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**STABLE PHARMACEUTICAL BEADS CONTAINING
MEDICAMENT INCORPORATED IN SYNTHETIC
COPOLYMER BY BEAD POLYMERIZATION**

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The present invention relates to pharmaceutical preparations in bead form, especially for oral administration, which contain the active ingredient, or mixture of active ingredients, incorporated in physiologically acceptable synthetic polymers, that can be dissolved or swollen by the stomach juice and/or intestinal juice, and to the manufacture of such pharmaceutical preparations.

Hitherto, solid pharmaceutical preparations, for example, for oral administration, were made by aggregating the active ingredient, either alone or in admixture with known adjuvants, for example, starch, sugar, talc, flavouring agents, and the like, and compressing the aggregate into flat circular discs of varying porosity on a tablet compressing machine. Preparations in this form are a further development of the powder which constitutes a single dose. They have many advantages over powders in that they permit more exact dosage, are easier for the patient to take, and permit more accurate selection of the region where resorption is to take place, for example, the mucous membranes of the mouth or of the gastrointestinal tract. Furthermore, tablets have a longer storage life because they present a small surface area to the hostile environment than powders. A feature which both tablets and powders have in common is that they release the medicament quickly. More recently, attempts have been made to control the release of active ingredients from solid pharmaceutical preparations of the kind defined by means of different methods of manufacture. Such pharmaceutical preparations are known as "prolonged release" or "sustained release" tablets. The purpose of these tablets is to release the active ingredient, either with or without an initial dose, over a period of several hours, the release being effected either continuously or in portions, the object being to keep the level of active ingredient in the blood as constant as possible. To this end, the medicament is coated with a material which is resistant to the acid secretion of the stomach but which is soluble in the secretion of the small intestine, thus preventing quick and premature release in the stomach. The materials first used for such coatings were natural products such as fats and waxes, and these were followed by synthetic adjuvants, which were mainly acrylic and cellulose derivatives. In a further development of the "prolonged release" form, the medicaments are mixed with synthetic materials of an appropriate grain size which are inert towards and insoluble in the intestinal juice, for example, polyvinyl chloride or polystyrene, and the mixture is compressed into tablets by a known method. The soluble medicament slowly diffuses out of this porous "housing." The great drawback to this so-called classical form of prolonged-release tablet is that even very slight and uncontrollable changes in the mode of production result in very great differences in the porosity of the preparation or its "housing" and this, in turn, makes for big differences in the rate at which the active ingredient is released. A process for the manufacture of pharmaceutical preparations having properly controllable release properties has recently been described in which the medicament, or mixture of medicaments, is admixed with synthetic materials and adjuvants and the mixture is proc-

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essed into tablets free from pores by the known injection-moulding process.

The pharmaceutical preparations of the invention have substantial technical and pharmacological advantages over the preparations known hitherto. They have a smooth surface which may be transparent or opaque and can be attractively coloured as required. Their manufacture is simple in comparison with other products, especially injection-moulded tablets, since expensive apparatus is not required. They are suitable for both small-scale and large-scale production. Furthermore, the size of the beads can be controlled in a very simple manner, which means that the release of the active ingredient can also be precisely controlled in respect of both amount and time. It has also been found that, in many cases, active ingredients incorporated in such preparations are more stable because the material with which they are coated or in which they are embedded is protective and mechanically stable. They also show a high degree of resistance to atmospheric influence. Since they generally exhibit a low degree of permeability to water, the preparations made by the process of the invention are specially suitable for hygroscopic medicaments and/or medicaments that are sensitive to moisture.

The preparations made by the process of the invention may be used per se, for example, in the form of granules, if desired, in capsules, or suspended in a liquid, for example, as a suspension or in the form of a syrup. However, the product may also be admixed with adjuvants, and compressed into tablets in the customary manner.

The synthetic materials used are those whose monomers can be subjected to bead polymerization in the presence of the active ingredients and which, when cured, yield a physiologically acceptable polymer of adequate strength that can be at least swollen, e.g. dissolved by the gastrointestinal juices. Synthetic materials of the kind defined are advantageously copolymers of methacrylic acid and methylmethacrylate, acrylic acid and acrylic acid methyl ester, vinyl acetate and crotonic acid, styrene and acrylic acid, and/or maleic anhydride, vinyl methyl ether and maleic acid anhydride and/or fumaric acid and/or itaconic acid, and the swelling capacity and alkali-solubility of the synthetic material can be regulated by changing the proportion of free acid present in the copolymer.

The ratio of active ingredient to synthetic material in the preparations of the invention depends on the dosage of active ingredient and the desired rate of release.

The new preparations may also contain fillers or swelling agents, for example, paraffins, starch derivatives, talc, stearates, and also electrolytes. Furthermore, interface-active substances such as fatty alcohols or fatty acids may be added to render lipophilic substances hydrophilic, and substances which render hydrophilic substances lipophilic, such as alkylamines, for example, hexadecylamine, or organic silicones, for example, dimethyldichlorosilane. They may also contain the medicament, or mixture of medicaments, or parts thereof, enveloped in wax or fat, and also synthetic resins that are insoluble in the stomach juice and/or intestinal juice and that are not swollen thereby, and thus constitute a "prolonged release" preparation.

The new pharmaceutical preparations of the invention are obtained when a medicament, or a mixture of medicaments, if desired or required, together with fillers and swelling agents and/or further adjuvants, is subjected to bead polymerization in admixture with monomers which yield physiologically acceptable synthetic materials which are dissolved or swollen by the stomach juice and/or intestinal juice when polymerized. In the said process, the medicament or mixture of medicaments, may be dissolved or suspended in the monomers, the adjuvants added, and

the mixture thus obtained dispersed, for example, by stirring, in a dispersing agent with which it is immiscible, for example, water, in such a manner that beads having the requisite degree of fineness are obtained. Polymerization may even be carried out at room temperature if the appropriate monomers are used, although it is normally carried out at an elevated temperature. The beads that are formed are separated from the dispersing agent, washed, and dried.

The catalyst used is one of those normally employed for this reaction, for example, an inorganic or organic peroxide, for example, benzoyl peroxide and tertiary-butyl hydroperoxide or an azonitrile, for example, α -azodiisobutyronitrile. An organic tertiary-amine, an iron salt, manganese, cobalt, a sulphinic acid or a sulphite can be added to accelerate polymerization.

The following examples illustrate the invention.

Example 1

10 grams of 5-(1-cyclohexenyl)-5-ethyl-calcium barbiturate and 32 grams of a vinyl acetate-crotonic acid copolymer (92:8) are dissolved in a mixture of 40 grams of methacrylic acid monomer and 25 grams of methylmethacrylate monomer. The viscous solution is emulsified in 200 millilitres of a solution of 0.4 gram of sodium polyacrylate and 20 grams of sodium sulphate in 100 millilitres of water in a vessel provided with stirring means, a reflux condenser and a tube for the introduction of gas; 0.5 millilitre of benzoyl peroxide is added, and the batch is polymerized at about 60° C. at a stirring speed of 200 r.p.m. and with the introduction of CO₂. Polymerization is finished after about 2 hours, and the product consists of dull white beads between 0.1 and 3.0 millimetres in diameter and having a smooth surface. The beads are washed with distilled water and, if desired, dried at 40° C.

Example 2

10 grams of acetyl-para-phenetidine and 30 grams of a copolymer from acrylic acid ethyl ester, tertiary butyl-acrylamide and acrylic acid are dissolved or suspended in a mixture comprising 40 grams of methacrylic acid monomer and 27 grams of methylmethacrylate monomer. The suspension is further treated and polymerized in a manner analogous to that described in Example 1, but at a temperature of 50° C. and a stirring speed of 500 r.p.m. Polymerization is finished after about 2 hours, the product comprising yellowish white beads having a mean diameter of 0.2 to 0.3 millimetre.

Example 3

100 grams of 2-ethyl-2-phenyl-glutarimide are dissolved in a solution of 30 grams of a vinyl acetate-crotonic acid copolymer (92:8) in 40 grams of methacrylic acid monomer and 30 grams of methyl-methacrylate monomer. The solution is emulsified in 550 millilitres of a solution of 0.4 gram of sodium polyacrylate and 20 grams of sodium sulphate in 100 millilitres of water in a manner analogous to that described in Example 1. 0.5 gram of α -azo-isobutyronitrile is added, and the batch is polymerized for 3 hours at a temperature of 60° C., while stirring at 500 r.p.m. White beads having a mean diameter of 0.4 to 0.6 millimetre are obtained.

Example 4

25 grams of papaverine base and 20 grams of a vinyl acetate-crotonic acid copolymer (92:8) are dissolved in 43 grams of methyl-methacrylate monomer. The solution is emulsified in 275 millilitres of a solution of 0.4 gram of sodium polyacrylate and 20 grams of sodium sulphate in 100 millilitres of water in a manner analogous to that described in Example 1. 0.3 millilitre of benzoyl peroxide is added, and the batch is polymerized at 50° C. at a stirring speed of 200 r.p.m. After 1 hour, greenish brown beads having a mean diameter of 1 to 3 millimetres are obtained.

Example 5

15 grams of arachis oil, 15 grams of a copolymer from acrylic acid ethyl ester, tertiary butylacrylamide and acrylic acid and 20 grams of 4-dimethylamino-1-phenyl-2:3-dimethylpyrazolone-5 are triturated with 50 grams of methylmethacrylate, and then further treated and polymerized in a manner analogous to that described in Example 1, but at a stirring speed of 500 r.p.m. Yellowish white beads having a mean diameter of 0.2 to 0.4 millimetre are obtained.

Example 6

10 grams of hydrocortisone are suspended in 90 grams of a mixture comprising 3 grams of methylmethacrylate, 3 grams of polyvinyl acetate-crotonic acid copolymer (92:8) and 4 grams of methacrylic acid. 0.5 millilitre of benzoyl peroxide is added and the suspension is emulsified in 250 millilitres of a solution comprising 0.4 gram of sodium polyacrylate and 20 grams of sodium sulphate per 100 millilitres of water. The batch is then polymerized for 3 hours at 60° C. while stirring at 250 r.p.m. and with the introduction of CO₂. White beads having a mean diameter of 0.7 to 2.0 millimetres are obtained.

Example 7

25 grams of N-[6-methoxy - 2 - (methoxymethyl)-4-pyrimidinyl]-sulphanilimide are dissolved at 70° C. in 75 grams of a mixture comprising 3 grams of polyvinyl acetate-crotonic acid copolymer (92:8), 3 grams of methylmethacrylate and 4 grams of methacrylic acid. 0.07 gram of α -azoisobutyronitrile is added and the mixture is then emulsified in 250 millilitres of a solution of 0.4 gram of sodium polyacrylate and 20 grams of sodium sulphate in 100 millilitres of water. The batch is polymerized for 2 hours at 70° C. while stirring at 300 r.p.m. and with the introduction of CO₂. Yellow translucent beads having a mean diameter of 0.5 to 1.0 millimetre are obtained.

Example 8

15 grams of 3-acetyl-amino-2:4:6-tri-iodobenzoic acid (Acetrizons DCI) in the form of the sodium salt are dissolved at 70° C. in 85 grams of a mixture comprising 3 grams of methylmethacrylate, 3 grams of polyvinyl acetate-crotonic acid copolymer (92:8) and 4 grams of methacrylic acid. 0.2 gram of benzoyl peroxide is added and the mixture is then emulsified in 250 millilitres of a solution of 0.3 gram of high-molecular polyethylene glycol and 10 grams of sodium sulphate in 100 millilitres of dilute hydrochloric acid (0.01 N). The batch is polymerized for 3 hours at 70° C. while stirring at 250 r.p.m. and with the introduction of CO₂. White beads having a mean diameter of 0.5 to 1.0 millimetre are obtained.

Example 9

20 grams of N - [6-methoxy - 2 - (methoxymethyl)-4-pyrimidinyl]-sulphamylamide are dissolved at 70° C. in 80 grams of a mixture comprising 10% of methacrylic acid, 40% of methyl methacrylate, 30% of polyvinyl acetate crotonic acid copolymer (92:8) and 20% of divinylbenzene. After dispersion in 300 ml. of a saturated aqueous solution of sodium sulfate with 0.4% of polyacrylate having a pH value of 6, the batch is copolymerised with the addition of 0.2 gram of azoisobutyronitrile at 70° C. for 5 hours at a stirring rate of 300 rotations per minute.

The resulting beads show a half value period for the release of active substance of one hour in artificial intestinal juice having a pH value of 7.5 at 37° C.

Example 10

20 grams of N-[6-methoxy - 2 - (methoxymethyl)-4-pyrimidinyl]-sulphamylamide are processed with 80 grams of a mixture of 50% of methacrylic acid, 30% of a copolymer of polyvinyl acetate+crotonic acid (92:8) and 20% of divinylbenzene under the same conditions as described in Example 9 to form beads.

The resulting beads show a half value period for the release in artificial stomach juice of 2½ hours.

Example 11

20 grams of N-[6-methoxy - 2 - (methoxymethyl)-4-pyrimidinyl]-sulphamylamide are polymerized with 80 grams of a mixture of 50% of methacrylic acid, 20% of a copolymer from polyvinyl acetate+crotonic acid (92:8) and 30% of divinylbenzene, as described in Example 9, at a stirring rate of 150-180 rotations per minute, to form beads.

The resulting beads show a half value period for the release of the active substance of 3½ hours.

Example 12

20 grams of N-[6-methoxy - 2 - (methoxymethyl)-4-pyrimidinyl]-sulphamylamide are polymerized with 80 grams of a mixture of 50% of methacrylic acid, 15% of a copolymer from polyvinyl acetate+crotonic acid (92:8) and 35% of divinylbenzene to form beads in the manner described in Example 11.

The resulting beads show a half value period for the release of active substance of 11½ hours.

What is claimed is:

1. Pharmaceutical oral, controlled-size, bead dosage-form preparations, 0.1 to 3.0 mm. in diameter, which contain a predetermined dosage of active medicament, stabilized by being incorporated by bead polymerization in physiologically acceptable synthetic copolymers which are alkali-soluble or at least swollen by the gastro-intestinal juices, said copolymers being selected from the group consisting of copolymers of methacrylic acid and methylmethacrylate, acrylic acid and acrylic acid methyl ester, vinyl acetate and crotonic acid, styrene and acrylic acid, and/or maleic anhydride, vinyl methyl ether and maleic acid anhydride and/or fumaric acid and/or itaconic acid, wherein control of the size of the beads controls the release of the active medicament in respect of both amount and time and wherein the ratio of active medicament to synthetic copolymer is correlated to the dosage of active medicament, the desired rate of release and regulation of the swelling capacity and alkali solubility of the synthetic copolymer by changing the proportion of free acid present in the copolymer.

2. Pharmaceutical preparations in bead form as claimed in claim 1, which contain at least parts of the medicaments enveloped in waxes or fats.

3. Pharmaceutical preparations in bead form as claimed in claim 1, which contain fillers, swelling agents and/or interface-active substances.

4. Pharmaceutical preparations in bead form as claimed in claim 1, which contain synthetic materials that are insoluble in the gastro-intestinal juices and that are not swollen thereby.

5. Pharmaceutical preparations in bead form as claimed in claim 1, which contain as synthetic polymers copolymers from methacrylic acid and methylmethacrylate.

6. Pharmaceutical preparations in bead form as claimed in claim 1, which contain as synthetic polymers copolymers from acrylic acid and acrylic acid methyl ester.

7. Pharmaceutical preparations in bead form as claimed in claim 1, which contain as synthetic polymers copolymers from vinyl acetate and crotonic acid.

8. Pharmaceutical preparations in bead form as claimed in claim 1, which contain as synthetic polymers copolymers from styrene and at least one member of the group selected from acrylic acid, maleic acid anhydride, fumaric acid, itaconic acid.

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