolin-2-yl)-2,1,3-benzothiadiazol-4-ylamine and its chemical structure is as shown in Formula 1.

![Chemical Structure of Tizanidine](image)

**Formula 1**

Tizanidine is available as immediate-release tablets (2 mg, 4 mg) and modified-release micropellet capsules (6 mg and 12 mg) with SIRDALUD® commercial
name of Novartis Company; available as immediate release capsules (2, 4, 6 mg) and tablets (2, 4 mg) with ZANAFLEX® commercial name of Acorda (US) and Cephalon (UK).

The SIRDALUD® MR (modified release) micropellet capsule contains 6.864 mg of Tizanidine hydrochloride (Tizanidine HCl) equivalent to 6 mg of Tizanidine as the active ingredient. The initial dose recommended in the treatment of spasticity due to neurological disorders is 6 mg once daily; the daily dose may be increased by 1 capsule of 6 mg every half-week or every week, if necessary. The usual dose ranges from 6 to 24 mg per day. According to clinical experiences, once a day, a total of 12 mg doses given as two 6 mg capsules or one 12 mg capsule was the optimum dose for the majority of patients and rarely 24 mg was required.

SIRDALUD® MR micropellet capsule formulation contains sucrose, ethyl cellulose, shellac, talc, corn starch, gelatin, titanium dioxide (E 171), black iron oxide.

ZANAFLEX® (Acorda) immediate release capsule contains Tizanidine HCl as active ingredient and hydroxypropylmethylcellulose (HPMC), silicon dioxide, sugar spheres, titanium dioxide, gelatin and colorants (US 20140341985 A1). The pellets in the ZANAFLEX® capsule are produced by Elan Corporation with SODAS® (Spheroidal Oral Drug Absorption System) multiparticulate drug delivery technology.

Patent application of Acorda, US20150038539 A1, relates to a method for increasing the absorption of the tizanidine. In the patent, immediate-release and multiparticle forms comprising Tizanidine HCl are disclosed. These forms contain sugar spheres. In the formulation, the sugar sphere is coated with a solution containing Tizanidine HCl, hydroxypropylmethylcellulose (HPMC), talc, and preferably organic acid (fumaric acid) using a fluid bed system.

In the article (Thriveni et al., IJPSR, 2013; No. 4 (4): 1614-1625), sustained release multiple particulate forms containing Tizanidine HCl have been disclosed.
In this study, sugar spheres are coated with 3.5% (w/w) active ingredient, 3% (w/w) polyvinylpyrrolidone as binder (PVP K30), talc and sugar. During this coating process an organic solvent (isopropyl alcohol) is used. The coated sugar spheres are coated with the second layer comprising ethyl cellulose N-50 and (1-4 %w/w) hydroxypropylmethylcellulose E5 (HPMC E5) (1-4% w/w) in 1:1 ratios, in the presence of organic solvent. The fluid bed method is used for coating this second layer. The obtained pellets (F2-F5 samples in the article) are filled into the capsule. The dissolution profile of product obtained is compared to the dissolution profile of ZANAFLEX® capsule. As a result, it was found that the dissolution profiles of F2-F5 samples were not similar when compared to the innovator product. According to this study, the dissolution profile of sample F7 comprising 2% ethyl cellulose N-50 and 2% Eudragit L-100 combination in the second layer were found to be similar to the dissolution profile of the pellets with the innovator product.

Patent application of Acorda, US20160030399 A1, discloses immediate release oral dosage forms of tizanidine containing multiparticles. In these forms, there are Tizanidine or a pharmaceutically acceptable salt thereof in the range of 2 mg to 12 mg and at least one pharmaceutically acceptable excipient. This formulation is coated on a sugar sphere.

Patent application of Evonik Röhm GmbH, WO2006102965 A1, relates to multiparticulate forms containing controlled release pellets having three layers. In the form, there is an inner core comprising a neutral core, polymer, resin or protein; a layer comprising the active ingredient; and an outer layer comprising methacrylate copolymer. In the patent, it is mentioned that the inner layer contains a shellac.

The shellac is a natural product commonly used as a coating agent on tablet cores. However, there are a number of disadvantages. There are color differences after coating with shellac. The reproducibility of studies with shellac is difficult. There is a supply shortage due to the decrease in production in the market. If shellac is
in alcohol solution, its structure changes in storage conditions. Shellac tends to polymerize. This feature can prevent the solid pharmaceutical product from being dispersed in the stomach or intestine as desired. One of the most common problems is the drying of the shellac after a certain period of time. Shellac is creating problems in the production and storage of multi-particulate forms.

The organic solvent is used during the production of the multiparticulate forms. However, the risk of organic solvent toxicity is not preferred due to a number of disadvantages such as the risk of explosion during production. In addition, it is not ecologically suitable because it may also cause environmental contamination. On the other hand, the nonuse of organic solvents is also safer for the patient. Since it is problematic that the residual impurity related to the solvent is present on the finished product. This impurity remains a danger to human health.

In multiparticle dosage forms, there are particles containing one or more active ingredients dispersed in the subunits. These subunits or particles can be pellets or spherical particles. They typically have a layer-like structure or a matrix structure.

A variety of modified release pharmaceutical forms for oral administration are known. The release of the active ingredient must be controlled as a function of the therapeutic purpose and also of the pharmacological properties of the active ingredient. Multiparticulate dosage forms are particularly used in modified release systems. These forms have many advantages over single unit dosage forms. Multiparticulate systems can produce the desired controlled release behavior and are distributed as subunits. Among the forms, oral preparations still have great importance. Multiparticulate drug forms can be applied to capsules (e.g., hard gelatin capsules) or packaged in a sachet or compressed into tablets.

There are many parameters that are important in the production of the multiparticulate dosage form. For the treatment of a high-quality multiparticulate form, selection of suitable excipients, weight of the form, distribution of
ingredients, a suitable production process and a good formulation design are important factors.

Summary of the Invention

The object of the present invention is to provide an oral sustained release pharmaceutical formulation comprising multiparticulate forms comprising tizanidine or a pharmaceutically acceptable salt thereof.

Another object of the present invention is to provide an oral pharmaceutical formulation comprising a sustained release multiparticulate forms, free of organic solvent.

A further object of the present invention is to provide an oral pharmaceutical formulation comprising a sustained release multiparticulate form containing a layer comprising active ingredient and low viscosity hydroxypropylmethylcellulose coating sugar sphere; and low viscosity hydroxypropylmethylcellulose and ethylcellulose coating the first layer at a certain ratio.

Another object of the present invention is to provide an oral pharmaceutical formulation comprising sustained release multiparticulate forms with the desired dissolution profile by the use of the active ingredient, low viscosity hydroxypropylmethylcellulose and ethyl cellulose at certain ratio.

Another object of the present invention is to provide an oral pharmaceutical formulation with a pH independent dissolution profile releasing no more than 25% within the first hour, at least 40% after 4 hours and at least 85% after 12 hours, measured by USP Type I apparatus (basket), at 100 rpm in dissolution media at different pHs (0.1 N HCl, pH 4.5, pH 6.8) (within 24 hours).
Detailed Description of the Invention

The present invention relates to a sustained release formulation comprising tizanidine or a pharmaceutically acceptable salt thereof for oral administration.

The formulation of the invention comprises multiparticulate forms.

The term "multiparticulate" is used as a particle having more than one discrete unit, pellet, granule, bead, minitablet or mixtures thereof.

Important factors in the development of the present invention comprising sustained release multiparticulate forms comprising tizanidine or a pharmaceutically acceptable salt thereof; selection of suitable excipients, weight of the form, distribution of ingredients, a suitable production process and a good formulation design.

The present invention is an oral pharmaceutical formulation comprising sustained release multiparticulate forms comprising tizanidine or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the invention, the present invention comprises sugar sphere. The active ingredient may be present in the sugar sphere or in any of the layers covering the sugar sphere.

The present multiparticulate form comprises a sugar sphere, an active ingredient layer coating the sugar sphere, and a release control layer coating the active ingredient layer.

Preferably, the present multiparticulate form comprises an active ingredient layer comprising tizanidine or a pharmaceutically acceptable salt thereof, and binder; a release control layer comprising pore former and release modifier.

For determining the release characteristics of the present invention, the choice of binder, the concentration of the binder (% weight/total weight) are critical
parameters. In a preferred embodiment of the invention, the binder is selected from a group comprising binding gelatin, hydroxypropylcellulose (HPC), hydroxypropylmethylcellulose (HPMC), methyl cellulose, polyvinyl pyrrolidone, sucrose, starch and mixtures thereof. Preferably, the binder is hydroxypropylmethylcellulose.

In the preferred embodiment of the present invention, hydroxypropylmethylcellulose is selected from a group comprising Methocel™ E5, Methocel™ E5 LV, Methocel™ E15 LV, Methocel™ E50 LV, Methocel™ K100 LV, and Methocel™ F50 LV, Methocel™ E3 LV, Methocel™ E6, Methocel™ K3, Methocel™ A15, Methocel™ K15M and Methocel™ K100M, Methocel™ K4000M and mixtures thereof. Preferably, hydroxypropylmethylcellulose has low viscosity (150 centipoise (cP) and below, at 20°C degree, in 2% aqueous solution). The low-viscosity hydroxypropylmethylcellulose is selected from a group comprising Methocel™ E5 (5cP), Methocel™ E5 LV (5cP), Methocel™ E15 LV (15cP), Methocel™ E50 LV (50cP), Methocel™ K100 LV (100cP), and Methocel™ F50 LV (50cP), Methocel™ E3 LV, Methocel™ E6 and mixtures thereof.

Due to the variety of chemical and physical properties of the release modifiers, the release modifier selection, the concentration of the release modifier (% weight / total weight) are critical parameters, especially for determining the release characteristics. In a preferred embodiment of the invention, the release modifier is selected from a group of starch, sugar, ethyl cellulose, microcrystalline cellulose, Eudragit® (methacrylate copolymer), sodium carboxymethyl cellulose, polyvinyl acetate (Kollicoat® SR), hydroxypropylcellulose and mixtures thereof. Preferably, the release modifier is ethyl cellulose.

Ethyl cellulose is preferably used in the form of aqueous dispersion. The aqueous dispersion form contains ethyl cellulose dry weight in the range of 10 to 50% of the total weight of the aqueous dispersion. Preferably, the aqueous dispersion contains from 10% to 40%, more preferably from 15% to 30%, most preferably
from 15% to 25% ethyl cellulose dry weight of the total weight of the aqueous dispersion.

The present invention relates to multiparticulate form comprising an sugar sphere coated with an active ingredient layer comprising tizanidine or a pharmaceutically acceptable salt thereof and low-viscosity hydroxypropylmethylcellulose; and the active ingredient layer coated with a release control layer comprising low-viscosity hydroxypropylmethylcellulose and ethyl cellulose.

In the preferred embodiment of the invention, the oral pharmaceutical formulation comprising the sustained release multiparticulate does not contain organic solvent.

The invention preferably comprises tizanidine or equivalent amount of salt in an amount ranging from 2 mg to 24 mg, preferably from 6 mg to 12 mg. Preferably, the pharmaceutically acceptable salt of tizanidine is used. In the preferred embodiment of the invention, tizanidine HCl is used.

In the preferred embodiment of the invention, the low viscosity hydroxypropylmethylcellulose present in the first layer, which is also the active ingredient layer, is present in certain proportions. In this layer, low viscosity hydroxypropylmethylcellulose is preferably present in an amount of 1 to 10% by weight, more preferably 2 to 6% by weight based on the total weight.

In the preferred embodiment of the invention, the combination of low viscosity hydroxypropylmethylcellulose and ethyl cellulose in the second layer, the release control layer, is present in certain proportions. In this layer, the low viscosity hydroxypropylmethylcellulose is preferably present in an amount of 0.1% to 10%, more preferably from 0.1% to 5%, even more preferably from 0.5% to 4%. In this layer, hydroxypropylmethylcellulose is preferably used for its pore former function.

In the preferred embodiment of the invention, the ethyl cellulose co-present with the low viscosity hydroxypropylmethylcellulose in the second layer is preferably
present in an amount of 0.1 to 50% by weight, more preferably from 10 to 40% by weight, even more preferably from 10 to 30% by weight. In this layer, hydroxypropylmethylcellulose is preferably used for its pore former function.

In the preferred embodiment of the invention, the combination of low viscosity hydroxypropylmethylcellulose and ethyl cellulose in the second layer is present at certain ratios. Thus, an oral pharmaceutical formulation comprising a multiparticulate form which provides sustained release with the desired dissolution profile is achieved.

In a preferred embodiment of the invention, the weight ratio of ethyl cellulose and low viscosity hydroxypropylmethylcellulose in the release control layer is in the range of 5:1 to 20:1. Preferably, the weight ratio is between 8:1 and 20:1, more preferably between 8:1 and 13:1. Most preferably, the weight ratio is 8:1 to 10:1.

The multiparticulate form is preferably filled into a soft or hard gelatin capsule, or packaged in a sachet or compressed into tablets.

In a preferred embodiment of the invention, at least one sustained release multiparticulate form is present in a soft or hard gelatin capsule.

The pharmaceutical formulation of the invention is used for the treatment of painful muscle spasms due to problems with spasticity and musculoskeletal system.

In the preferred embodiment of the invention, the multiparticulate form is pellet.

In a preferred embodiment of the invention, the pellets are filled in a hard gelatin capsule.

The dissolution profile of the present invention containing said multiparticulate form is determined according to the following procedure:
The dissolution test is carried out at 100 rpm for 24 hours using the USP apparatus I (basket) in each of the following media. As the dissolution medium:

900 ml of 0.1 N HCl, for pH 1.2 medium,

900 ml of acetate buffer for pH 4.5 medium, and

900 ml of phosphate buffer is used for pH 6.8 medium.

The amount of time-dependent released active ingredient was determined by HPLC.

In the present invention, the active ingredient has a pH-independent dissolution profile; an oral dosage form comprising a multiparticulate form in any of the above dissolution media displays a dissolution profile that results in:

- no more than 25% within the first hour,

- at least 40% after 4 hours and

- at least 85% tizanidine released after 12 hours.

According to the present invention, the desired dissolution profile is provided by the different characteristic features of the two layers covering the sugar sphere. More particularly, the desired dissolution profile is provided by means of certain ratios of the release control layer content.

In the preferred embodiment of the invention oral dosage forms are prepared from multiparticulate forms. Oral dosage forms may contain, in addition to the multiparticulate forms, one or more excipients selected from the group consisting of filler, lubricant, antistatic agent, dispersant, surfactant, glidant.

In one embodiment of the invention, said dosage forms comprise a pharmaceutically acceptable filler selected from the group comprising calcium
sulfate, dibasic calcium phosphate, lactose, mannitol, microcrystalline cellulose, starch, sucrose and mixtures thereof.

In a preferred embodiment of the invention said dosage forms comprise a pharmaceutically acceptable lubricant selected from the group comprising calcium stearate, glycerin, vegetable oil, magnesium stearate, mineral oil, polyethylene glycol, propylene glycol group and mixtures thereof.

In a preferred embodiment of the invention, said dosage forms comprise a pharmaceutically acceptable antistatic agent selected from the group comprising kaolin, talc, silicon dioxide and mixtures thereof.

In the preferred embodiment of the invention, said dosage forms comprise a pharmaceutically acceptable disintegrant selected from the group comprising alginate, croscarmellose sodium, crospovidone, sodium starch glycollate, pregelatinized starch and mixtures thereof.

In the preferred embodiment of the invention, surfactant is selected from the group comprising polysorbate, sodium lauryl sulfate and mixtures thereof.

In the preferred embodiment of the invention, glidant is selected from the group comprising colloidal silicon dioxide, magnesium stearate, starch, talc and mixtures thereof.

In the present invention, frequently used coating methods known in the pharmaceutical industry can be used to accomplish coatings in the form of multiparticulates. However, the fluidized bed coating system is particularly preferred.

In a preferred embodiment of the invention said multi particulate form comprises:

- 50% to 80% by weight of sugar sphere,

- in the active ingredient layer;
- 3% to 10% by weight of tizanidine hydrochloride

- 2% to 6% by weight of low viscosity HPMC

- in the release control layer;

- 10% to 30% by weight of ethyl cellulose

- 0.5% to 4% of low viscosity HPMC

- 0.1 to 10% by weight of talc

Another embodiment of the invention is a method of preparing capsule dosage form comprising multiparticulate form comprising the steps of:

- Preparation of coating solutions

- Coating of sugar sphere with coating solution containing active ingredient and binder,

- Coating of the active ingredient layer with coating solution containing pore former and release modifier,

- drying of the multiparticulate form after coating.

- filling multi-particulate forms into hard gelatin capsule

The following examples are intended to further illustrate the invention and are not to be construed as limiting the invention.

**Examples**

**Example 1- Multiparticulate Form Composition**
The table below (Table 1) contains the formulation information of the oral pharmaceutical forms comprising the multiparticulate. The multiparticulate forms are in pellet form.

**Table 1. Examples of Multiparticulate Oral Pharmaceutical Form**

<table>
<thead>
<tr>
<th>Inner Core</th>
<th>Example I (% w/w)</th>
<th>Example II (% w/w)</th>
<th>Example III (% w/w)</th>
<th>Example IV (% w/w)</th>
<th>Example V (% w/w)</th>
<th>Example VI (% w/w)</th>
<th>Example VII (% w/w)</th>
<th>Example VIII (% w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar Sphere</td>
<td>75.53</td>
<td>75.03</td>
<td>76.22</td>
<td>76.47</td>
<td>76.72</td>
<td>76.96</td>
<td>77.09</td>
<td>62.28</td>
</tr>
<tr>
<td>Active Ingredient Layer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tizanidine HCl</td>
<td>4.47</td>
<td>4.42</td>
<td>4.49</td>
<td>4.51</td>
<td>4.52</td>
<td>4.53</td>
<td>4.65</td>
<td>3.54</td>
</tr>
<tr>
<td>Hydroxypropyl methyl cellulose (HPMC)</td>
<td>4.40</td>
<td>4.40</td>
<td>4.47</td>
<td>4.49</td>
<td>4.50</td>
<td>4.51</td>
<td>4.50</td>
<td>3.52</td>
</tr>
<tr>
<td>Release Control Layer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
<td>15.20</td>
<td>12.58</td>
<td>12.78</td>
<td>12.82</td>
<td>12.87</td>
<td>12.91</td>
<td>12.93</td>
<td>-</td>
</tr>
<tr>
<td>Hydroxypropyl methyl cellulose (HPMC)</td>
<td>-</td>
<td>3.15</td>
<td>1.60</td>
<td>1.28</td>
<td>0.99</td>
<td>0.5</td>
<td>0.52</td>
<td>1.38</td>
</tr>
<tr>
<td>Tale Eudragit NE30D</td>
<td>0.40</td>
<td>0.42</td>
<td>0.43</td>
<td>0.43</td>
<td>0.40</td>
<td>0.44</td>
<td>0.40</td>
<td>15.41</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>13.87</td>
</tr>
</tbody>
</table>

The weight ratios of ethylcellulose to HPMC in the release control layer of the multiparticulate oral pharmaceutical formulations of Table 1 are given below (Table 2).

**Table 2. Weight Ratios of Ethyl Cellulose: HPMC in the Release Control Layer**

<table>
<thead>
<tr>
<th>Ethyl Cellulose : HPMC</th>
<th>Example I</th>
<th>Example II</th>
<th>Example III</th>
<th>Example IV</th>
<th>Example V</th>
<th>Example VI</th>
<th>Example VII</th>
<th>Example VIII</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*</td>
<td>4:1</td>
<td>8:1</td>
<td>10:1</td>
<td>13:1</td>
<td>20:1</td>
<td>25:1</td>
<td>**</td>
</tr>
</tbody>
</table>

* It contains only Ethyl cellulose, not HPMC.

** It is the Eudragit® NE30D to HPMC ratio. The ratio is 10:1.

Coating of pellets containing tizanidine HCl was carried out according to the formulations given in Table 1. The sugar sphere is coated with the active ingredient layer, and subsequently the release control layer. Methocel™ E5, ethyl
cellulose (Surelease®) and Eudragit® NE30D are placed in different concentrations in coating solutions prepared in water presence. Coating and drying processes were performed with Solidlab II fluid bed dryer system.

The coating conditions of the pellets are as follows (Table 3):

<table>
<thead>
<tr>
<th>Table 3. Fluid Bed Coating Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spray speed</td>
</tr>
<tr>
<td>Atomized air pressure</td>
</tr>
<tr>
<td>Input air flow rate</td>
</tr>
<tr>
<td>Inlet air temperature</td>
</tr>
<tr>
<td>Product temperature</td>
</tr>
</tbody>
</table>

The coated pellets are dried in a fluidized bed at 40°C for about 20 minutes. During the drying process, the air flow rate is maintained at about 150 m³/h. Solidlab II fluid bed dryer system was used for coating and drying processes.

The pellets are filled into a hard gelatin capsule.

**Example 2 – Dissolution Test**

Dissolution tests were carried out on the formulations in Example 1 in the light of the following parameters. Each capsule contains 6 mg Tizanidine equivalent to Tizanidine HCl salt.

<table>
<thead>
<tr>
<th>Table 4. Dissolution Test Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissolution Media</td>
</tr>
<tr>
<td>Volume</td>
</tr>
<tr>
<td>Apparatus</td>
</tr>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Speed</td>
</tr>
<tr>
<td>Analysis Method</td>
</tr>
</tbody>
</table>
Example 3 – Comparative Results of Dissolution Tests

The dissolution test results below were performed using the pH 6.8 phosphate buffer (24 hours) in Table 4.

Formulation examples (I-VII) were compared against 24-hour drug release in pH 6.8 phosphate buffer.

Table 5. Dissolution Profile (Example I-VII)

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>% Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example I</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
</tr>
<tr>
<td>12</td>
<td>79</td>
</tr>
<tr>
<td>13</td>
<td>82</td>
</tr>
<tr>
<td>19</td>
<td>90</td>
</tr>
<tr>
<td>24</td>
<td>94</td>
</tr>
</tbody>
</table>

The dissolution test results below were performed using 0.1 N HCl (24 hours), pH 4.5 acetate buffer (24 hours) and pH: 6.8 phosphate buffer (24 hours) in Table 4. Example IV (ethyl cellulose: HPMC to weight ratio 10: 1) was used for the test.

Table 6. Example IV dissolution test in three pH media

<table>
<thead>
<tr>
<th>Time (hour)</th>
<th>% Drug Release</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Example IV</td>
</tr>
<tr>
<td></td>
<td>pH: 1.2</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Time (hour)</td>
<td>% Drug Release</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td></td>
<td>Example IV</td>
</tr>
<tr>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>76</td>
</tr>
<tr>
<td>7</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>89</td>
</tr>
<tr>
<td>13</td>
<td>91</td>
</tr>
<tr>
<td>19</td>
<td>93</td>
</tr>
<tr>
<td>24</td>
<td>93</td>
</tr>
</tbody>
</table>

The dissolution test results in Table 7 below were obtained in 900 ml pH 6.8 phosphate buffer (24 hours).

Example IV (ethyl cellulose: HPMC to weight ratio 10: 1) and Example VII (Eudragit: HPMC to weight ratio 10: 1) were used for the test.

**Table 7. Comparative Dissolution test results of Example IV and VII**

It is possible to develop a wide variety of applications around these basic concepts, and the invention, which is essentially as set forth in the claims, can not be limited to the examples disclosed herein.
CLAIMS

1. A sustained release formulation in the multiparticulate form comprising tizanidine or a pharmaceutically acceptable salt for oral administration, wherein said multiparticulate form comprises:
   - sugar sphere coated with active ingredient layer comprising tizanidine or a pharmaceutically acceptable salt thereof and low viscosity hydroxypropylmethylcellulose;
   - active ingredient layer coated with release control layer comprising low-viscosity hydroxypropylmethylcellulose and ethyl cellulose; and wherein
   - the ratio of ethyl cellulose:hydroxypropylmethylcellulose in the release control layer is in the range of 5:1 to 20:1 by weight.

2. The multiparticulate form according to claim 1, wherein the ratio of ethyl cellulose:hydroxypropylmethylcellulose in the release control layer is in the range of 8:1 to 13:1 by weight.

3. The multiparticulate form according to claim 2, wherein the ratio of ethyl cellulose:hydroxypropylmethylcellulose in the release control layer is in the range of 8:1 to 10:1 by weight.

4. A multiparticulate form according to any of the preceding claims wherein tizanidine or a pharmaceutically acceptable salt thereof releases in accordance with the following dissolution profile as measured by in one of the buffers which are 900 ml of 0.1 N HCl, 900 ml of pH 4.5 acetate buffer and 900 ml of pH 6.8 phosphate buffer, at 100 rpm, according to USP apparatus I (basket),
   - no more than 25% within the first hour
   - at least 40% after 4 hours
- at least 85% after 12 hours

5. The multiparticulate according to any one of the preceding claims, wherein the tizanidine salt is tizanidine hydrochloride.

6. The multiparticulate form of any one of claims 1-5, wherein the viscosity of the low-viscosity hydroxypropylmethylcellulose used in the production of multiparticulate form is no more than 150 cP.

7. The multiparticulate form according to any one of claims 1-6, wherein the hydroxypropylmethylcellulose used in the production of multiparticulate form is one or more of the low viscosity hydroxypropylmethylcellulose having a viscosity of 5 cP, 15 cP, 50 cP, 100 cP.

8. The multiparticulate form according to any one of claims 1-7, wherein the low viscosity hydroxypropylmethylcellulose present in the active ingredient layer is present in an amount of 0.1 to 5% by weight, more preferably 0.5 to 4% by weight, based on the total weight of the multiparticulate form.

9. The multiparticulate according to any one of claims 1-8, wherein the multiparticulate form is selected from a group of particle having more than one discrete unit, pellet, granule, bead, minitablet and mixtures thereof.

10. The multiparticulate according to claim 9, wherein the multiparticulate form is pellet.

11. The multiparticulate form according to any one of claims 1 to 10, wherein it comprises the following substances in the amounts specified according to the weight of the multiparticulate form:

- 50% to 80% by weight of sugar sphere,

- in the active ingredient layer;
- 3% to 10% by weight of tizanidine hydrochloride

- 2% to 6% by weight of low viscosity HPMC

- in the release control layer;

- 10% to 30% by weight of ethyl cellulose

- 0.5% to 4% of low viscosity HPMC

- 0.1 to 10% by weight of talc

12. The oral dosage form comprising multiparticulate form according to any one of claims 1-11, wherein the dosage form is a capsule, sachet or tablet.

13. The oral dosage form according to claim 12, wherein it is a capsule.

14. An oral dosage form according to any one of claims 12 to 13, wherein it comprises one or more excipients selected from the group comprising of filler, lubricant, antistatic agent, dispersant, surfactant, glidant and mixtures thereof.

15. The oral dosage form according to any one of claims 12-14, wherein the amount of Tizanidine or pharmaceutically acceptable salt in the unit dosage form is in the range of 2 mg to 24 mg, preferably 6 mg to 12 mg.

16. The oral dosage form according to any one of claims 12-15, wherein tizanidine or a pharmaceutically acceptable salt thereof releases in accordance with the following dissolution profile as measured by in one of the buffers which are 900 ml of 0.1 N HCl, 900 ml of pH 4.5 acetate buffer and 900 ml of pH 6.8 phosphate buffer, at 100 rpm according to USP apparatus I (basket),

- no more than 25% within the first hour

- at least 40% after 4 hours
- at least 85% after 12 hours

17. The oral dosage form according to any of claims 12-16, wherein the use of the multiparticulate form according to any of claims 1-11 in the manufacture of a medicament is for the treatment of painful muscle spasms due to problems with spasticity and musculoskeletal system.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/50 A61K31/433
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, CHEMABS Data, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>Y</td>
<td>THRVENI M ET AL: &quot;Design and evaluation of sustained release multiparticulate system of Tizanidine hydrochloride&quot;, INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH - IJPSR, SOCIETY OF PHARMACEUTICAL SCIENCES AND RESEARCH, IN, vol. 4, no. 4, 1 April 2013 (2013-04-01), page 1614, XP009501370, ISSN: 0975-8232, DOI: 10.13040/IJPSR.0975-8232.4(4).1614-25 cited in the application the whole document abstract page 1615, right-hand column, line 18 - page 1616, left-hand column, line 9 tables 1,2,7 figures 3-6,8-15 -----</td>
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See patent family annex.

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Date of the actual completion of the international search
9 November 2017

Date of mailing of the international search report
17/11/2017

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Authorized officer
Marchand, Petra
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