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Ref Expediente No 02-077 184

Solicitud PCT de Patente de Invención denominada "Sistema de Liberación Controlada para la Droga Ciprofloxacina Administrada Oralmente una Vez al Día"
Solicitante Ranbaxy Laboratories Limited

Dario Cárdenas Navas, identificado como aparece al pie de mi firma y obrando en mi condición de apoderado de la sociedad Ranbaxy Laboratories Limited, solicitante de la patente en referencia, atentamente solicito al Despacho se sirva adoptar una decisión en este asunto a la mayor brevedad

Atentamente,



Dario Cárdenas Navas
CC 17 066 629 de Bogotá
T P 1 250 del Consejo Superior de la Judicatura

ADM/da/Tecnicos/grupos/comunicacion/
F o P-708

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PATENT ABSTRACTS OF JAPAN

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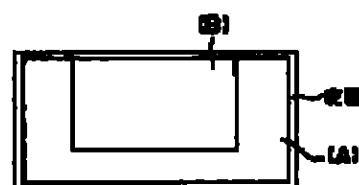
(21)Application number 03-284093 (71)Applicant BAYER YAKUHIN KK
(22)Date of filing 04.10 1991 (72)Inventor NISHIOKA TAKAAKI
KURATANI KENJI

(54) MEDICE RELEASE SOLID PHARMACEUTICAL PREPARATION OF GASTRIC SUSPENDING TYPE SUSTAINED

(57)Abstract

PURPOSE To obtain a pharmaceutical preparation capable of providing the medicinal release at a stable release rate from a medicine-containing pharmaceutical preparation part through a coating film while surely making the medicine suspend and stay in the stomach by acquiring the expansion and buoyancy in a volume expanding pharmaceutical preparation part.

CONSTITUTION This gastric suspending solid pharmaceutical preparation is constructed from (A) a volume expanding pharmaceutical preparation part containing a water-swellaable gel-forming polymer and a water-expandable foaming agent dispersed in the polymer and (B) a medicine-containing pharmaceutical preparation part, laminated to the pharmaceutical preparation part (A) or embedded therein so as to expose a part thereof This pharmaceutical preparation is further coated with a water-permeable and elastic film composed of a water-insoluble polymer



DETAILED DESCRIPTION

[Detailed Description of the Invention]

[0001] About oral sustained-release solid preparations, in more detail, in an internal use pyloric stomach, this invention carries out long duration suspension stagnation, emits a drug gradually, and relates to the suspension mold drug sustained-release solid preparations in the stomach which supply the therapy effective dose of a drug over long duration.

[0002] The most general thing as the systemic administration root of a drug is the internal use root, and internal use pharmaceutical preparation forms about 90% of all pharmaceutical preparation. Therefore, various devices are performed in order to raise the effectiveness of the drugs of the internal use pharmaceutical preparation field, and safety. For example, prodrug-ization by chemical modification etc. is one of the approach of the. Moreover, as a device by the pharmaceutical preparation-ized technique, pharmaceutical preparation-ization of an enteric coated preparation, durability pharmaceutical preparation, etc. is mentioned.

[0003] However, case [like the drug in which the absorption part of a drug is carrying out localization to the specific part in a gastrointestinal tract, especially the upper part of a gastrointestinal tract, for example, ciprofloxacin,], the good thing of bioavailability is not obtained in usual durability thru/or a usual sustained release drug.

[0004] in order to expect continuous effectiveness from the specific part in a gastrointestinal tract, only when it will not become if a drug transport system does not have ruble pine **** in the specific location in a gastrointestinal tract beyond a certain fixed time amount, and drug release is performed within a specific organ, the drug which can expect effectiveness also exists. For example, an inhibitor, pepstatin, etc. to a stomach pepsin are also the same as if emission of a drug is not continuously performed within the stomach, when it is meaningless and considers ****-ization of various kinds of antacid.

[0005] The stagnation pharmaceutical preparation in the stomach is developed as a new drug transport system recently, and some are proposed. For example, the thing (suspension mold — JP,62-195323,A —) which meant making it float in the stomach JP,62-207208,A, JP,62-283919,A, JP,1-102020,A etc. absorbs stomach juice and expands the volume. What delays stomach pylorus passage (swelling mold U S Pat No 4434153 specification etc.), what was designed so that it might become the special configuration which develops and extends under the stomach milieu interne (temperature, pH), and is held in the stomach (form status change-ized mold — JP,62-26215,A —) JP,2-29268,A, JP,3-163011,A, etc. have the things (adhesion mold JP,63-101332,A etc.) made to adhere to stomach walls using the adhesion matter. Among these, gastric mucosa is damaged the top where special configurations (the shape of a decussation cylinder and a wind mill etc.), therefore manufacture are difficult also for the uncertainty of adhesion in stomach walls with active movement, and the form status change-ized mold which a question is in effectiveness and safety from the stimulative problem to gastric mucosa especially, and can be called newest approach, or, as for the adhesion mold, troubles, like there is a possibility of barring passage of food are pointed out. On the other hand, although a suspension mold and a swelling mold are techniques developed comparatively for many years, manufacture is easy and there is no invasion to a living body, and since it is safe, it is attractive.

[0006] The pharmaceutical preparation which distributed the minute pill which contains a chief remedy in an advanced water bloating tendency polymer matrix on the above-mentioned U S Pat. No 4434153 specifications is indicated. However, since it will take time amount that a gel layer is formed in a front face

and stomach juice permeates the interior if stomach juice is contacted, before swelling in sufficient magnitude (diameter of about 1.5-2cm) to bar stomach pylorus passage, possibility of being discharged from the stomach is large, and the satisfying stagnation effectiveness in the stomach is not acquired.

[0007] Moreover, the suspension mold pharmaceutical preparation in the stomach which made the foaming layer expose outside is indicated by above-mentioned JP,62-283919,A with the tablet which consists of a chief remedy layer and a foaming layer. In order that a foaming layer may contact direct stomach juice, there is an advantage of foaming certainly, but since the produced air bubbles separate easily by stomach contraction movement or contact to contents, buoyancy does not improve, so that it was expected and is not given to ** for which collapse of pharmaceutical preparation already waits conversely for a naked tablet, and the expected stagnation effectiveness in the stomach.

[0008] This invention is developed for the purpose of offering suspension in the stomach / stagnation mold drug gradual release system which has improved the fault of the conventional stagnation pharmaceutical preparation in suspension / swelling type stomach like the above, and according to this invention The cubical-expansion nature pharmaceutical preparation part containing the foaming agent component of the water fizz distributed in the gel plasticity polymer of water bloating tendency, and this polymer (A), With the floating solid preparations in the stomach which consisted of drug content pharmaceutical preparation parts (B) laid under this pharmaceutical preparation part (A) so that a laminating might be carried out to this pharmaceutical preparation part (A) or it might be exposed of the part, *****, The suspension mold drug sustained-release solid preparations in the stomach characterized by covering this pharmaceutical preparation with the coat which has elasticity with the water permeability it is further opaque from a water-insoluble nature polymer are offered

[0009] Hereafter, the pharmaceutical preparation of this invention is further explained to a detail

[0010] (A) Cubical-expansion nature pharmaceutical preparation part when contents, such as food, are in the stomach, even after making this invention pharmaceutical preparation float in the stomach, and the volume's expanding and discharging stomach contents towards a small intestine, by controlling the discharge from the pylorus, this pharmaceutical-preparation part (A) delays the elimination rate in the stomach, and achieves the function make the residence time in the stomach of this invention pharmaceutical preparation extend as a result.

[0011] It is the water fizz (it is here) which carried out the deer and was distributed in the polymer of the gel plasticity which has the property to swell when this pharmaceutical preparation part (A) contacts water (A-1) bloating tendency, i.e., water, and this (A-2) polymer Water fizz mainly consists of a foaming agent component which says the property in which generate gas when water or stomach juice is contacted, and the polymer which carried out [above-mentioned] gelation is made to foam.

[0012] As a gel plasticity polymer (A-1) of the above-mentioned water bloating tendency, the high polymer which the volume huge-izes and which can be permitted pharmaceutically is usable, for example, sodium alginate, carrageenan, Pori (hydroxy acrylic methacrylate), Pori (ethyleneoxide), konnyaku powder, etc. are mentioned at the same time it gels underwater

[0013] When it **** in the usual making tablet compressive force (about 1 ton/cm²), it fabricates to a tablet with a diameter [of 10mm], and a thickness of about 4mm and this is immersed in 25-degree C water especially, the polymer in which a diameter has the high expansion coefficient which becomes twice [at least] at least 1.5 times and 12 hours after after 2 hours preferably twice [at least] 12 hours after is suitable. Moreover, it is still more convenient if the polymer is excellent in compression-molding nature (shaping is

possible also at a small compression pressure) as the example of such a polymer -- Al Cox R E- 240 [the product made from Akinari Chemical industry], and POLYOXR WSR Coagulant Pom (ethyleneoxide) of 4 million-5 million is mentioned for the molecular weight which may come to hand by trade names, such as [a product made from Union Carbide Corp]

[0014] On the other hand, if avirulent gas is generated when water or stomach juice is contacted, especially a limit does not have the foaming agent component (A-2) distributed in the above-mentioned polymer (A-1), for example, it can illustrate the combination of a hydrogencarbonate or a hydrogencarbonate, and an organic acid. The organic acid which the sodium hydrogencarbonate (sodium bicarbonate) is usually suitable as a hydrogencarbonate, and can be permitted pharmaceutically [a tartaric acid, a succinic acid, a citric acid, etc.] as an organic acid is mentioned gas

[0015] Since a hydrogencarbonate can avoid it being possible to perform coating processing beforehand by water-soluble polymers, such as hydroxypropylcellulose and hydroxypropyl methylcellulose, and being able to attain stabilization to moisture absorption of a hydrogencarbonate by this, and contacting an organic acid and directly as occasion demands, its chemical stability of a hydrogencarbonate improves 7

[0016] Although both operating rate can be changed in the large range according to the class of the hydrogencarbonate which it is not strictly restricted and is used, and/or organic acid etc. when using it combining a hydrogencarbonate and an organic acid, generally it is convenient 2 1-1 2, and to consider as within the limits of 1 1 to 1 1 2 especially by the mole ratio of a hydrogencarbonate pair organic acid

[0017] Although it can change according to extent of foaming with which the content of the above-mentioned foaming agent component (A-2) is not restricted strictly, either and it is wished to the class and pharmaceutical preparation of a foaming agent etc., generally it is 5 - 20 % of the weight preferably one to 25% of the weight on the basis of the weight of this pharmaceutical preparation part (A)

[0018] moreover, the gel plasticity polymer (A-1) and foaming agent component (A-2) which have the water bloating tendency stated to this pharmaceutical preparation part (A) above -- in addition in order to raise the reinforcement when fabricating to solid preparations, for example, a tablet, if needed furthermore -- a hypoviscosity type (viscosity -- 6 0cp - 10 0cp extent; -- 2% water solution --) 20-degree C hydroxypropylcellulose, methyl cellulose, a hydroxymethyl cellulose, etc can be blended in a proper amount

[0019] When this invention pharmaceutical preparation is administered orally, in order that this pharmaceutical preparation part (A) may make suspension within the stomach easy, the thing with the smallest possible specific gravity is desirable, and especially less than 0.8 thing usually has [less than one] advantageous specific gravity. Moreover, various additives, such as said various polymers and a foaming agent, have as much as possible small bulk density, and the thing excellent in compression-molding nature is recommended

[0020] (B) Drug content pharmaceutical preparation part this pharmaceutical preparation part is a ***** type thing, its ***** is also good, or it is the pharmaceutical preparation part containing a drug which achieves the function as a drug reservoir of the drug transport system of this invention, and its ***** is [this pharmaceutical preparation part (B) is an erosive matrix type thing, and] also good

[0021] In the case of ***** type [former], this pharmaceutical preparation part (B) can be formed by blending suitably with a drug (chief remedy) other adjuvant components usually used for the further usual tablet manufacture by the disintegration agent. As other adjuvant components which carboxy-methyl-starch sodium, cross carmellose sodium, cross POPIDON, alpha-ized starch, carboxymethylcellulose sodium, etc

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are mentioned, and can be blended as a disintegration agent if needed, for example, binders, such as lubricant, starches, such as excipient, magnesium stearates, such as a lactose, mannite, starch, a dextrin, and crystalline cellulose, talc, and waxes, tragacanth, gelatin, a polyvinyl pyrrolidone, and polyvinyl alcohol, etc are mentioned, for example

[0022] In the case of erosive matrix type [latter], moreover, this pharmaceutical preparation part (B) Therefore, it can prepare on a known pharmaceutical preparation technique as an erosive tablet (erosion tablet) To a drug (chief remedy), for example, methyl cellulose, hydroxypropyl methylcellulose, A hydroxymethyl cellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, It can form by blending water-soluble well-known polymers which can be permitted pharmaceutically, such as polyvinyl alcohol and a polyvinyl pyrrolidone, and the adjuvant component besides **** further mentioned above by the case. *expans*

[0023] Generally, when [that water solubility is / a drug (chief remedy) / large and/or] a dissolution rate is large, or when there are few effective doses, the erosive matrix type is more suitable. So that the part may expose this invention solid preparations by using as a core tablet the drug content pharmaceutical preparation part (B) described above, as shown in drawing 1 It can be laid under the cubical-expansion nature pharmaceutical preparation part (A), and can be constituted by the so-called gestalt of a "bull eye" (Bull-Eye eye of a bull) For example, the cubical-expansion nature pharmaceutical preparation part (A) and the drug content pharmaceutical preparation part (B) can be constituted by the gestalt of the multilayered tablet by which the laminating was carried out as a layer, respectively as shown in drawing 2 and 3

[0024] Shaping of such solid-state pharmaceutical preparation of a gestalt can be performed using a usual multilayer tableting machine or a usual nucleated tableting machine etc.

[0025] Thus, although especially the magnitude of the solid preparations fabricated is not restricted, in the case of the **** multilayered tablet shown in drawing 2 and drawing 3 , generally, a diameter is in 7-12mm, thickness is within the limits of 3-7mm, and it is appropriate for the ratio of the sum total thickness of the sum total thickness pair pharmaceutical preparation part (B) of a pharmaceutical preparation part (A) that it is within the limits of 2 1-1 2 Moreover, as for 8-12mm and thickness, in the case of the **** dry coated tablet shown in drawing 1 , generally, it is desirable [the whole diameter] that the diameter of 4-7mm and a core tablet is thick in 4-8mm, and it is thick within the limits of 2-5mm

[0026] The solid preparations which consist of a pharmaceutical preparation part (A) described above and (B) are covered with the coat which has elasticity further with the water permeability it is opaque from a water-insoluble nature polymer

[0027] As a water-insoluble nature polymer used for this covering, for example, cellulose acetate phthalate, A methacrylic acid methacrylic acid methyl copolymer, a methacrylic acid methacrylic acid ethyl copolymer, Although hydroxypropylmethylcellulose phthalate, hydroxypropyl-methylcellulose acetate succinate, carboxy methyl ethyl cellulose, ethyl cellulose, an aminoalkylmetaacrylatecopolymer, etc are mentioned The aminoalkylmetaacrylatecopolymer marketed from Roehm Pharma by the trade name of for example, Eudragit RS30DL and Eudragit RS100L especially is used suitably Moreover, when it is the purpose which adjusts the water permeability of the coat which consists of this water-insoluble nature polymer, an aminoalkylmetaacrylatecopolymer, an alkylmetaacrylate copolymer, etc which are marketed from Roehm Pharma by Eudragit RS30D or the trade name of Eudragit L30D-55 when reducing water permeability can be blended or it raises water permeability, a pullulan, a hydroxymethyl cellulose, etc. can be blended

[0028] Furthermore, as for the coat which consists of a water-insoluble nature polymer, it is desirable to have a certain amount of elasticity, and when this polymer itself is lacking in elasticity, it can raise the elasticity of

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a coat by blending a plasticizer Citric-acid triethyl, Tween 80, a triacetin, monoglyceride, a polyethylene glycol 6000, etc. are mentioned as the example of the plasticizer which can be used, and these can usually be used for it in 20 or less % of the weight of an amount to polymer solid content.

[0029] Coating of the constituent for coat formation stated above can be performed using the tablet coating method of itself known, for example, can be performed using the coating machines (example a high coating machine, a doria coating machine, AKUA coating machine, etc.) of an aeration mold

[0030] Although the thickness of the coat formed is changeable over the large range depending on a class, water permeability demanded of the polymer to be used, especially generally 20-300-micron about 50-200 microns are suitable for it.

[0031] As a drug which may be applied to the solid preparations of this invention stated above If it administers orally and is absorbed within an alimentary canal, there will be especially no limit For example, barbitals, chlorpromazine, levodopa, diazepam, pneuma, such as imipramine, — a nervous system — ** agent, — acetaminophen and aspirin — beta-blocker agents [, such as alleviation-of-fever painkilling antiphlogistic, diphenhydramine hydrochloride /, such as antihistamine, propranolol hydrochloride], such as ibuprofen, ketoprofen, and indomethacin, Spironolactone, Antihypertensives, such as diuretic, captopril, such as acetazolamide and furosemide, and bunazosin hydrochloride, Diltiazem hydrochloride, Coronary vasodilators, such as isosorbide dinitrate, Nifedipine, nicardipine hydrochloride, Antihypemics [, such as calcium antagonist, pravastatin], such as nisoldipine and nitrendipine, Theophylline, Antitussives, such as codein phosphate, Digestive, synthetic aluminum silicate, such as a pepsin and diastase, antacid [, such as magnesium oxide,], — antiulcer drug [, such as cimetidine], — vitamin compound [, such as a riboflavin,], — tetracyclines — Synthetic antimicrobials, such as various antibiotic, ofloxacin, such as penicillins and a cephem system, and ciprofloxacin, although anticancer drugs [, such as antifungal, 5-FU,], such as thio kona ZORU and a griseofulvin, etc are raised The drug an absorption part or whose site of action is the stomach or the small intestine upper part especially, for example, the ciprofloxacin of synthetic antimicrobials, especially various antacid, etc. are suitable.

[0032] if stomach juice is contacted first according to the solid preparations of this invention -- a water permeability coating layer — a connoisseur -- intermediary stomach juice permeates an internal cubical-expansion nature pharmaceutical preparation part and a drug content pharmaceutical preparation part promptly

[0033] In a cubical-expansion nature pharmaceutical preparation part, the foaming agent which lives together reacts with water, air bubbles are produced, and this accelerates expansion of a bloating tendency polymer further at the same time an altitude bloating tendency polymer absorbs moisture and begins expansion gradually Since the trap of the air bubbles is carried out to the outside coating film at this time and it is hard to separate outside, cubical expansion and suspension-ization are performed very effectively, and expand in diameter of about 1.5-2cm in the usual residence time in the stomach (about 2 hours), and acquire sufficient buoyancy to float to stomach juice

[0034] On the other hand, in a drug content pharmaceutical preparation part, the erosive matrix layer containing a drug or the saturated-solution layer of a drug is formed with the stomach juice which permeated, and the drug release by which the emission rate was stabilized according to the diffusion device through the outside coating film is obtained

[0035] Consequently, floating and piling up in the stomach certainly, the solid preparations of this invention can continue emitting a drug until they collapse with stomach juice and are discharged from the pylorus

[0036] Next, an example and the example of a trial explain this invention still more concretely

[0037]

[Example]

145.77g of preparation ciprofloxacin hydrochloride of an example 1 (1) drug content pharmaceutical preparation part, carboxy-methyl-starch sodium (ExplotabR 8.5g, 9.1g of lactic acids, and AEROJIN 0.83g were mixed to homogeneity, and spraying granulation was carried out, having used as the binder the solution which melted hydroxypropylcellulose (HPC-L* Nisso) 3.4g and 1.7g of sodium lauryl sulfate to 164.9g of purified water) After having carried out the minus sieve of this granulation object by the sieve which has a 0.84mm opening, adding magnesium stearate (0.70g) and mixing for 5 minutes by the V shaped rotary mixer, it tableted in tableting pressure force 4.5kN, and 5mm in the diameter of 6mm and thickness and cylindrical tablet 1000 lock with a weight of 170mg were obtained. The degrees of hardness of a tablet are 110N-120N, decay time is about 4 minutes (with water use, the JP conformity / no disk), and it is *****

[0038] (2) After adding 46g of 10% water solutions of hydroxypropylcellulose (HPC-SSL** Nisso) and kneading to 41.4g of preparation sodium hydrogencarbonates of a cubical-expansion nature pharmaceutical preparation part, it dried enough at 50 degrees C. 23g of obtained dry matters was mixed with polyethylene oxide (AlcoxR E-240 Akinari chemistry) 18.86g and 17.25g of citric acids to homogeneity, and 1.15g of magnesium stearates was added further, and it mixed for 5 minutes.

[0039] (3) After putting in 230mg of fine particles first obtained by (2) into the mortar (10mm of diameters) of the coalesce single-engined tableting machine of a drug content pharmaceutical preparation part and a cubical-expansion nature pharmaceutical preparation part and accustoming horizontally, The tablet obtained by (1) was carried in the center, direct making tablet shaping (compressive force 2kN) was carried out, and it considered as the tablet with 6mm [in the diameter of 10mm of the configuration (refer to drawing 1) in which the drug content part was inserted in the crevice of a concave cubical-expansion nature pharmaceutical preparation part, and thickness], and a weight of 400mg. Degrees of hardness are 90N-110N, and are *****

[0040] (4) 94g of purified water is added to coating citric-acid triethyl (Citroflex R2-fizer company) 6g, and the churning dissolution was carried out, and amino acrylic methacrylate copolymer RS(EudragitR RS30 DL Roehm Pharma)100g was added further, and it agitated for about 3 hours, and considered as the suspension for coatings, and pan coating of the tablet obtained by (3) was carried out with the conventional method. The amount of coatings was made into 4 % of the weight to tablet weight.

[0041] * Hydroxypropylcellulose by Nippon Soda Co., Ltd., viscosity 6.0 - 10.0CP (2% water solution, 20 degrees C), 53.4 - 77.5% of hydroxypropyl radicals, true specific gravity 1.2224

[0042] ** Hydroxypropylcellulose by Nippon Soda Co., Ltd., viscosity 2.0 - 2.9CP (2% water solution, 20 degrees C), 53.4 - 77.5% of hydroxypropyl radicals, true specific gravity 1.22

[0043] Weighing capacity of the same constituent (drug content section) as example 2 example 1 (1) and the weight of 170mg is carried out. After putting in into the mortar (diameter 10mm) of a single-engined tableting machine previously and making a front face into Taira, it is filled up with the same constituent (cubical-expansion section) as example 1 (2), and the weight of 230mg on it, and tablets by compressive-force 9.8kN. Diameter The bilayer lock (10mm, thickness 5.3mm, and weight 400mg) (refer to drawing 2) was manufactured. Film coating was performed to this like example 1 (4).

[0044] After putting in previously the same constituent (cubical-expansion section) as example 3 example 1 (2), and the weight of 1.15mg into the mortar (diameter 10mm) of a single-engined tableting machine and

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making a front face into Taira, It is filled up with the constituent (drug content section) same on it as example 1 (1), and the weight of 170mg, and a front face is made into Taira. It was filled up with the still more nearly same constituent (cubical-expansion section) as example 1 (2) on it, and the weight of 115mg, tableted by compressive-force 9 8KN, and the three-layer lock (diameter 10mm, thickness 5 3mm, and weight 400mg) (refer to drawing 3) was manufactured Film coating was performed to this like example 1 (4) [0045] A tablet diameter is 20mm and ***** 20mm and 24 hours after 15mm and 6 hours after 2 hours after, floating, while feeding into the method elution test liquid of a station (purified water) the tablet obtained in the example example 1 of a trial, and the surface coating film's expanding gradually by internal foaming, and maintaining suspension The elution of hydrochloric-acid SHIPUROKISASHIN at this time is as being shown in drawing 4 The rate of elution 24 hours after the tablet of an example 1 is 46%, and the zero-order emission-elution pattern stabilized until after 32 hours was obtained.

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United States Patent [19]
Augello et al

[11] **Patent Number** **5,985,323**
[45] **Date of Patent** **Nov 16, 1999**

[54] **MICROCRYSTALLINE CELLULOSE/
ALGinate WET GRANULATION
EXCIPIENT/BINDER**

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Reier Somerset both of N.J**

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[22] **Filed** **Mar 23, 1998**

[51] **Int. Cl.⁶** **- - - - - A61K 9/16, A61K 9/20**

[52] **U.S. Cl.** **- - - - - 424/464; 424/465, 424/489-
514/779 514/781**

[58] **Field of Search** **- - - - - 424/464, 465
424/489 514/779 781**

[56] **References Cited**
U.S. PATENT DOCUMENTS
5,366,742 11/1994 Tunon, Jr et al. 426/96
Primary Examiner—James M. Spear
**Attorney, Agent, or Firm—Ratner & Prestia, Robert L.
Anderson**

[57] **ABSTRACT**
The present invention discloses an improved excipient composition for use as an excipient/binder for wet granulation of pharmaceuticals, a process for preparing the excipient composition its use in granular pharmaceutical compositions, and compressed pharmaceutical tablets made from the granular pharmaceutical compositions. The excipient composition comprises a dried aqueous slurry of microcrystalline cellulose wetcake and a low viscosity alginate

8 Claims, No Drawings

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then mixed, forming a uniform slurry before being homogenized in a single stage at 10,342 kPa (1500 psi). The homogenized slurry was then spray dried using a disk dryer at an inlet temperature of 198.9° C (385° F) and an outlet temperature of 106.7° C (224° F). The dry powder that was produced had a loose bulk density of 0.43, loss of weight upon drying of 2.0%, and 20% of the particles were larger than 200 mesh (74 microns).

EXAMPLE 2

The procedure of Example 1 was followed except that 45 kilograms of wetcake, 359.6 liters of water and 3.175 kilograms of low viscosity sodium alginate were used to prepare the slurry. Prior to homogenization 340 grams of calcium chloride was added to the slurry. The homogenized slurry was then spray dried using a disk dryer at an inlet temperature of 232.2° C (450° F) and an outlet temperature of 118.3° C (245° F). The dry powder that was produced had a loose bulk density of 0.39, loss of weight upon drying of 1.8%, and 18% of the particles were larger than 200 mesh (74 microns).

EXAMPLE 3

The procedure of Example 1 was followed except that 68 kilograms of colloidal wetcake, 208.2 liters of water and 5.67 kilograms of low viscosity sodium alginate were used to prepare the slurry. The dry powder that was produced had a loose bulk density of 0.58, loss of weight upon drying of 2.5%, and 7% of the particles were larger than 200 mesh (74 microns).

EXAMPLE 4

In a stainless steel Hobart mixer were placed 3298 grams of acetaminophen and 495 grams of microcrystalline cellulose coprocessed with low viscosity sodium alginate, 85.15 prepared as described in Example 1. These materials were blended for five minutes before 1250 grams of deionized water was slowly added until all powder was incorporated into granular particles. This granulation required 10 minutes after which the granules were dried on a paper-lined tray which was placed in a 60° C oven for 4 hours and then allowed to remain in the oven overnight. The dried granular material was passed through a #16 US standard mesh screen and then was placed in a Patterson-Kelley twin shell blender. To this blender were added 178 grams of croscarmellose sodium and 989.5 grams of Avicel® PH 102. These ingredients were mixed for 10 minutes after which 39.5 grams of magnesium stearate which had been passed through a #45 US standard mesh screen was added to the blender. Mixing was continued for an additional 5 minutes. This formulation was compressed on a B₂ tablet press using tooling to prepare caplet-shaped tablets. The average weight, thickness, and hardness of these tablets were 0.7556 grams, 5.867 mm (0.2310 inch), and 11.4 Kiloponds, respectively. The disintegration time for these tablets averaged 100 seconds, and their friability was 0.265% after 4 minutes. Dissolution of the active ingredient in 900 mL of 0.05 M phosphate buffer using USP Apparatus 2 equipped with a paddle (USP 23 procedure) was 95% after 30 minutes. This is Example 4a in Table 1. Examples 4b and 4c were prepared in the same manner except that 1750 grams and only 800 grams of deionized water were used in Examples 4b and 4c respectively.

TABLE 1

	Example		
	4a	4b	4c
(grams)			
Ingredients			
Acetaminophen	3298	3298	3298
MCC/Na alginate ^a	495		
MCC/NaCl alginate ^b		495	
Polyvinylpyrrolidone ^c			150
Glucanate USP ^d	1250	1750	800
Croscarmellose sodium ^e	178	178	183
MCC ^f	989.5	989.5	1043.5
Magnesium stearate	39.5	39.5	42.5
Tablet Properties			
Average weight (grams)	0.7556	0.759	ND ^g
Thickness (mm)	5.8452	5.867	ND
Hardness (Kp)	11.40	8.05	ND
Friability ^h (%)	0.265	0.323	ND
Disintegration (seconds)	100	34	ND
Dissolution (95%) ⁱ	95	95	ND

^aPrepared in Example 1
^bPrepared in Example 2
^cPolyvinylpyrrolidone 20/32, sold by BASF Corporation
^dAc-DL-Sol ®, FMC Corporation, Philadelphia, PA 19103
^eAvicel® PH-102, FMC Corporation, Philadelphia, PA 19103
^fNot measured because "tapping off" occurred during tableting, indicating inferior tablets
^gFriability measurements were made after 4 minutes
^hDissolution measurements were taken after 30 minutes

EXAMPLE 5

In a stainless steel Hobart mixer were placed 3040 grams of ibuprofen and 570 grams of microcrystalline cellulose coprocessed with low viscosity sodium alginate, 85.15 prepared as described in Example 1. These materials were blended for five minutes before 1200 grams of deionized water was slowly added until all powder was incorporated into granular particles. This granulation required 10 minutes after which the granules were dried on a paper-lined tray which was placed in a 50° C oven for 4 hours and then allowed to remain in the oven overnight. The dried granular material was passed through a #16 US standard mesh screen and then was placed in a Patterson-Kelley twin shell blender. To this blender were added 205 grams of croscarmellose sodium and 1140 grams of Avicel® PH 102. These ingredients were mixed for 10 minutes after which 45.5 grams of magnesium stearate which had been passed through a #45 US standard mesh screen was added to the blender. Mixing was continued for an additional 5 minutes. This formulation was compressed on a B₂ tablet press using tooling to prepare caplet-shaped tablets. The average weight, thickness, and hardness of these tablets were 0.6580 grams, 5.585 mm (0.2199 inch), and 2.81 Kiloponds, respectively. The disintegration time for these tablets averaged 35 seconds, and their friability was 0.30% after 4 minutes. Dissolution of the active ingredient in 900 mL of 0.05 M phosphate buffer using USP Apparatus 2 equipped with a paddle (USP 23 procedure) was 85% after 60 minutes. This is Example 5a in Table 2. Examples 5b and 5c were prepared in the same manner except that only 800 grams of deionized water was used in Example 5c.

particles. The granules were dried on a paper-lined tray which was placed in a 60° C. oven for 3.5 hours. The dried granular material was milled through a 0.9 mm Co-mill screen and then was placed in a Patterson-Kelley twin shell blender. To this blender was added 120 grams of croscarmellose sodium (Ac-Di-Sol). These ingredients were mixed for 10 minutes after which 40 grams of magnesium stearate which had been passed through a #30 US standard mesh screen was added to the blender. Mixing was continued for an additional 5 minutes. This formulation was compressed on a rotary tablet press (Model 512) using tooling to prepare caplet-shaped tablets. The average weight, thickness, and hardness of these tablets were 0.592 gram, 6.223 mm (0.245 inch), and 11.1 Kiloponds, respectively. The disintegration time for these tablets averaged 782 seconds, and their friability was 1.38% after 4 minutes with capping of the tablets. This is Example 7a in Table 5. Examples 7b, and 7c were prepared in the same manner using different granulating agents. The compositions of these caplets and the results are summarized in Table 5.

TABLE 5

Ingredients	Example		
	7a (grams)	7b (grams)	7c (grams)
Acetaminophen	3360	3338.8	3338.8
MCC ^a	400	—	500.8
Sodium alginate	80	—	—
MCC/Na alginate ^b	—	500.8	—
Deionized water	1250	1250	1350
Croscarmellose sodium ^c	120	120	120
Magnesium stearate	40	40	40
Tablet Properties			
Average weight (grams)	0.592	0.591	0.594
Thickness (mm)	6.223	6.096	6.231
Hardness (Kp)	11.1	10.89	5.53
Friability ^d (%)	1.38	0.52	5.97
Disintegration (seconds)	782	666	77

Avicel® PH-101, FMC Corporation, Philadelphia, PA 19103

^aPrepared in Example 1

^bAc-Di-Sol®, FMC Corporation, Philadelphia, PA 19103

^cFriability measurements were made after 4 minutes

EXAMPLE 8

On a vertical granulator (Model FMVG-25 Powrex Corporation) were placed 3457.5 grams of acetaminophen and 495 grams of microcrystalline cellulose coprocessed with low viscosity sodium alginate, 95:5 prepared by the method described in Example 1. The blade of the granulator was operated at 603 rpm and the chopper at 1592 rpm. These materials were blended for five minutes before approximately 1250 grams of deionized water was sprayed into the granulator at a rate of 155 grams/minute. The addition of water required 7 minutes and was followed by continued granulation for five minutes. The granules were dried on a paper-lined tray which was placed in a 60° C oven for 2.5 hours. The dried granular material was passed through a #16-18 mesh screen and then was placed in a Patterson-Kelley twin shell blender. To this blender were added 187

grams of croscarmellose sodium (Ac-Di-Sol, FMC Corporation, Philadelphia, Pa 19103) and 1037.5 grams of Avicel® PH 102 (FMC Corporation, Philadelphia, Pa 19103). These ingredients were mixed for 10 minutes after which 41.2 grams of magnesium stearate which had been passed through a #30 US standard mesh screen was added to the blender. Mixing was continued for an additional 5 minutes. This formulation was compressed on a rotary tablet press (Model 512) using tooling to prepare caplet-shaped tablets. The average weight, thickness, and hardness of these tablets were 0.765 gram, 5.751 mm (0.2264 inch), and 9.43 Kiloponds, respectively. The disintegration time for these tablets averaged less than 3 minutes, and their friability was 0.32% after 4 minutes. This is Example 8a.

The procedure of Example 8a was followed exactly substituting as the binder microcrystalline cellulose coprocessed with low viscosity sodium alginate (90:10) prepared by the method of Example 1. The wet granulation of this material and acetaminophen after drying had a water content of 1.352 wt %, and the water content of the final mixture prior to compression was 2.332 wt %. The weight, thickness, and hardness of these tablets were almost identical to those prepared in Example 8a, and their friability was 0.387%. This is Example 8b.

What is claimed:

1. An excipient composition comprising particles of a dried aqueous slurry consisting essentially of unattired microcrystalline cellulose wetcake and a low viscosity alginate selected from the group consisting of low viscosity sodium alginate and a sodium, calcium salt complex of low viscosity sodium alginate in which the low viscosity alginate has a viscosity in the range of 40 to 80 cps.

2. The composition of claim 1 in which the alginate is low viscosity sodium alginate.

3. A process for preparing the composition of claim 1 comprising the steps of (a) forming an aqueous slurry of undried unattired microcrystalline cellulose wetcake, (b) adding the alginate to the stirred slurry (c) forming a uniform slurry in which the microcrystalline cellulose and alginate are uniformly distributed (d) drying the uniform slurry and (e) recovering the a particulate composition.

4. The composition of claim 1 in which the weight ratio of microcrystalline cellulose to alginate is from 95.5 to 75:25.

5. The composition of claim 1 in which the weight ratio of microcrystalline cellulose to alginate is from 95:5 to 85:15.

6. The composition of claim 1 in which the alginate is low viscosity sodium alginate having a viscosity in the range of 40 to 80 cps and the weight ratio of microcrystalline cellulose to alginate is in the range of 95.5 to 85:15.

7. A granular pharmaceutical composition comprising the granulation composition of any of claims 1, 2, 4, 5 or 6 in admixture with a medicinally effective amount of a pharmaceutically active ingredient.

8. A compressed pharmaceutical tablet comprising the pharmaceutical composition of claim 7 admixture with a pharmaceutically acceptable compatible binder, diluent, disintegrant, flavoring agent, lubricant or mixture thereof.

* * * * *

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCI
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D C , Enero 11 de 2007

Abogado
DARÍO CÁRDENAS NAVAS

ASUNTO	Radicación No	02 077 184
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No	602
	Folios	0

Título de la solicitud "Sistema de liberación controlada para la droga ciprofloxacín administrada oralmente una vez al día "

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico

Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 101 - 168 y el capítulo reivindicatorio de los folios 169 – 179 de la solicitud

Objeto de la Invención

El objeto de la presente solicitud de patente de invención consiste en

Una formulación de tabletas para la liberación controlada que comprende ciprofloxacín, de 0.1% a 8.0% de un agente de viscosidad (goma xantán o HPMC) y/o un agente de gelificación (alginato de sodio), 5.0% a 15% de un agente que genera gas (carbonato o bicarbonato) y 3.0% a 15% de un agente de expansión (PVP) (reivindicaciones 1–20 y 24–37) y libera más del 50 % de la droga en menos de 4 horas (reivindicaciones 21–23 y 38–43)

El problema planteado en esta solicitud es la necesidad de una formulación de ciprofloxacín que mantenga un nivel sanguíneo efectivo, de manera que el paciente no necesite la administración de múltiples dosis durante el día

Para resolver este problema técnico la solicitud en estudio proporciona la formulación de tabletas que comprende ciprofloxacín, un agente de viscosidad (goma xantán o HPMC) y/o un agente de gelificación (alginato de sodio), un agente que genera gas (carbonato o bicarbonato) y un agente de expansión (PVP)

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El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC A 61 K 9/46, A 61 K 9/22, A 61 K 9/26 A 61 K 9/20, A 61 K 9 714

También se reivindica prioridad de la Solicitud de Patente de los Estados Unidos US 09 517 887 de marzo 3 de 2000, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido

Con respecto a los Art. 28 y 30 de la D 486

El artículo 28 de la Decisión 486 establece *"La descripción deberá divulgar la invención de manera suficientemente clara y completa para su comprensión y para que una persona capacitada en la materia técnica correspondiente pueda ejecutarla. La descripción de la invención indicará el nombre de la invención e incluirá la siguiente información*

- a) el sector tecnológico al que se refiere o al cual se aplica la invención,*
- b) la tecnología anterior conocida por el solicitante que fuese útil para la comprensión y el examen de la invención, y las referencias a los documentos y publicaciones anteriores relativas a dicha tecnología,*
- c) una descripción de la invención en términos que permitan la comprensión del problema técnico y de la solución aportada por la invención, exponiendo las diferencias y eventuales ventajas con respecto a la tecnología anterior,*
- d) una reseña sobre los dibujos, cuando los hubiera,*
- e) una descripción de la mejor manera conocida por el solicitante para ejecutar o llevar a la práctica la invención, utilizando ejemplos y referencias a los dibujos, de ser éstos pertinentes, y,*
- f) una indicación de la manera en que la invención satisface la condición de ser susceptible de aplicación industrial si ello no fuese evidente de la descripción o de la naturaleza de la invención*

El artículo 30 de la Decisión 486 establece *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción*

Las reivindicaciones podrán ser independientes o dependientes. Una reivindicación será independiente cuando defina la materia que se desea proteger sin referencia a otra reivindicación anterior. Una reivindicación será dependiente cuando defina la materia que se desea proteger refiriéndose a una reivindicación anterior. Una reivindicación que se refiera a dos o más reivindicaciones anteriores se considerará una reivindicación dependiente múltiple"

La descripción divulga la invención de manera suficientemente clara y completa para su comprensión, tal como lo establece el Art 28 de la decisión 486 de la Comisión Andina. Menciona el sector tecnológico al que pertenece, los antecedentes de la técnica, la divulgación del problema técnico, la solución propuesta y la ventaja frente a la tecnología anterior.

Pero en cuanto a las reivindicaciones 21-23 y 38-43 se observa que no definen la formulación, porque mencionan que libera más del 50 % de la droga en menos de 4 horas, lo cual no la caracteriza. Se recuerda que el resultado a alcanzar no es una característica técnica de la invención. Las reivindicaciones deben definir la invención por sus características esenciales, en este caso por medio de los componentes que la conforman. La invención no queda definida por el resultado a alcanzar (tal como liberar más del 50 % de la droga en menos de 4 horas), puesto que lo reivindicado incluiría no sólo la solución propuesta por el solicitante, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Debe hacerse la corrección necesaria.

Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que "El

estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40°

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es marzo 3 de 2000, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación anterior y se encontró el siguiente documento que anticipa el objeto de esta solicitud

No	Documento	Título	Fecha de Publicación
D1	JP 08 024 959	Medice release solid pharmaceutical preparation of gastric suspending type sustained	Feb 1, 1994
D2	US 5985 323	Microcrystalline cellulose/alginate wet granulation excipient/binder	Nov 16, 1999

Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica

La formulación de tabletas para la liberación controlada que comprende

- **Ciprofloxacín**
- **un agente de viscosidad (goma xanthan) y/o un agente de gelificación (alginato de sodio)**
- **un agente que genera gas (carbonato ó bicarbonato) y**
- **un agente de expansión (PVP)**

se conocía en D1, que es el documento del arte más cercano, porque menciona previamente los cuatro componentes de esta solicitud ciprofloxacín, un agente de viscosidad (goma xanthan ó HPMC) y/o un agente de gelificación (alginato de sodio), un agente que genera gas (carbonato ó bicarbonato) y un agente de expansión (PVP) La tableta objeto de esta solicitud no parece tener una ventaja técnica sobre lo enseñado en D1

El problema planteado en esta solicitud la necesidad de una formulación de ciprofloxacín que mantenga un nivel sanguíneo efectivo, de manera que el

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paciente no necesite la administración de múltiples dosis durante el día, se había solucionado en D1, la cual ofrece una tableta que se suspende en el estómago y libera la droga gradualmente. Además D2 contiene el alginato, por lo cual se considera que para un experto sería obvio combinar estos dos documentos. De manera que el objeto de esta solicitud no tiene nivel inventivo.

Lo reivindicado tendría nivel inventivo si presentara propiedades sorprendentes en comparación con la tableta del estado del arte y resolviera un problema que no se hubiese resuelto en la técnica. Se requiere al solicitante el aclarar, si es que existen, cuáles son tales propiedades.

Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	JP 06 024 959	1-20 y 24-37	Nivel inventivo
D2	US 5985 323	1-20 y 24-37	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 19 ENE 2007

CONCEPTO TÉCNICO No 34	EXAMINADOR TÉCNICO Código 202007
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EXAMEN TÉCNICO DE FONDO			
Nº Radicación	02 077184	Fecha de presentación	30-08-2002
Nº Prioridad	US 09 517 887	Fecha de Prioridad	03-03-2000

Palabras clave	ciprofloxacina	tableta	Liberación
Controlada			

CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A 61 K 9/46, A 61 K 9/22, A 61 K 9/26 A 61 K 9/20, A 61 K 9 714

DOCUMENTOS CORRESPONDIENTES EN OTROS PAÍSES	
Patente Original	WO 01 64183
Otros	OA12381 (A) MXPA02008568 (A) EP1263409 (A0) EE200200497 (A) CA2400950 (A1)

BASES DE DATOS CONSULTADAS			
OEPM	Epoline	Espacenet	Oficina US

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Documento	Fecha	Relv. Asociadas
WO 01 64183	Sept 7, 2001	1-20 y 24

ANTERIORIDADES ENCONTRADAS		
Documento de Patentes	Relv. Asociadas	Relevancia
JP 06 024 959	1-20 y 24	Nivel inventivo
US 5985 323	1-20 y 24	Nivel inventivo
LITERATURA NO PATENTES		
Documento no Patentes	Relv. Asociadas	Relevancia

Observaciones	

Fecha del examen	Enero 11 de 2007
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