Title: PHARMACEUTICAL PELLET COMPOSITIONS FOR CONTROLLED RELEASE

Abstract: The present invention provides a pharmaceutical composition in the form of pellet wherein controlled release of pharmacologically active substances can be effected. The present invention is characterized by a pharmaceutical composition for controlled release pellets, consisting essentially of: a) one or more pharmacologically active substances; b) one or more lipids having a low-melting point of less than 70°C and existing as a solid at room temperature; c) one or more hydrophilic substances; and d) one or more water-insoluble binding agents, prepared without melting the lipids.
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:  
— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.
Description
PHARMACEUTICAL PELLET COMPOSITIONS FOR
CONTROLLED RELEASE

Technical Field

[1] The present invention relates to a pharmaceutical composition for controlled release pellets prepared by use of a solid lipid and a water-insoluble binding agent in conjunction with a pharmacologically active substance, without melting the lipid at high temperature.

[2] In particular, the present invention enables preparation of pellets in which poorly-mixable lipid components and hydrophilic active substances are homogeneously miscibilized by formation of lipid pellets through low-temperature solid phase heat processing below 60°C, thereby facilitating easy control of release rate and being suited for controlled release of heat-labile drugs.

Background Art

[3] Korean Patent Laid-open Publication No. 2003-0072557 discloses a matrix in which an active ingredient is uniformly dispersed in lipid materials selected from fatty alcohols, triglyceride, partial glyceride and fatty acid esters. This patent prepares the matrix by warming lipid materials to 90°C or higher to obtain a clear molten liquid, suspending a drug of interest therein, and then cold-spraying the resulting suspension to prepare a matrix of the active ingredient. In contrast, the present invention is characterized by formation of solid pellets in which the active ingredient is uniformly dispersed through solvent granulation, even without melting of solid lipids. Generally, these lipid materials are difficult to form into pellets by simple use of solvents or by conventional water-soluble binding agents commonly used in the art. As such, even after granulation, physico-chemical properties and shapes of pellets are easily damaged, rendering secondary processing impossible, and leading to burst release of drugs. Meanwhile, the present inventors have demonstrated that controlled release pellets can be prepared by forming pellet precursors using the water-insoluble binding agent relative to low-melting solid lipids, and heat-processing the pellet precursors at a tepid temperature of less than 60°C. Therefore, the present invention is a method having very high productivity whereby preparation of solid formulations can be implemented using existing equipment and apparatuses widely used in the art, such as fluid bed dryers, centrifugal granulators and hot air dryers.

resulting mixture, an aqueous suspension, aqueous emulsion, aqueous gel or organic solvent solution of an acrylate polymer or water-insoluble cellulose derivative and water and granulating the resulting mixture to obtain a sustained release composition. Although this patent exhibits similarities to the present invention in that a water-insoluble binding agent is used in the preparation of the sustained release pharmaceutical composition, there is no disclosure of low melting-point lipids and low temperature heat processing as are employed in preparation of the sustained release pellets in accordance with the present invention.

Korean Patent Laid-open Publication No. 2002-0011992 discloses a method for preparing a porous matrix, comprising dissolving an active substance in a volatile solvent to form a drug solution, combining the solution with a pore-forming agent to form an emulsion or suspension, and then removing the volatile solvent and pore-forming agent from the emulsion or suspension so as to yield a porous drug matrix. However, the method of this patent involves use of hydrophilic polymers, sugars, pegylated excipients and tonicity agents as the pore-forming agent, does not mention lipid components and describes immediate-release characteristics only, not sustained release characteristics.

Korean Patent Publication No. 1997-0004906 B1 discloses a method for preparing a sustained release preparation using water-soluble or water-insoluble polymeric materials and fatty acids, alcohols and waxes, in conjunction with buspirone and salts thereof as an active substance. In this patent, however, it is described that sustained release is accomplished by simple granulating and tableting of the mixed components, without preparation of pellets through heat processing. In particular, examples in this patent describe only hydrogel (a water-soluble polymer)-forming sustained release tablets and mention of water-insoluble polymers is made only in claims.

Korean Patent Laid-open Publication No. 2003-0036877 discloses a sustained release composition comprising a metformin salt as the active substance and a hydrophobic polymer and other hydrophobic materials. This patent employs fatty components derived from fatty acids and shellac, rosin, polyethylene and the like, as the hydrophobic polymer and hydrophobic materials, but is characterized in that the hydrophobic materials and active substance are mixed and melted by typical hot-melt methods. As such, this patent is different from the method of the present invention involving granulation without a warming process, followed by low-temperature heat processing to form pellets.

Disclosure of Invention
Technical Problem

As described above, conventional arts use solid lipids for the purpose of controlled
release, but they are characterized in that preparation is carried out by hot melt methods, or melt injection and then cooling. Therefore, there is a significant difference between conventional methods and the present invention using a solvent granulation method at room temperature and subsequent low-temperature heat processing so as to form sustained release pellets. In addition, the present invention is remarkably advantageous in that it is possible to prepare sustained release lipid pellets without high temperature treatment and thereby the sustained release technology of the present invention is applicable to a variety of heat-labile drugs. In addition, upon preparing pellets using lipids as a main base material, there was not found any case in the conventional arts wherein application of a granulation method using solvents relative to the lipid base material was made. Further, in accordance with the present invention, it is advantageously possible to effect homogeneous dispersion and miscibilization between water-soluble active substances (i.e., active substances that are immiscible with liquid lipids, due to their high polarity) and insoluble or water-soluble excipients (i.e., excipients that are immiscible with liquid lipids, due to their high polarity or intrinsic insolubility), which was substantially impossible in lipid processing using conventional melting methods, and thereby realize easy control of release rate.

Additionally, some of the conventional arts control release characteristics of drugs simply by mixing or wet granulating solid lipids, followed by direct tableting or compression. That is, existing techniques have demonstrated that it is possible to control release characteristics without melt processing only when tablet formulations are prepared by physical compression, specifically by tableting methods commonly used in the art. Nonetheless, in this case, since substantial release control depends upon compressibility of tablet formulations, when compressed lipid formulations disintegrate in the gastrointestinal tract, release of the drug of interest sharply increases, thereby making it nearly impossible to control drug release. In contrast, the present invention has proved that it is possible to prepare lipid pellets having greatly superior controlled release properties by preparing a mixed composition of a low melting point solid lipid and water-insoluble binding agent, and subjecting the composition to solvent granulation and low-temperature heat processing, without a lipid compression molding or molten lipid molding process.

**Technical Solution**

In accordance with an aspect of the present invention, the above and other objects can be accomplished by the provision of a pharmaceutical composition for controlled release pellets, consisting essentially of:

- a) one or more pharmacologically active substances;
- b) one or more lipids having a low-melting point of less than 70°C and existing as a
solid at room temperature;

c) one or more hydrophilic substances; and

d) one or more water-insoluble binding agents,

wherein the pellets are prepared without melting the lipids.

Therefore, depending upon physico-chemical properties of the pharmacologically active substances and pharmacodynamic factors, it is possible to reduce adverse side effects due to sharply increased blood concentration of drugs upon immediate release and to effect controlled release of the active substance so that the duration of action and the efficacy of the drug can be extended. In addition, by mixing immediate release pellets and the sustained release pellets of the present invention, it is possible to make the combined release patterns such that an initial blood concentration of the drug can be rapidly increased to the concentration that is capable of exerting the drug action or higher and thereafter, can be maintained at such a blood concentration.

Pharmacologically active substances that are applicable to the present invention include, but are not limited to, antihypertensives, anti-hyperlipidemics, anti-obesity drugs, anti-diabetics, prostatic hypertrophy treatment, drugs for improving sexual function, immunosuppressive drugs, anti-ulcer drugs, narcotic and non-narcotic analgesics, anesthetics, anti-inflammatory analgesics, antihypertensives, steroidal hormones, tranquilizers, antidepressants, sedative hypnotics, antipsychotics, anti-convulsants, antispasmodics, anti-emetics, antitussives, rhinitis drugs, antibiotics, antifungal agents, anti-viral agents, blood flow agents, cardiovascular drugs, osteoporosis therapies and the like.

As specific examples of respective drugs, mention may be made of the followings:

The antihypertensives may include amlodipine maleate, amlodipine besylate, felodipine, nifedipine, lercanidipine, nicardipine, diltiazem, lacidipine, enalapril, ramipril, fosinopril, cilazapril, imidapril, captopril, atenolol, carvedilol, doxazosin, terazosin and prazosin.

The anti-hyperlipidemics may include simvastatin, atorvastatin, lovastatin, fenofibrate, pravastatin, fluvastatin, gemfibrozil and bezafibrate.

The anti-obesity drugs may include orlistat, sibutramine, Camellia sinensis, cholestyramine, colesterin, phentermine, benzphetamine, diethylpropion, phenidimetrazine and bontril.

The anti-diabetics may include glimepiride, rosiglitazone, pioglitazone, CKD-501, metformin, gliclazide, acarbose, voglibose, glibenclamide and repaglinide.

The prostatic hypertrophy treatments may include finasteride, tamsulosin, tolterodine and propiverine.

The drugs for improving sexual functions may include tadalafil, sildenafil, vardenafil, yohimbin, yohimbe, apomorphine, phenotolamine and testosterone.
[25] The immunosuppressive drugs may include cyclosporine, tacrolimus, mycophenolate (mofetil) and azathioprine.

[26] The anti-ulcer drugs may include ranitidine, rebamipide, cimetidine, omeprazole, famotidine, nizatidine, teprenone, misoprostol, rabeprazole, roxatidine, ecabet, pantoprazole, lansoprazole and esomeprazole.

[27] The narcotic and non-narcotic analgesics may include paracetamol, caffeine, propifenasone, ibuprofen, tramadol, deanol, ketorolac, clonixine, mefenamic acid, acetyl salicylic acid, methionine, pranoprofen, fentanyl, codeine, oxycodone, morphine, pethidine and dihydrocodeine.

[28] The anesthetics may include lidocaine, bupivacaine, oxybuprocaine, propofol, sevoflurane, enflurane, midazolam and isoflurane.

[29] The anti-inflammatory analgesics may include acetclofenac, talniflumate, diclofenac, loxoprofen, naproxen, meloxicam, celecoxib, nabumetone, etodolac, piroxicam, rofecoxib, nimesulide, dexibuprofen, diacerhein and zaltoprofen.

[30] The antirheumatics may include hydroxychloroquine, bucillamine and penicillamine.

[31] The steroidal hormones may include methylprednisolone, prednisolone, deflazacort, dexamethasone, triamcinolone, hydrocortisone, betamethasone, colistin, clobetasol, desoxymethasone and desonide.

[32] The tranquilizers may include alprazolam, buspirone, tofasopam, diazepam, clotiazepam, etizolam, lorazepam, hydroxyzine, bromazepam and ethyl loflazepate.

[33] The antidepressants may include paroxetine, fluoxetine, sertraline, venlafaxine, mirtazapine, Hypericum perforatum, quinupramine, trazodone, amitriptyline, moclobemide and milnacipran.

[34] The sedative hypnotics may include triazolam, zolpidem, doxylamine, flunitrazepam, chloral hydrate, brotizolam, phenobarbital, zopiclone, estazolam, flurazepam and midazolam.

[35] The antipsychotics may include risperidone, olanzapine, clozapine, quetiapine, haloperidol, zotepine and nemonapride.

[36] The anti-convulsants may include valproic acid, gabapentin, carbamazepine, topiramate, oxcarbazepine, vigabatrin, lamotrigine and phenytoin.

[37] The antispasmodics may include tioproamide, cimetropium bromide, otilonium, pinaverium bromide, phloroglucinol, caroverine, scopalamine butylhydroxide, difemerine, mebeverine, glycopyrronium hydroxide, aclatonium napadisilate and fenoverine.

[38] The anti-emetics may include ondansetron, granisetron, scopalamine, tropisetron, dimenhydrinate, pyridoxine, ramosetron, meclozine and chlorphenamine.

[39] The antitussives may include methylephedrine, chlorphenamine, dextromethorphan,
dihydrocodeine, guaifenesin, noscapine, lysozyme, acebrophylline, levodropropizine, sulfogaiaicol, phenylephrine, benproperine, pseudoephedrine, formoterol, salbutamol, bambuterol, fenoterol, terbutaline, clenbuterol, procaterol, fluticasone, salmeterol, formoterol and budesonide.

[40] The rhinitis drugs may include phenylpropanolamine, chlorphenamine, Atropa belladonna, brompheniramine, phenylephrine, tripolidine, glycyrhizic acid, cetirizine, ebastine and terfenadine.

[41] The antibiotics may include netilmicin, isepamicin, ribostamycin, micronomicin, amikacin, astromycin, tobramycin, gentamycin, sisomicin, kanamycin, cefaclor, ceftriaxone, cefmetazole, cefazedone, cefotaxime, cefotiam, flomoxef, ceftezol, cephradine, cefotaxime, cefadroxil, cefprozil, cefpiramide, cefoperazone, ceftazidime, cefdinir, cefpodoxime proxetil, sulbactam, cefmox, ceftizoxime, cefditoren pivoxil, cefuroxime axetil, cefamandole, cefotetan, cephalaxin, ceforanide, cefbuperazone, ceftrizine, cefuroxime, cefepime, cefetam pivoxil, cefroxadine, cefazolin, cefmenoxime, vancomycin, teicoplanin, fusidic acid, spectinomycin, fosfomycin, meropenem, imipenem, cilastatin, aztreonam, loracarbef, amoxicillin, clavulanic acid, ampicillin, bacampicillin, piperacillin, ciclicillin, tazobactam, sulbamicillin, ciprofloxacin, levofloxacin, ofloxacin, norfloxacin, tosufloxacin, perfloxacin, lomefloxacin and sparfloxacin.

[42] The antifungal agents may include itraconazole, fluconazole, terbinafine, amphotericin B, ketoconazole and nystatin.

[43] The anti-viral agents may include lamivudine, acyclovir, famcyclovir, valacyclovir, methisoprinol, ribavirin, oseltamivir, gancyclovir, imiquimod, indinavir, nelfinavir, stavudine and zidovudine.

[44] The blood flow agents may include Ginkgo biloba, nicergoline, nimodipine, pentoxifylline, proxyphylline, coumarin, kallidinogenase, Melilotus officinalis, ajmalicine, almitrine, citicoline, vinburnine, ascorbic acid, acetyl carnitine, oxiracetam, choline and piracetam.

[45] The cardiovascular drugs may include digoxin, methylidigoxin, nicorandil, trimetazidine, molsidomine, dilazep, isosorbide nitrate and nitroglycerin.

[46] The osteoporosis therapeutics may include alendronic acid, pamidronic acid, menatetrenone, salcatonin and elcatonin.

[47] In addition, pharmaceutically acceptable salts of the above-mentioned materials are also encompassed within the scope of the active substances of the present invention.

[48] In addition, the lipid component having a low melting point of less than 70°C and existing as a solid at room temperature in accordance with the present invention may include one or more materials selected from fatty acids, fatty alcohols, fatty acid-fatty alcohol esters, fatty acid glycerol esters, fatty acid propylene glycol esters, sorbitan
fatty acid esters and sucrose fatty acid esters. Since these materials all have low melting points within the range of 45 to 70°C, they are employed in preparation of pellets having uniform drug content and controlled release in accordance with the present invention through low temperature processing. Further, since these lipids commonly have a structure of an alkyl chain containing more than 10 carbon atoms and thus are fat-soluble, they will control release of drugs in an aqueous solution or in serous fluid of the body. Lipid components in accordance with the present invention may include one or more materials selected from fatty acids such as stearic acid and lauric acid; fatty acid-fatty alcohol esters such as cetyl palmitate and myristyl myristate; fatty acid glycerol esters such as glyceryl monostearate, glyceryl palmitostearate and glyceryl behenate; fatty acid propylene glycol esters such as propylene glycol monostearate; sorbitan fatty acid esters such as sorbitan monopalmitate and sorbitan monostearate; and sucrose fatty acid esters such as sucrose laurate (HLB = 1 to 5) and sucrose stearate (HLB = 1 to 7). In addition, these low-melting point lipids are soluble or are partially dispersible/soluble in alcohols or organic solvents and thus it is possible to form pellet precursors through granulation via the use of a mixed solvent containing the organic solvent. More specifically, without being limited to the following, physico-chemical properties of lipids utilized in the present invention are listed in Table 1 below.

Table 1
Melting point of low-melting point lipids and their solubility in various solvents

<table>
<thead>
<tr>
<th>Lipid</th>
<th>m.p. (°C)</th>
<th>Solubility with respect to solvents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stearic acid</td>
<td>&gt; 54</td>
<td>Benzene, chloroform, ether, ethanol, hexane, PG</td>
</tr>
<tr>
<td>Stearyl alcohol</td>
<td>55-62</td>
<td>Chloroform, ethanol, ether, hexane, PG, oils</td>
</tr>
<tr>
<td>Glyceryl monostearic acid</td>
<td>55-60</td>
<td>Hot ethanol, ether, chloroform, hot acetone, mineral oils, fixed oils</td>
</tr>
<tr>
<td>Glyceryl palmitostearic acid</td>
<td>52-55</td>
<td>Chloroform</td>
</tr>
<tr>
<td>Glyceryl behenate</td>
<td>65-77</td>
<td>Hot chloroform, hot MC</td>
</tr>
<tr>
<td>Sorbitan monopalmitate</td>
<td>43-48</td>
<td>Oils, solvents</td>
</tr>
<tr>
<td>Sorbitan monostearic acid</td>
<td>53-57</td>
<td>Oils, solvents</td>
</tr>
<tr>
<td>Sucrose stearic acid (HLB 3)</td>
<td>51-69</td>
<td>Hot ethanol, hot PG*</td>
</tr>
<tr>
<td>Sucrose lauric acid (HLB 1)</td>
<td>51-61</td>
<td>Hot oils, hot ethanol, hot PG*</td>
</tr>
<tr>
<td>Sucrose lauric acid (HLB 5)</td>
<td>&lt; 70</td>
<td>Water, ethanol*</td>
</tr>
</tbody>
</table>

* solvents or oils maintained at a temperature of about 70°C

The hydrophilic material used in the present invention is a concept opposite to lipophilicity and refers to material having relatively superior solubility in water. In order to form characteristics and shapes of lipid pellets without hot melting and to have grindability in a granulation process, hydrophilic components are necessary. That is, since both solid lipids and water-insoluble binding agents of the present invention have the characteristics and shapes of lipids when they are partially or completely dissolved in the mixed solvent and then granulated, they are not pulverized but mashed even after being dried, and thereby, particles cannot be obtained. Therefore water-soluble materials that do not behave like lipids during grinding are required in order to achieve effective solvent granulation and to produce uniform granules. The hydrophilic material may be at least one selected from saccharides, amino acids, inorganic electrolytes and water-soluble polymers. Saccharides include, but are not limited to, white sugar, lactose, fructose, mannitol, sorbitol, xylitol, inositol, isomalt, maltitol, alpha, beta and gamma cyclodextrin and their derivatives, for example carboxymethyl
cyclodextrin, methyl cyclodextrin, maltosyl cyclodextrin, hydroxyethyl cyclodextrin, hydroxypropyl cyclodextrin and sulfobutyl (ester) cyclodextrin. All saccharides may be in monosaccharide or oligosaccharide form. Amino acids include, but are not limited to, alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, glycine, serine, threonine, cysteine, glutamine, tyrosine, asparagine, alginine, lysine, histidine, asparaginic acid and glutamic acid, trytophan or oligopeptides containing less than 10 component amino acids. Inorganic electrolytes include, but are not limited to, sodium chloride, sodium carbonate, sodium bicarbonate, dicalcium phosphate, calcium carbonate, ferric oxide. The water-soluble polymers include, but are not limited to, polysaccharides such as starches and their derivatives including hydroxyethyl starch, cellulose derivatives such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose and carboxymethyl cellulose, alginic acid such as alkali metal salts of alginic acid dextrin and its derivative such as maltodextrin, pyrrolidone derivatives such as polyvinylpyrrolidone, alkylene oxides such as polyoxyethylene and poloxamer, acrylic acid derivatives such as carbomer, and vinyl alcohols such as polyvinyl alcohol.

[52] The water-insoluble binding agent in accordance with the present invention refers to a material that is completely insoluble in water and is soluble in a solvent in which an organic solvent has been mixed, and exhibits strong bindability to lipid base materials upon drying. The present inventors have made attempts to form pellet precursors by application of various water-soluble polymeric binding agents and cross-linked polymeric binding agents, inorganic binding agents and saccharide binding agents, which are widely utilized in the pharmaceutical field, without lipid melting. However, due to inherent properties of solid lipids, any binding agent cannot provide binding capacity sufficient to form pellet precursors without melting the lipid at high temperature. In contrast, since the water-insoluble binding agents in accordance with the present invention are solubilized by the mixed solvent containing the organic solvent, in particular in the granulation process, it is possible to effect homogeneous miscibilization between the binding agents and solid lipids without the warming process. Furthermore, after removal of the organic solvent, firm lipid pellet precursors are formed. As water-insoluble binding agents that can be utilized in the present invention, mention may be made of shellac and maize prolamain, Zein, derived from natural products, acrylic acid derivatives, for example, polymethacrylate and its derivatives, such as polymethylmethacrylate, polyethylmethacrylate, polydimethy-laminomethylmethacrylate and polytrimethylaminomethylmethacrylate, cellulose derivatives such as hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate and a hydrophobic fatty acid derivative of hydroxypropyl methylcellulose (product name: Sangelose), and any combination thereof.
The following process may be used to prepare the above-mentioned pharmaceutical composition, although the present invention is not limited to the following process. Firstly, there will be specifically illustrated a process for preparing pellet precursors via the use of room-temperature granulation without a warming process.

The pharmacologically active substance, low-melting point solid lipid and hydrophilic substance are mixed without melting, and if necessary, the resulting mixture is screened through a standard mesh screen having a mesh size of 60 or higher to render the mixture homogeneous. Then, the water-insoluble binding agent is dissolved in the mixed solvent containing the organic solvent to prepare a binding solution which is subsequently used, or the water-insoluble binding agent is previously mixed in the above mixture and then the mixture is used for a subsequent process. As the organic solvent contained in the mixed solvent, mention may be made of chloroform, methylene chloride, diethyl ether, tetrahydrofuran, acetone, isopropyl alcohol, ethanol, benzene, hexane and any combination thereof. Tetrahydrofuran, acetone and isopropyl alcohol and ethanol, among them, are water-miscible and thus can be used by mixing with less than 50% (by volume) of water. The binding solution or mixed solvent is physically mixed and kneaded with the final powdered mixture so as to prepare a slurry or sludge material. The resulting materials are passed through a standard mesh screen having a mesh size from 10 to 30 to form particles which are then dried under warm air or vacuum to remove the mixed solvent. Dried particles are additionally passed through a standard mesh screen having a mesh size from 10 to 45 to prepare pellet precursors having a uniform particle size.

Subsequent heat processing at low temperature, which is carried out for the prepared pellet precursors, will now be described in detail. Pellet precursors are rotated at a high speed, or floated, or allowed to stand in an apparatus such as a fluid bed dryer, a centrifugal granulator, a tablet coater, a cabinet dryer or the like. This is followed by low-temperature heat processing for 10 minutes to 24 hours by continuous injection of warm air at a predetermined temperature of less than 60°C to the apparatus, thereby preparing controlled release pellets. At this time, low-temperature heat processing is characterized in that this process is carried out at below the melting point of the lipids and is initiated with the pellet precursors in solid phase, and lipid pellets are matured to achieve controlled release while continuously maintaining the solid phase during the entire processing time. In this manner, it will be possible to form controlled release pellets in which lipid components are homogeneously miscibilized with pharmacologically active substances or pharmacological excipients, regardless of their hydrophilicity or hydrophobicity.

**Brief Description of the Drawings**
The above and other objects, features and other advantages of the present invention will be more clearly understood from the following detailed description taken in conjunction with the accompanying drawings, in which:

Fig. 1 is a dissolution curve of tamsulosin hydrochloride by pharmaceutical formulations of Examples 1 through 6; and

Fig. 2 is a dissolution curve of carvedilol by pharmaceutical formulations of Examples 7 through 9.

**Best Mode for Carrying Out the Invention**

**EXAMPLES**

Now, the present invention will be described in more detail with reference to the following examples. These examples are provided only for illustrating the present invention and should not be construed as limiting the scope and spirit of the present invention.

**Examples 1 through 6**

For examples 1 through 6, as shown in Table 2 below, tamsulosin hydrochloride as a pharmacologically active substance, glycerol palmitostearate as a lipid component, sodium alginate and lactose as hydrophilic substances, and croscarmellose sodium as a conventional disintegrating agent were mixed and the resulting mixture was passed through a 60 mesh standard screen to prepare a homogeneous mixture. As a water-insoluble binding agent, powdered zein was homogeneously admixed to the mixture, and shellac was dissolved in 90% ethanol to obtain a transparent solution, which was used as a binding solution.

**Table 2**

<table>
<thead>
<tr>
<th></th>
<th>Example 1</th>
<th>Example 2</th>
<th>Example 3</th>
<th>Example 4</th>
<th>Example 5</th>
<th>Example 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamsulosin HCl</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Glyceryl palmitostearate</td>
<td>20</td>
<td>17</td>
<td>19</td>
<td>19</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Sodium alginate</td>
<td>13</td>
<td>16</td>
<td>12</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Zein</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Shellac</td>
<td>7</td>
<td>6.55</td>
<td>7</td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>90% Ethanol</td>
<td>8.6</td>
<td>8.1</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
<td>8.6</td>
</tr>
</tbody>
</table>

*Provided that 90% ethanol is by volume (mL).

Next, to the homogeneous mixture of Examples 1 through 6, the thus-prepared
binding solution was added and kneaded into a slurry or sludge which was then sieved through a 14-mesh screen to perform granulation. Then, the granulates were dried to remove the mixed solvent, and sieved through a 16-mesh screen to perform granulation. Dried granulates were charged to a centrifugal granulator and subjected to low-temperature heat processing with high-speed rotation at an exhaust temperature of 54±1°C for 1 hour, so as to prepare pellets containing tamsulosin hydrochloride. Capsules were filled with the prepared pellets in an amount of 0.2 mg tamsulosin hydrochloride per capsule.

66] Examples 7 through 9

For examples 7 through 9, as shown in Table 3 below, carvedilol as a pharmacologically active substance, sucrose laurate (HLB = 1) as a lipid component, and beta-cyclodextrin as a hydrophilic substance were mixed and the resulting mixture was passed through a 60 mesh standard screen to prepare a homogeneous mixture. As a water-insoluble binding agent, powdered zein was homogeneously admixed to the mixture, and shellac was dissolved in 90% ethanol to obtain a transparent solution, which was used as a binding solution.

68] Table 3

<table>
<thead>
<tr>
<th>Pharmaceutical compositions of Examples 7 through 9 (Unit: gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
</tr>
<tr>
<td>Sucrose laurate (HLB = 1)</td>
</tr>
<tr>
<td>Beta-cyclodextrin</td>
</tr>
<tr>
<td>Zein</td>
</tr>
<tr>
<td>Shellac</td>
</tr>
<tr>
<td>90% Ethanol</td>
</tr>
</tbody>
</table>

*Provided that 90% ethanol is by volume (ml).

69] Next, to the homogeneous mixture of Examples 7 through 9, the thus-prepared binding solution was added and kneaded into a slurry or sludge which was then sieved through 14-mesh screen to perform granulation. Then, the granulates were dried to remove the mixed solvent and sieved through a 16-mesh screen to perform granulation. Dried granulates were charged to a centrifugal granulator and subjected to low-temperature heat processing with high-speed rotation at an exhaust temperature of 56±1°C for 1 hour, so as to prepare pellets containing carvedilol. Tablets were formulated by filling with the prepared pellets in an amount of 25 mg carvedilol per tablet, and additionally adding 15% of lactose, 5% of microcrystalline cellulose and 1% of magnesium stearate, based on the total weight, followed by mixing and compressing the mixture into a tablet.
Examples 10 through 13

For examples 10 through 13, as shown in Table 4 below, ranitidine hydrochloride as a pharmacologically active substance, stearic acid as a lipid component, and polyvinyl alcohol as a hydrophilic substance were mixed and the resulting mixture was passed through a 60 mesh standard screen to prepare a homogeneous mixture. As a water-insoluble binding agent, powdered Zein was homogeneously admixed to the mixture, and shellac was dissolved in ethanol to obtain a transparent solution, which was used as a binding solution.

Table 4

<table>
<thead>
<tr>
<th>Pharmaceutical compositions of Examples 10 through 13</th>
<th>Example 10</th>
<th>Example 11</th>
<th>Example 12</th>
<th>Example 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine HCl</td>
<td>300</td>
<td>300</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Stearic acid</td>
<td>300</td>
<td>400</td>
<td>300</td>
<td>400</td>
</tr>
<tr>
<td>Polyvinyl alcohol</td>
<td>50</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Zein</td>
<td>25</td>
<td>25</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Shellac</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Ethanol</td>
<td>480</td>
<td>480</td>
<td>520</td>
<td>520</td>
</tr>
</tbody>
</table>

(Unit: gram)

*Provided that ethanol is by volume (ml).

Next, except for the binding solution as described above, the homogeneous mixture of Examples 10 through 13 were floated in a fluid-bed dryer and granulated by passing through a 14-mesh screen while spraying the binding solution. After completion of binding solution spraying, the granulates were thoroughly dried to remove the solvent. Subsequently, the dried granulates were subjected to low-temperature heat processing while being floated at an exhaust temperature of 56± 1 °C for 1 hour, thereby preparing pellets containing ranitidine hydrochloride. Capsules were filled with the prepared pellets in an amount of 150 mg ranitidine hydrochloride per capsule.

Examples 14 through 16

For examples 14 through 16, as shown in Table 5 below, tramadol hydrochloride as a pharmacologically active substance, glycercyl monostearate as a lipid component, and lactose as a hydrophilic substance were mixed and the resulting mixture was passed through a 60 mesh standard screen to prepare a homogeneous mixture. As a water-insoluble binding agent, powdered polymethacrylate (Eudragit RS PO) was homogeneously mixed with the mixture, and Zein was dissolved in 80% ethanol to obtain a transparent binding solution.

Table 5
Pharmaceutical compositions of Examples 14 through 16  
(Unit: gram)

<table>
<thead>
<tr>
<th></th>
<th>Example 14</th>
<th>Example 15</th>
<th>Example 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol HCl</td>
<td>200</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Glyceryl monostearate</td>
<td>150</td>
<td>200</td>
<td>250</td>
</tr>
<tr>
<td>Lactose</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Eudragit RS PO</td>
<td>25</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Zein</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>80% Ethanol</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
</tbody>
</table>

*Provided that 80% ethanol is by volume (ml).

Next, to the homogeneous mixture of Examples 14 through 16, the thus-prepared binding solution was added and kneaded into slurry or sludge which was then sieved through a 14-mesh screen to perform granulation. Then, the granulates were dried to remove the mixed solvent, followed by granulation by sieving through a 16-mesh screen. Dried granulates were charged to a centrifugal granulator and subjected to low-temperature heat processing with high-speed rotation at an exhaust temperature of 56±1 °C for 1 hour, so as to prepare pellets containing tramadol hydrochloride. Capsules were filled with the prepared pellets in an amount of 150 mg tramadol hydrochloride per capsule.

**Experimental Examples 1 through 6**

In order to confirm a controlled release dissolution, dissolution test was carried out for each of the capsules prepared in Examples 1 through 6.  

6 capsules, from the respective Examples, were tested at 100 rpm and 37 ±0.5°C. 2 hours after initiation of the dissolution test, 5 ml of eluate was aliquoted from 500 ml of a dissolution medium (pH 1.2) containing 0.2% Tween 80. Immediately afterwards, pellets were transferred to 500 ml of a dissolution medium (pH 7.2) and 5 ml of eluate was aliquoted 3 and 5 hours after initiation of the dissolution test. Eluates aliquoted at 2, 3 and 5 hours after dissolution test initiation, respectively, were filtered through a membrane filter having a pore diameter of 0.45 µ and the resulting filtrate was subjected to the following HPLC analysis conditions so as to calculate elution rate and to obtain a dissolution curve.

< HPLC analysis of tamsulosin hydrochloride >

- Column : Kromasil C18 (4.6 mm × 150 mm, 5 µ)
- Column temperature : 40°C
- Detector : UV 225 nm
- Flow rate : 1.0 ml/min
- Injection volume : 100 µ
- Mobile phase : mixed solution of pH 2.0 perchlorate buffer/acetonitrile (65/35)

**Experimental Examples 7 through 9**
In order to confirm a controlled release dissolution, dissolution test was carried out for tablets prepared in Examples 7 through 9.

6 tablets, from each of Examples 7 through 9, were tested at 90 rpm and 37±0.5°C. 2, 6 and 12 hours after initiation of the dissolution test, respectively, 5 ml of eluate was aliquoted from 1000 ml of a dissolution medium (pH 4.5). Aliquoted eluates were filtered through a membrane filter having a pore diameter of 0.45 µm and the resulting filtrate was subjected to the following HPLC analysis conditions so as to calculate dissolution rate and to obtain dissolution curve.

< HPLC analysis of carvedilol >

Column : Kromasil C18 (4.6 mm × 250 mm, 5 µ)
Detector : UV 285 nm
Flow rate : 1.5 mL/min
Injection volume : 40 µl
Mobile phase : mixed solution of pH 2.0 phosphate buffer/methanol (50/50)

**Industrial Applicability**

The present invention enables preparation of pellets in which lipid components and hydrophilic active substances are homogeneously miscible by formation of lipid pellets through low-temperature heat processing below 60°C, and thereby it is easy to control a release rate thereof and particularly suited for controlled release of heat-labile drugs.

Although the preferred embodiments of the present invention have been disclosed for illustrative purposes, those skilled in the art will appreciate that various modifications, additions and substitutions are possible, without departing from the scope and spirit of the invention as disclosed in the accompanying claims.
Claims

[1] A pharmaceutical composition for controlled release pellets, consisting essentially of:
a) one or more pharmacologically active substances;
b) one or more lipids having a low-melting point of less than 70°C and existing as a solid at room temperature;
c) one or more hydrophilic substances; and
d) one or more water-insoluble binding agents, wherein the pellets are prepared by granulation using a mixed solvent containing an organic solvent, without melting the lipids, and then low-temperature heat processing at a solid phase.

[2] The composition according to claim 1, wherein the water-insoluble binding agent is selected from shellac, zein of the prolamin family, polymethacrylate, polymethylmethacrylate, polyethylmethacrylate, polydimethylaminoethylmethacrylate, polytrimethylaminoethylmethacrylate, hydroxypropyl methylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, a hydrophobic fatty acid derivative of hydroxypropylmethyl cellulose, and mixtures thereof.

[3] The composition according to claim 2, wherein the water-insoluble binding agent is selected from shellac, zein, polymethacrylate and its derivatives, and mixtures thereof.

[4] The composition according to claim 3, wherein the water-insoluble binding agent is selected from shellac, zein and mixtures thereof.

[5] The composition according to claim 1 or 2, wherein the pharmacologically active substance is tamsulosin, carvedilol, ranitidine, tramadol or pharmaceutically acceptable salts thereof.

[6] The composition according to claim 5, wherein the pharmacologically active substance is tamsulosin or pharmaceutically acceptable salts thereof.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC7 A61K 47/30, A61K 9/16**

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)
IPC7 as above

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and applications for inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
ekIPASS, Patmed (lipid AND hydrophilic AND (shellac OR zein OR polymethacrylate OR hydroxypropyl methylcellulose) AND (sustained OR controlled))

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>WO 02/45693 A1 (BYKGULDEN LOMBERG CHEMISCHE FABRIK GMBH) 13 JUN. 2002</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>See the whole document.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>US 4772475 (YAMANOUCHI PHARMACEUTICAL CO.) 20 Sep. 1988</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>See the whole document.</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>WO 00/72827 A2 (ACUSPHERE, INC.) 07 Dec. 2000</td>
<td>1-6</td>
</tr>
<tr>
<td></td>
<td>See the whole document.</td>
<td></td>
</tr>
</tbody>
</table>

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
  "A" document disclosing the general state of the art which is not considered to be of particular relevance
  "E" earlier application or patent but published on or after the international filing date
  "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
  "O" document referring to an oral disclosure, use, exhibition or other means
  "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
21 JUNE 2005 (21.06.2005)

Date of mailing of the international search report
21 JUNE 2005 (21.06.2005)

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Danjan-dong, Seo-gu, Daejeon 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer
LEE, Mi Jeong

Telephone No. 82-42-481-5601

Form PCT/ISA/210 (second sheet) (January 2004)
## INTERNATIONAL SEARCH REPORT

### Information on patent family members

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 02/45693 A1</td>
<td>13.06.2002</td>
<td>US 20040058896 A1</td>
<td>25.03.2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2004514736 T2</td>
<td>20.05.2004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2430826 AA</td>
<td>13.06.2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 62000009 A2</td>
<td>06.01.1987</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0553297 A1</td>
<td>24.03.1993</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0194838 A2</td>
<td>17.09.1986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE 3650657 C0</td>
<td>02.01.1998</td>
</tr>
<tr>
<td>WO 00/72827 A2</td>
<td>07.12.2000</td>
<td>US 20050068710 A1</td>
<td>17.03.2005</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 20020142050 A1</td>
<td>03.10.2002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 6610317</td>
<td>26.08.2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2003500438 T2</td>
<td>07.01.2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1180020 A2</td>
<td>20.02.2002</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (January 2004)