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(54) Title: CONTROLLED-RELEASE MULTIPLE UNIT PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention relates to a controlled-release multiple unit formulation and processes of preparation thereof. The formulation comprises (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a pharmaceutically active ingredient, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

CONTROLLED-RELEASE MULTIPLE UNIT PHARMACEUTICAL COMPOSITIONS

Field of the Invention

The present invention relates to a controlled-release multiple unit formulation and processes of preparation thereof.

Background of the Invention

Some medical conditions are best treated by administration of a pharmaceutical which is formulated to allow the active substance or ingredient to act as quickly as possible. Such a formulation may comprise an injectable solution or a readily dissolvable tablet or capsule. This type of formulation is useful, for instance, for treating acute pain, such as headaches, or pain associated with sudden trauma, such as an accident.

Other medical conditions are best treated by administration of a pharmaceutical in such a way as to sustain its action over an extended period of time. This type of administration is useful, for example, for treating chronic pain, such as that associated with rheumatic or arthritic conditions, or for the treatment of a chronic cardiovascular condition. It can be achieved by repeated administration of an immediate-release tablet or capsule at frequent intervals, for instance every four hours. However, this is generally inconvenient, especially during the night, when it is often necessary to awaken a patient to administer the tablet or capsule. In addition, such multiple dosing may lead to undesirable fluctuations in the plasma concentration of the active substance.

It has previously been proposed to produce a formulation which will release the active substance therein at a controlled rate such that the amount available in the body to treat the condition is maintained at a relatively constant level over an extended period of time. Particularly suitable periods are twelve hours and twenty-four hours, since such formulations need only be taken once or twice a day to maintain an effective treatment of the condition.

Numerous systems have been developed and marketed for the purpose of obtaining an extended release and for reducing the number of daily administrations. Examples of such are the matrix systems, reservoir systems, osmotic drug delivery systems and other monolithic systems.

The controlled-release dosage forms often result in the reduction or elimination of fluctuations in drug concentration in the blood, which improves disease state management. In addition, because the controlled-release dosage form reduces the maximum concentration of drug in the blood relative to an immediate release formulation of the same dose, the controlled-release formulation may minimize side effects, and may result in less potentiation or reduction in drug activity with chronic use.

For extended-release dosage forms containing very high quantities of active principle, avoiding excessively rapid release (dose dumping) is particularly very critical as it can lead to toxic effects, which are undesirable. Moreover, such systems are dependent upon gastric emptying rates and transit times and are also associated with a lot of intra- and inter-individual variations.

These disadvantages have led to a shift in modified release technology, from the use of monolithic systems to multiple unit systems, wherein each individual unit is formulated with modified release characteristics. The final dosage form comprises a multiplicity of individual units contained in a formulation in such a form that individual units will be made available from the formulation in the gastrointestinal tract.

Multiple unit dosage forms possess large surface area, which promotes complete and uniform absorption, minimize peak plasma fluctuations and thus reduce the potential for systemic side effects. A further advantage of these dosage forms is that high local concentrations of the active substance in the gastrointestinal system is avoided, due to the units being distributed freely throughout the tract.

U.S. Patent No. 5,783,215 relates to a formulation of beads which comprises (i) a core unit of a soluble or insoluble inert material, (ii) a first layer on the core unit comprising an active ingredient dispersed in a hydrophilic polymer, (iii) an optional second layer of hydrophilic polymer covering the first layer, and (iv) an outermost membrane layer effective for controlled-release of the active ingredient.

U.S. Patent No. 5,213,811 relates to a sustained drug release composition for a cardiotonic agent. The composition comprises beads with a coating containing the drug and a second coat of ethyl cellulose and polyvinyl acetate phthalate.

Modified release and immediate release of drug from the same dosage form has been attempted by combining more than one type of units having different release profiles.

For example, U.S. Patent No. 6,599,529 relates to a multiparticulate modified release composition that includes a combination of immediate release particles and modified release particles.

In the above approach the units having different release profiles should be mixed homogenously, as improper mixing may cause batch- to-batch variations in the release profiles. Further, preparation of separate units having immediate and modified release profiles may be a lengthy and cumbersome process.

PCT application WO 02/34240 relates to a dosage form for the oral delivery of a pain management drug and/or non-steroidal anti-inflammatory drug (NSAID) comprising: a biologically inert pellet having coated thereon: an inner layer comprising a dose of the pain management drug and/or NSAID or a pharmaceutically acceptable salt thereof admixed with a binder agent, and an outer rate controlling layer comprising a water insoluble polymer.

U.S. Patent No. 4,341,759 relates to a method of preparing a preparation made up by bodies comprising an active component in decreasing concentration towards the surface of the bodies. The method comprises coating a particle with a composition comprising the active component in a continuous coating operation whereby the concentration of the active component is decreased.

EP 277874 relates to a multilayer interpolymer for addition to rigid thermoplastic matrices and comprises relatively soft non-crosslinked polymer core, crosslinked elastomeric layer, and an outer non-elastomeric, relatively hard layer.

All the above-mentioned patents/applications describe formulations comprising at least two layers over the core. The disadvantage is that the number of layers required involves complex coating procedures. These procedures are not cost effective and are time consuming. There is still a need for a dosage form which is simple to manufacture and provides extended release.

Summary of the Invention

In one general aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a pharmaceutical active ingredient, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

The core unit may comprise one or more of water-soluble, water-insoluble or water-swellable material. Examples comprise one or more of sugar, a non-pareil seed, microcrystalline cellulose, celphere, sand silicon dioxide, glass, plastic, polystyrene, hydroxypropyl methylcellulose or mixtures thereof.

Pharmaceutically active ingredients can comprise one or more gastrointestinal sedatives, antacids, analgesics, non-steroidal anti-inflammatory agents, coronary vasodilators, peripheral and cerebral vasodilators, antiinfectives, antibiotics, antiviral agents, antiparasitic agents, anticancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal agents, laxatives, dietary supplements, immunodepressants, hypocholesterolemiants, hormones, enzymes, antispasmodics, antianginal agents or mixtures thereof.

In another aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a non-steroidal anti-inflammatory agent, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

Water-insoluble polymers can comprise one or more of ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate or mixtures thereof.

Hydrophilic polymers can comprise one or more of polyvinylpyrrolidone (PVP), gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates or mixtures thereof.

Water-soluble components include one or more sugars, amino acids, polyols, maltodextrins, organic acids or salts, sugar alcohols, polydextrose, glycols or mixtures thereof.

In another aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a

mixture of a pharmaceutical active ingredient, ethyl cellulose, hydroxypropyl methylcellulose and polyethylene glycol.

In yet another aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a non-steroidal anti-inflammatory agent, ethyl cellulose, hydroxypropyl methylcellulose and polyethylene glycol.

The nonsteroidal anti-inflammatory agents may be selected from one or more of acemetacin, acetylsalicylic acid, aceclofenac, bufexamac, diclofenac, diflunisal, ethenzamide, etofenamate, fenbufen, fenoprofen, feprazone, flobufen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, isoxicam, kebuzone, ketoprofen, ketorolac, lonazolac, lornoxicam, meclofenamic acid, mefenamic acid, metamizol, mofebutazone, nabumetone, naproxen, niflumic acid, oxaprozin, oxyphenbutazone, paracetamol, phenidine, phenylbutazone, piroxicam, propacetamol, propyphenazone, salicylamide, sulindac, tenoxicam, tiaprofenic acid, tolmetin, etodolac, meloxicam, nimesulide, physiologically acceptable salts thereof or mixtures thereof.

In one aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of aceclofenac, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

In another aspect there is provided a controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of aceclofenac, ethyl cellulose, hydroxypropyl methyl cellulose and polyethylene glycol.

In yet another embodiment there is provided a process for the preparation of a controlled-release multiple unit formulation comprising the steps of:

a. suspending/dissolving at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component in a solvent,

b. dispersing/dissolving the pharmaceutical active ingredient in the suspension/solution of step (a),

c. coating the dispersion/solution of step (b) over inert cores,

d. drying the coated cores.

In another aspect the controlled-release multiple unit formulation may be filled into hard gelatin capsules or compressed into tablets.

The controlled-release multiple unit formulation may further include one or more pharmaceutically acceptable inert excipients selected from the group consisting of binders, diluents, disintegrants, surfactants, plasticizers, lubricants/glidants, coloring agents, and flavoring agents.

Detailed Description of the Invention

The controlled-release multiple unit formulation of the present invention comprises an inert core coated with a mixture of the pharmaceutical active ingredient, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component. The active layer acts as the rate-controlling layer without the requirement for additional outer layers. The active ingredient can be in direct contact with gastrointestinal fluid, has very high surface area and enhances absorption especially at the lower parts of the gastrointestinal tract. In addition the controlled-release multiple units, can be formulated as capsules and tablet dosage forms with fewer manufacturing steps resulting in a cost-effective and time-saving process.

The term "multiple unit formulation", as used herein, refers to a pharmaceutical composition that includes one or more individual coated units contained in the formulation in such a form that the individual units will be available from the formulation upon disintegration of the formulation in the stomach. The multiple unit pharmaceutical composition or formulation may be a capsule or a tablet that disintegrates in the stomach to give individual units. The multiple units may be formulated as granules, pellets or beads.

The term "controlled-release", as used herein, includes any type of controlled-release including prolonged release, sustained release, modified release and extended release.

The core may comprise one or more of water-soluble, water-insoluble or water-swellable materials. Examples include one or more of sugar, non-pareils, microcrystalline cellulose, celphere, sand, silicon dioxide, glass, plastic, polystyrene, ethyl cellulose or

hydroxypropyl methylcellulose. The sugar may include one or more of glucose, mannitol, lactose, xylitol, dextrose, and sucrose.

The pharmaceutical active ingredient may be selected from one or more gastrointestinal sedatives, antacids, analgesics, non-steroidal anti-inflammatory agents, coronary vasodilators, peripheral and cerebral vasodilators, antiinfectives, antibiotics, antiviral agents, antiparasitic agents, anticancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal agents, laxatives, dietary supplements, immunodepressants, hypocholesterolemiants, hormones, enzymes, antispasmodics, antianginal agents, medicinal products that affect the heart rate, medicinal products used in the treatment of arterial hypertension, antimigraine agents, medicinal products that affect blood clotting, antiepileptics, muscle relaxants, medicinal products used in the treatment of diabetes, medicinal products used in the treatment of thyroid dysfunctions, diuretics, anorexigenic agents, antiasthmatics, expectorants, antitussive agents, mucoregulators, decongestants, hypnotics, antinausea agents, hematopoietic agents, uricosuric agents, plant extracts, contrast agents or mixtures thereof.

Nonsteroidal anti-inflammatory agents may be selected from one or more of Acemetacin, Acetylsalicylic acid, Aceclofenac, Bufexamac, Diclofenac, Diflunisal, Ethenzamide, Etofenamate, Fenbufen, Fenoprofen, Feprazone, Flobufen, Flufenamic acid, Flurbiprofen, Ibuprofen, Indomethacin, Isoxicam, Kebuzone, Ketoprofen, Ketorolac, Lonazolac, Lornoxicam, Meclofenamic acid, Mefenamic acid, Metamizol, Mofebutazone, Nabumetone, Naproxen, Niflumic acid, Oxaprozin, Oxyphenbutazone, Paracetamol, Phenidine, Phenylbutazone, Piroxicam, Propacetamol, Propyphenazone, Salicylamide, Sulindac, Tenoxicam, Tiaprofenic acid, Tolmetin, Etodolac, Meloxicam, Nimesulide, physiologically acceptable salts thereof or mixtures thereof.

Water-insoluble polymers may comprise one or more of ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate, co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate, or mixtures thereof.

Hydrophilic polymers may comprise one or more of polyvinylpyrrolidone (PVP), gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose, carboxymethyl

cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, carboxyethyl cellulose, carboxymethylhydroxyethyl cellulose, acrylic acid polymers, polymethacrylates, any other pharmaceutically acceptable polymer or mixtures thereof.

Different grades of the same polymer with varying viscosities may also be utilized for controlling the release rate.

Examples of water-soluble components include one or more sugars, amino acids, polyols, maltodextrins, organic acids or salts, sugar alcohols, polydextrose, glycols or mixtures thereof.

The coating layer may additionally comprise other additives selected from one or more of plasticizers, wetting agents, lubricants, coloring agents or mixtures thereof.

Plasticizers may be one or more of propylene glycol, triethylene glycol, oleic acid, ethyleneglycol monooleate, triethyl citrate, triacetin, diethyl phthalate, glyceryl monostearate, dibutyl sebaccate, acetyl triethylcitrate, castor oil or mixtures thereof.

Suitable wetting agents include one or more of gelatin, casein, lecithin (phosphatides), glycerol monostearate, cetostearyl alcohol, cetomacrogol, emulsifying wax, polyethylene glycols, polyoxyethylene stearates, sodium dodecylsulfate, partial fatty acid esters of polyhydroxy ethylene sorbitan, such as, polyethylene glycol sorbitan monolaurate, monopalmitate, monostearate and monooleate; polyethylene glycol sorbitan tristearate and trioleate; polyethylene glycol sorbitan monolaurate and monostearate; polyethylene glycol sorbitan monooleate, polyhydroxyethylene fatty alcohol ethers; polyoxyethylene fatty acid esters; ethylene oxide/propylene oxide block copolymers; sugar ethers and sugar esters; phospholipids and their derivatives; ethoxylated triglycerides, such as, the derivatives of castor oil (available under the trade name Cremophor); or mixtures thereof.

Lubricants may include one or more of talc, calcium stearate, magnesium stearate, polyethylene glycols, silicon dioxide, sodium lauryl sulphate, sodium stearyl fumarate, other suitable, other known lubricants, or mixtures thereof.

Coloring agents may be selected from any FDA approved colors for oral use.

The coating can be prepared by techniques recognized in the art. For example, one or more insoluble polymers can be mixed with one or more hydrophilic polymers and one

or more water soluble components, and suspended or dissolved to one or more solvents. The pharmaceutically active ingredient can be dispersed or dissolved in the mixture along with the other excipients.

The coating composition can be coated onto the inert core utilizing conventional methods known in the art. For example, the coating composition of the present invention may be coated onto the central core in a fluidized bed or pan. Other examples include spraying the composition of the present invention onto the core and immersing the core element in the coating composition. Alternatively, the coating composition may be applied to the core in a fluid bed bottom spray coater by having the inert cores suspended in an air stream, and the coating composition can be sprayed thereon. Various conventional coating apparatuses may be employed to facilitate this including, for example, a centrifugal fluidized bed coating apparatus, a pan coating apparatus, or a fluidized bed granulating coating apparatus. During the coating of the core and/or after the core is completely coated, the solvent can be removed by techniques known to one of ordinary skill in the art, such as by drying or curing.

The amount of coating applied should be sufficient to retard the release of the pharmaceutically active ingredient at a desired state. By varying the proportion of the coating on the core, different dissolutions of the active ingredient can be obtained. The coating composition can be applied to the core in a thickness sufficient to obtain the desired release profile of a therapeutically active agent when the coated substrate is exposed to aqueous solutions.

The controlled-release multiple unit formulation may further include one or more pharmaceutically acceptable inert excipients. Suitable pharmaceutically acceptable inert excipients may be selected from one or more of binders, diluents, disintegrants, surfactants, plasticizers, lubricants/glidants, coloring agents, flavoring agents or mixtures thereof.

Suitable solvents may include one or more of water, alcohols, ethyl alcohol, isopropyl alcohol; ketones, acetone, ethylmethylketone; halogenated hydrocarbons, dichloroethane, trichloroethane or mixtures thereof.

The process may further include filling the coated units into hard gelatin capsules or compressing the coated units into tablets. The process may further include applying a

functional (*e.g.*, enteric coating) or non-functional coating to the coated units. Either or both of the core and the coating layer may further include one or more pharmaceutically inert excipients.

The controlled-release multiple unit formulations of the present invention allow for highly reproducible release *in vivo* as the entire dosage form hydrates uniformly on contacting the gastrointestinal fluids.

The controlled-release multiple unit formulations can be tailored to prolong or extend the release and absorption of the pharmaceutical active ingredient for up to about 2 hours to about 24 hours depending upon the biological half-life of the active ingredient and composition of the active layer.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

EXAMPLES

Preparation of controlled-release multiple unit formulation of aceclofenac

Ingredients	**Example 1**	**Example 2**	**Example 3**
	% w/w	**% w/w**	**% w/w**
Aceclofenac	40.00	40.00	40.00
Non-pareil seeds (30-35 mesh)	33.72	33.6	33.6
Ethylcellulose (Ethocel 10cps)	15.95	-	10.00
Ethylcellulose (Ethocel 20cps)	-	16.00	-
Hydroxypropyl methyl cellulose (Methocel E5 LV)	3.98	4.00	10.00
Polyethylene glycol 400	1.58	1.6	1.6
Talc	3.58	3.6	3.6
Colloidal anhydrous silica	1.19	1.2	1.2
Isopropyl alcohol***	q.s	q.s	q.s
Water***	q.s	q.s	q.s

*** Evaporate during processing

Process

1. Ethylcellulose, Hydroxypropyl methylcellulose and Polyethylene glycol were suspended/dissolved in a mixture of Isopropyl alcohol and water.
2. Aceclofenac, Talc and Colloidal anhydrous silica were dispersed in the solution of step 1.
3. The dispersion of step 2 was coated over non-pareil seeds using a fluidized bed processor.

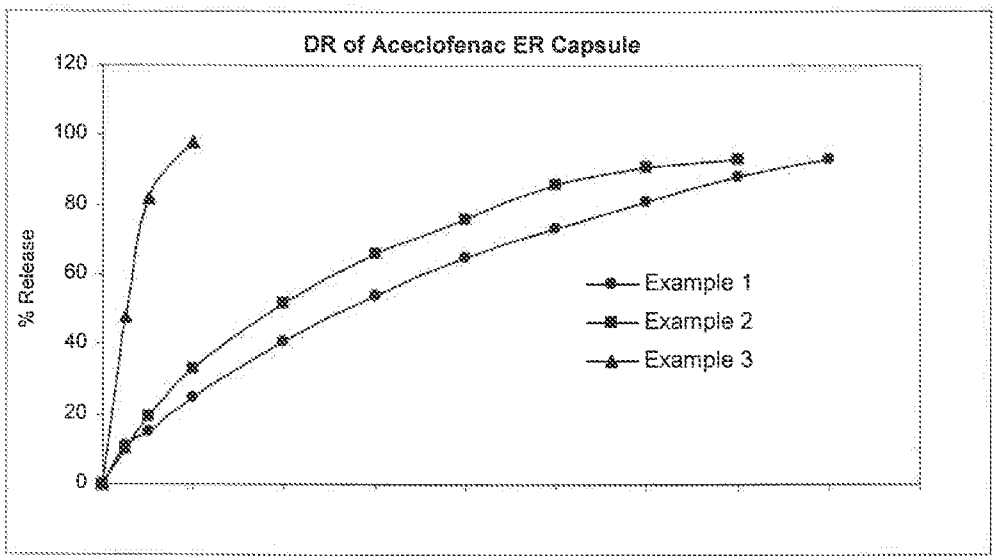
The coated units were dried and filled into hard gelatin capsules.

Table 1 and Figure 1 provide the drug release of Aceclofenac ER capsules prepared as per Examples 1-3 in simulated intestinal fluid (Phosphate buffer pH 6.8), 900 ml, USP 2 at 50 rpm.

Table 1: Drug Release (DR) of Aceclofenac ER capsules prepared as per Examples 1-3 in simulated intestinal fluid (Phosphate buffer pH 6.8), 900 ml, USP 2 at 50 rpm.

Time (h)	Percent (%) Drug Released		
	Example 1	Example 2	Example 3
0	0	0	0
0.5	11	10	48
1	15	19	82
2	25	33	98
4	41	52	-
6	54	66	-
8	65	76	-
10	73	86	-
12	81	91	-
14	88	93	-
16	93	-	-

Figure 1: Drug Release (DR) of Aceclofenac ER capsules prepared as per Examples 1-3 in simulated intestinal fluid (Phosphate buffer pH 6.8), 900 ml, USP 2 at 50 rpm.



We Claim:

1. A controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a pharmaceutically active ingredient, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

2. The formulation of claim 1, wherein the core unit comprises one or more of water-soluble, water-insoluble or water-swellable material.

3. The formulation of claim 1, wherein the pharmaceutically active ingredient comprises one or more of gastrointestinal sedatives, antacids, analgesics, non-steroidal anti-inflammatory agents, coronary vasodilators, peripheral and cerebral vasodilators, antiinfectives, antibiotics, antiviral agents, antiparasitic agents, anticancer agents, anxiolytics, neuroleptics, central nervous system stimulants, antidepressants, antihistamines, antidiarrheal agents, laxatives, dietary supplements, immunodepressants, hypocholesterolemiants, hormones, enzymes, antispasmodics, antianginal agents or a mixture thereof.

4. The formulation of claim 1, wherein the water-insoluble polymer comprises one or more of ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate or co-polymers of acrylate or methacrylate having a low quaternary ammonium content poly vinyl acetate or a mixture thereof.

5. The formulation of claim 1, wherein the hydrophilic polymer comprises one or more of polyvinylpyrrolidone (PVP), gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, acrylic polymers, polymethacrylates, or a mixture thereof.

6. The formulation of claim 1, wherein the water-soluble component comprises one or more of sugars, amino acids, polyols, maltodextrins, organic acids or salts, sugar alcohols, polydextrose, glycols or a mixture thereof.

7. The formulation of claim 1, wherein the formulation further comprises one or more fillers, binders, lubricants, glidants, plasticizers, colorants, flavoring agents, or mixtures thereof.

8. A controlled-release multiple unit formulation comprising: (i) a core unit of an inert material; and (ii) a coating layer comprising a mixture of a non-steroidal anti-inflammatory agent, at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component.

9. The formulation of claim 8, wherein the non-steroidal anti-inflammatory agent is selected from one or more of acemetacin, acetylsalicylic acid, aceclofenac, bufexamac, diclofenac, diflunisal, ethenzamide, etofenamate, fenbufen, fenoprofen feprazone, flobufen, flufenamic acid, flurbiprofen, ibuprofen, indomethacin, isoxicam, kebuzone, ketoprofen, ketorolac, lonazolac, lornoxicam, meclofenamic acid, mefenamic acid, metamizol, mofebutazone, nabumetone, naproxen, niflumic acid, oxaprozin, oxyphenbutazone, paracetamol, phenidine, phenylbutazone, piroxicam, propacetamol, propyphenazone, salicylamide, sulindac, tenoxicam, tiaprofenic acid, tolmetin, etodolac, meloxicam, nimesulide, physiologically acceptable salts thereof or mixtures thereof.

10. The formulation of claim 8, wherein the water-insoluble polymer comprises one or more of ethyl cellulose, hydroxypropylmethyl cellulose phthalate, cellulose acetate, cellulose acetate phthalate, cellulose acetate trimellitate or co-polymers of acrylate or methacrylate having a low quaternary ammonium content, poly vinyl acetate or a mixture thereof.

11. The formulation of claim 8, wherein the hydrophilic polymer comprises one or more of polyvinylpyrrolidone (PVP), gelatin, polyvinyl alcohol, starch and derivatives thereof, cellulose derivatives, acrylic polymers, polymethacrylates, or a mixture thereof.

12. The formulation of claim 8, wherein the water-soluble component comprises one or more of sugars, amino acids, polyols, maltodextrins, organic acids or salts, sugar alcohols, polydextrose, glycols, or a mixture thereof.

13. The formulation of claim 8, wherein the formulation further comprises one or more of fillers, binders, lubricants, glidants, plasticizers, colorants, flavoring agents, or a mixture thereof.

14. A process for preparing a controlled-release multiple unit formulation comprising the steps of:

a. suspending or dissolving at least one water-insoluble polymer, at least one hydrophilic polymer and at least one water-soluble component in a solvent to form a solution or suspension,

b. dispersing or dissolving a pharmaceutical active ingredient in the solution or suspension of step (a) to form a dispersion or solution,

c. coating the dispersion or solution of step (b) over inert cores to form coated inert cores, and,

d. drying the coated cores.

15. A controlled-release multiple unit formulation of claims 1 or 8 to be filled into hard gelatin capsules or compressed into tablets.