DRUG PARTICLES HAVING CONSTANT RELEASE AND IMMEDIATE RELEASE

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TECHNICAL FIELD

The present invention is related to sustained release drug particles having a release profile providing for more constant release and absorption of the drug active.

BACKGROUND OF THE INVENTION

This invention relates to pharmaceutical particles providing a prolonged release of the drug active as well as rapid absorption.

The administration of drugs orally oftentimes presents serious problems. In very many cases, it is necessary for the drugs to be absorbed from the gastro-intestinal tract into the bloodstream. When a drug is given by mouth, the assimilation is normally fairly rapid and the level in the blood reaches a maximum. Then it declines as the drug is excreted or otherwise removed from the bloodstream. The blood level falls and finally reaches a level so low that it is no longer effective and it is then necessary to take another dose. The peaks and valleys thus caused in blood level have several disadvantages. One is the necessity of taking frequent small doses in order to maintain a therapeutically desired blood level. This is awkward and presents a problem as the patient has to continue to take further doses. A second drawback is that in order to have a therapeutically useful blood level, each dose has to be fairly large so that after the blood level peak is reached and begins to subside, there will still remain sufficient of the drug to be useful. The necessity for large doses brings with it some problems. The large initial doses may be unacceptable or may produce some undesirable side reactions.

For the reasons set out above, various attempts have been made to slow up the release of drugs taken orally, producing a sustained release product. Sometimes it is felt desirable only to slow up the release sufficiently so that it extends over a long

enough time to even out the more marked peaks and valleys in blood level. In other cases, it may be desirable to prevent assimilation from the stomach but to permit assimilation from the intestine. Various coatings have been developed (i.e., enteric coatings) to achieve this purpose.

Some of the attempts at making improved sustained-release particles are reflected in patents issued in the area. One patent is U.S. 3,078,216, February 19, 1963 to Greif, which discloses sustained-release particles having a coating of water-insoluble wax and possibly, a second enteric coating. U.S. Patent 4,459,279, July 10, 1984 to Stricker et al., discloses drug granules having a coating of a water insoluble component and a water soluble component. As a final second coating an enteric polymer may be employed. European Patent Application 0 061 217, September 29, 1982 to Giudice et al., discloses drug particles having an inert core, a first layer of the drug and an outer second layer of polyvinyl pyrrolidone. European Patent Application 0 092 060, October 26, 1983 to Colombo et al., discloses drug particles having an enteric polymer in the drug core, a first coating designed to regulate the release of the drug and a second coating to protect the first coating.

While the above described references disclose delayed release drug particles, they as well as other prior art executions, do not provide complete answers to making totally satisfactory delayed release products, particularly those containing propionic acid derivatives.

Some drugs, such as ibuprofen do not appear to follow a pattern of constant release found for other drugs. Instead, the dissolution data for ibuprofen particles having a porous coating indicate that the controlling surface area is not the constant surface area of the porous coating, but the surface area of the ibuprofen particle which decreases with time as the drug dissolves. Thus, the dissolution rate decreases with time.

The decrease in dissolution rate with time of an ibuprofen particle having a porous coating can be compensated for if the resistance of the porous coating to diffusion also decreases with

time. This can be achieved by decreasing its thickness with time. The present invention provides a means of producing a coating on an ibuprofen particle that decreases in thickness at a rate such that the decrease in surface area of the ibuprofen particle as it dissolves is compensated for and the dissolution rate remains essentially constant.

It is therefore an object of the present invention to provide improved delayed release particles, having both a more uniform release pattern as well as rapid absorption of the drug by the body.

It is a further object of the present invention to provide an analgesic effective against a variety of pain, acute and chronic.

It is still a further object of the present invention to provide delayed release particles which are effective in the treatment of dysmenorrhea.

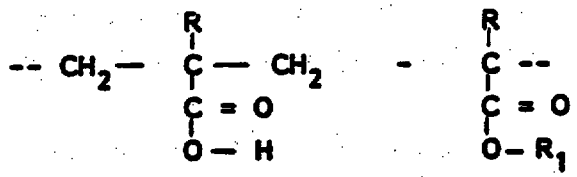
These and other objects will become readily apparent from the detailed description which follows.

As used herein all percentages and ratios are by weight unless otherwise specified.

The present invention relates to drug particles comprising:

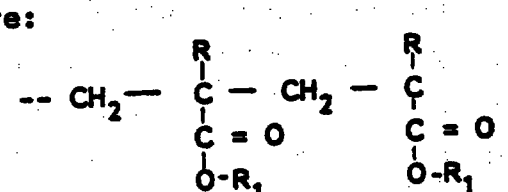
a) a drug active core wherein the drug active is a propionic acid derivative as hereinafter defined;

b) a first coating of an enteric material insoluble in the stomach but soluble in the intestines and selected from poly(meth)acrylic acid esters having the repeating structure:



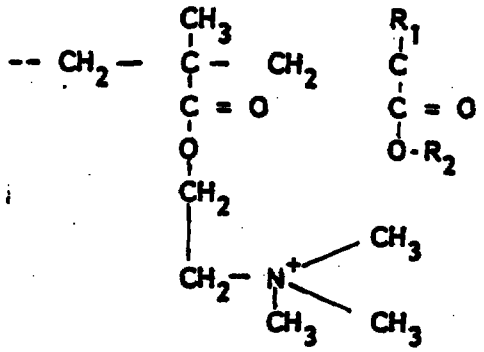
$R = H$ or CH_3; $R_1 = CH_3$ or C_2H_5

c) a second coating of a material insoluble in the stomach and intestines selected from poly(meth)acrylic acid esters having the repeating structure:



$R = H$ or CH_3; $R_1 = CH_3$ or C_2H_5

and mixtures thereof with quaternary ammonium poly(meth)acrylic acid esters having the repeating structure:



R_1 = H or CH_3; R_2 = CH_3 or C_2H_5

d) a third coating of a propionic acid derivative and hydrophilic excipients.

The essential as well as optional components of the present particles are described below. In the present application the following terms have the meanings given.

"Pharmaceutically-acceptable" or "pharmacologically-acceptable", as used herein, means that the ingredients used in the compositions are suitable for use in contact with the tissue of humans, without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

The term "comprising", as used herein, means that various other compatible components, including both active and inert

ingredients, can be conjointly employed in the compositions of this invention. The term "comprising" thus encompasses and includes the more restrictive terms "consisting of" and "consisting essentially of".

By "compatible" herein is meant that the components of the present invention are capable of being commingled without interacting in a manner which would substantially decrease the efficacy of the therapeutic under ordinary use conditions.

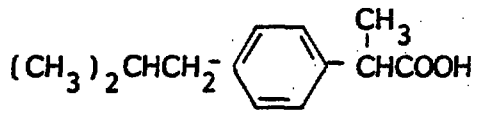
Drug Active

The drug active found useful in the particles of the present invention are propionic acid derivatives. Such compounds have both analgesic and anti-inflammatory activity and can be used at appropriate dosage levels in the present invention. The compounds are frequently used in their free acid form but also can be used in the form of their pharmaceutically accepted salts.

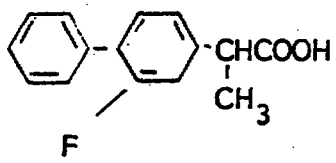
The propionic acid derivatives for use herein include, but are not limited to, ibuprofen, flurbiprofen, fenoprofen, ketoprofen, indoprofen, suprofen, and fluprofen. Structurally related propionic acid derivatives having similar analgesic and anti-inflammatory properties are also intended to be encompassed by this group. Structural formulas for representative group members are set forth below:

Propionic Acid Derivatives

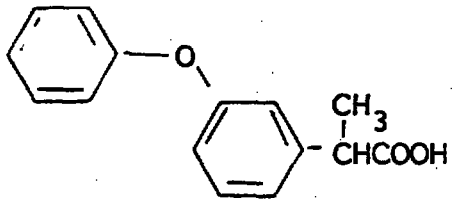
ibuprofen



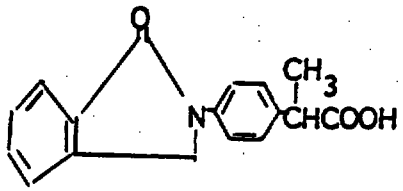
flurbiprofen



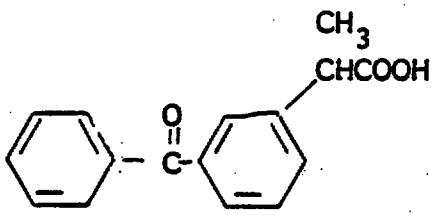
fenoprofen



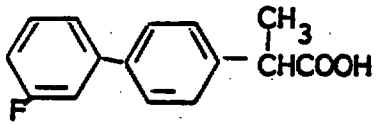
indoprofen



ketoprofen



fluprofen



Thus, "propionic acid derivatives" as defined herein are non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having a free $--CH(CH_3)COOH$ or $--CH_2CH_2COOH$ group (which optionally can be in the form of a pharmaceutically acceptable salt group, e.g., $--CH(CH_3)COO^-Na^+$ or $--CH_2CH_2COO^-Na^+$), typically attached directly or via a carbonyl function to a ring system, preferably to an aromatic ring system.

A drug preferred for use in the present compositions is ibuprofen.

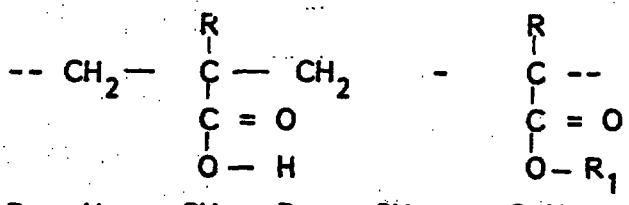
The drug active can form the entire core of the particles of the present invention or be combined with other pharmaceutically acceptable materials. The size of the core composition can be chosen to meet the formulator's needs but is preferably from about 0.1mm to about 2mm, most preferably from about 0.5mm to about 1.2 mm.

First Coating

The first coating used on the present particles is an enteric polymer which is insoluble in the stomach (i.e., acidic pH environment) but soluble in the intestines. A preferred material is Eudragit®

L30D offered by Rohm Pharma. This material is a copolymer, anionic in character,

having the following repeating structure:



R = H or CH_3; R_1 = CH_3 or C_2H_5

The L30D material has a mean molecular weight of about 250,000.

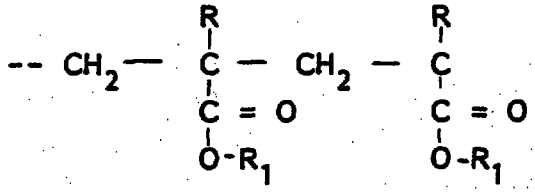
The first coating is preferably applied to the core so that the weight of coating solids is from 1% to 30% based on the total weight of the core plus coating solids, preferably from 2% to 20%.

Materials which modify the enteric coating can be used with the enteric. Such materials include pharmaceutically acceptable plasticizers such as triacetin which are compatible with the drug active. Plasticizers are used at a level of from about 0% to about 25%, preferably from about 0% to about 15% based on the weight of the solids in the first coating.

Second Coating

The second coating on the present particles serves as a diffusion barrier for the drug active.

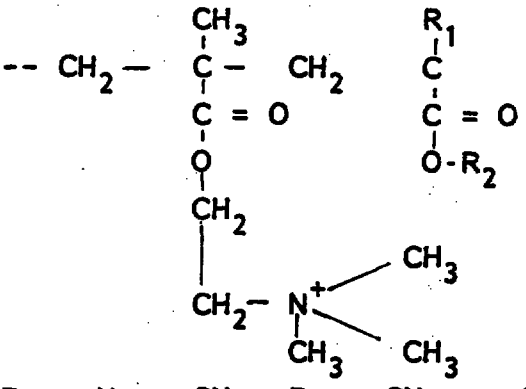
The material should be permeable to water and solubilized drugs but is not soluble at any of the pHs found in the stomach or the intestines. A preferred material is Eudragit® E 30D offered by Rohm Pharma. This material is a copolymer, neutral in character, having the following repeating structure:



R = H or CH_3; R_1 = CH_3 or C_2H_5

Eudragit® E-30D has a mean molecular weight of about 800,000

Materials which can be used as a partial replacement of Eudragit® E-30D are copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. The repeating structure is as follows:



R_1 = H or CH_3; R_2 = CH_3 or C_2H_5

The molar ratio of the ammonium groups to the remaining meth(acrylic) acid esters is 1:20 with a material identified as Eudragit® RL and 1:40 with a material identified as Eudragit® RS.

As with Eudragit® E-30D material, the RL and RS materials are permeable to water and to the drug actives but are virtually insoluble at any pH.

As with the first coating, the second coating may contain pharmaceutically acceptable materials which modify the coating. Such materials include hydroxypropyl methyl cellulose, talc, sodium chloride, and polysorbate 80 (POE [20] sorbitan monooleate). These materials are conventional adjuvant materials for use with coatings and can be used at levels found by the formulator necessary to give the effect desired (e.g., hydroxypropyl methyl cellulose up to about 8% of the acrylic polymer; talc up to about 35% of the acrylic polymer; polysorbate 80 up to about 4% of the acrylic polymer; and sodium chloride up to about 10% of the acrylic polymer).

The second coating is used in the present particles at a level such that the second coating is from 2% to 20% of the total solids in the core, the first coating and the second coating, preferably from 4% to 8%. The amount of

acrylic polymer in the second coating, on this same basis should be from about 1.2% to about 11.8%, preferably from about 2.4% to about 4.8%.

Third Coating

The third coating on the present particles is a mixture of the drug active and hydrophilic excipients. This coating helps to provide rapid absorption of the drug by the body.

The hydrophilic excipients include materials such as hydroxypropyl methyl cellulose (HPMC), lactose and polyvinylpyrrolidone (PVP K-30). Another material which is useful in this third coating is a surfactant such as polysorbate 80. The hydrophilic such as HPMC comprise from about 1% to about 30%, preferably from about 5% to about 15% of the third coating while the surfactant comprises from about 0.1% to about 5%, preferably from about 0.3% to about 3%. The amount of the third coating can be any amount desired by the formulator. It is generally, however, from 10% to 67%, preferably from 15% to 50% of the total coated particle weight.

It is an option in the present invention to apply a coating of a water soluble polymer such as a polyvinyl pyrrolidone to the core before the application of the first coat described above. This polymer would be present at a level of 0.2% to about 5.0% based on the weight of the core.

METHOD OF MANUFACTURE

A method for manufacturing the particles of the present invention is given in Example I.

FIELD OF USE

The particles of the present invention can be used in tablets, capsules or any other convenient form. As indicated previously, the drug actives are known for providing relief from a wide variety of pain.

The following examples further describe preferred embodiments within the scope of the present invention. They are given solely for illustration and are not to be construed as limitations of this invention as many variations thereof are possible without departing from the invention's scope.

EXAMPLES I, II & III

The following are representative particles of the present invention.

	Component	Weight % I	II	III
Core	Ibuprofen	69.0	76.6	41.4
	Polysorbate 80	--	--	0.2
	PVP XL	--	--	0.9
Pre-First Coating	Ibuprofen	--	--	25.37
	PVP K 30	--	--	0.62
	Polysorbate 80	--	--	0.06
First Coating	Eudragit® L 30D	4.2	4.3	4.2
	Triacetin	--	--	0.4
Second Coating	Eudragit® E 30D	3.8	3.8	1.80
	Hydroxypropyl methylcellulose	--	--	0.20
	Talc	--	--	1.0
	Polysorbate 80	--	--	0.05
Third	Ibuprofen	19.70	12.0	22.8
	Polysorbate 80	0.3	0.3	0.2
	Hydroxypropyl methylcellulose	3.0	3.0	0.8
		100.0	100.0	100.0

The particles described above are prepared by first compacting the ibuprofen at 115 psi to 195 psi, preferably from 145 to about 165 psi, in a roller compactor. The compaction is then milled and the resulting particles sieved to obtain particles in the range of 0.1mm to about 2.0mm, preferably from about 0.5mm to about 1.2mm.

The cores are then coated with the inner Eudragit® L 30D coating followed by the Eudragit® E 30D coating. A first coating dispersion is prepared by diluting the coating solids with water to obtain a dispersion having about 16.5% non-volatiles. The uncoated cores are then introduced into a Wurster fluidized bed coater using fluidizing air having a temperature of from about 35 to 60°C. The coating dispersion is next added to the coater by means of a peristaltic pump. The atomizing and fluidizing air flow rates and coating dispersion are adjusted to maintain a coating temperature of 25 to 40°C.

The cores with the first coating are subsequently coated with a dispersion of the Eudragit® E 30D. The dispersion having a solids concentration of about 20% is introduced into the coater using the same conditions used to apply the first coating. The cores with the two coatings are dried overnight at 50°C.

The final, third, coating is formed by combining the hydroxypropyl methylcellulose with water to form a 10% solution. This solution is then combined with polysorbate 80 and the combination applied to the previously coated particles with the ibuprofen using a centrifugal granulator (alternatively this coating may be applied using a Wurster coater). The conditions are adjusted so that the coating is applied at a temperature of from about 20-40°C. The final particles are dried overnight in a 50°C oven.

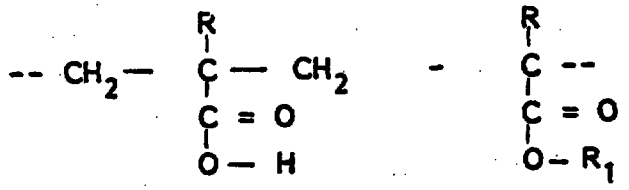
The coated particles exhibit excellent release of the ibuprofen over a period of many hours as well as rapid absorption of the ibuprofen by the body.

CLAIMS

1. Drug particles comprising:

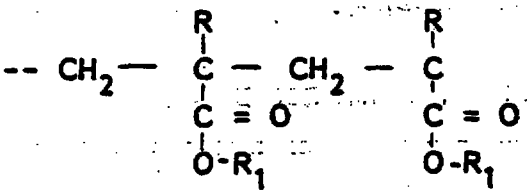
a) a drug active core wherein the drug active is a propionic acid derivative as hereinbefore defined;

b) a first coating of an enteric material insoluble in the stomach but soluble in the intestines and selected from poly(meth)acrylic acid esters having the repeating structure:



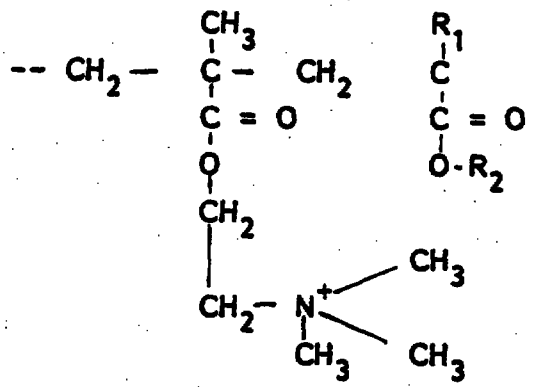
R = H or CH_3; R_1 = CH_3 or C_2H_5

c) a second coating of a material insoluble in the stomach and intestines selected from poly(meth)acrylic acid esters having the repeating structure:



R = H or CH_3; R_1 = CH_3 or C_2H_5

and mixtures thereof with quaternary ammonium poly(meth)acrylic acid esters having the repeating structure:



R_1 = H or CH_3; R_2 = CH_3 or C_2H_5

d) a third coating of a propionic acid derivative as hereinbefore defined and hydrophilic excipients.

2. Drug particles according to Claim 1 wherein the propionic acid derivative is selected from ibuprofen, indoprofen, flurbiprofen, fenoprofen, fluprofen, ketoprofen and suprofen.

3. Drug particles according to Claim 2 wherein the first coating is present at a level of from 1% to 30% of the total weight of the core and the first coating.

4. Drug particles according to Claim 3 wherein the second coating is present at a level of from 2% to 20% of the total weight of the core, the first coating and the second coating.

5. Drug particles according to Claim 4 wherein the third coating is present at a level of from 10% to 67% of the total weight of the core, the first coating, the second coating and the third coating.

6. Drug particles according to Claim 5 wherein the propionic acid derivative is ibuprofen.

7. Drug particles according to Claim 6 wherein the poly(meth)acrylic acid ester of the first coating has a mean molecular weight of about 250,000.

8. Drug particles according to Claim 7 wherein the poly(meth)acrylic ester of the second coating has a mean molecular weight of about 800,000.

9. Drug particles according to Claim 8 wherein the third coating is a mixture of ibuprofen, hydroxypropyl methylcellulose and Polysorbate 80.