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No. 06-098058- -00003-0000

Fecha. 2008-06-13 17.50 35 Dep. 2020 NUECREACIONE
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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 538

Referencia : Expediente No. 06098058
Asunto : Solicitud de patente para **RECUBRIMIENTOS
ENTERICOS PARA LOS SUSTRATOS ORALMENTE
INGERIBLES**
Solicitante : **BPSI HOLDINGS, INC.**
Clase : A61K 009/036
Publicada en : La Gaceta No. 583 de diciembre 18 de 2007
Fecha de Solicitud : 28 de septiembre de 2006

1. Yo, Emilio FERRERO, identificado como aparece al pie de mi firma, actuando como apoderado en el asunto de la referencia, atentamente, solicito se efectúe el examen de patentabilidad de la solicitud en referencia presentada de acuerdo con el Capítulo I del PCT y según lo establecido en el artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina. Para tal efecto presento junto con este escrito el recibo por valor de \$ 420.000.00, que corresponde a la tasa fijada según lo dispuesto en la resolución No. 44372 de 26 de diciembre de 2007.

2. Ruego atentamente a la Señora Jefe se sirva ordenar que se anexe este recibo para que se efectúe dicho examen y se continúe con el trámite de la solicitud.

Señora Jefe,


EMILIO FERRERO
T.P.A. No. 31.929

COLO-13741-841-001-5
SDC\AMG\ID-128008\WPC13741
No. M-2008-128008\SDC

United States Patent [19]

Weber et al.

[11] Patent Number: 4,668,517

[45] Date of Patent: May 26, 1987

[54] FURAZOLIDONE DOSAGE FORM

[75] Inventors: John B. Weber, Norwich, N.Y.;
Jesus T. Covarrubias, Jeronimo,
Mexico[73] Assignee: Norwich Eaton Pharmaceuticals, Inc.,
Norwich, N.Y.

[21] Appl. No.: 720,120

[22] Filed: Apr. 4, 1985

[51] Int. Cl.⁴ A61K 9/22; A61K 9/24[52] U.S. Cl. 424/469; 424/486;
424/436

[58] Field of Search 424/19-22

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Primary Examiner—Shep K. Rose
Attorney, Agent, or Firm—Milton B. Graff, IV; Jack D. Schaeffer; Richard C. Witte

[57] ABSTRACT

A furazolidone dosage unit form comprises the drug furazolidone, a sustained release matrix, and an enteric coating.

15 Claims, No Drawings

XV, No. 9 (September, 1978), pp. 769-776; Misra, N. P., S. C. Jain & R. S. Chachra, "Furazolidone in Typhoid Fever", *Current Medical Practice*, Vol. 16, No. 8 (August, 1972), pp. 345-349; Damany, S. J. & C. Bilgi, "A Comparative Trial of Furazolidone and Chloramphenicol in Typhoid Fever", *The Journal of the Indian Medical Association*, Vol. 55, No. 4 (Aug. 16, 1970), pp. 131-133; Karchmer, A. W., G. T. Curlin, M. I. Huq & N. Hirschhorn, "Furazolidone in Paediatric Cholera", *Bulletin of World Health Organization*, Vol. 43, No. 3 (1970), pp. 373-378; and Pierce, N. F., J. G. Banwell, R. C. Mitra, G. J. Caranasos, R. I. Keimowitz, J. Thomas & A. Mordal, "Controlled Comparison in Tetracycline and Furazolidone in Cholera", *British Medical Journal*, Vol. 3, (Aug. 3, 1968), pp. 277-280.

The effectiveness of furazolidone in the treatment of diseases affecting the colon and rectum, for example shigellosis and amoebiasis, is inconsistent. The results of studies involving the treatment of such diseases with furazolidone are provided in the following publications; Fish, C. H. & G. Jones, "Furazolidone in the Treatment of Institutional Shigellosis", *American Journal of Mental Deficiency*, Vol. 73, No. 2 (September, 1968), pp. 214-217; Haltalin, K. C. & J. D. Nelson, "Failure of Furazolidone Therapy in Shigellosis", *The American Journal of Diseases of Children*, Vol. 123, No. 1 (January, 1972), pp. 40-44; Huanambal, M. A., H. Espejo & W. Flores, "Furazolidone Treatment of Infectious Diarrheas Due to *Sigella* and *Salmonella*. Clinical and Bacteriological Evaluation", *Tribuna Medical (Mexico)*, No. 2 (December, 1980), pp. 25-30; Synge, H. N., and R. Sharma, "Clinical Trial of 'Furoxone' in Treatment of Intestinal Amoebiasis", *Current Medical Practice*, Vol. 11, No. 4 (April, 1967), pp. 221-223; Rao, M. H., "Observations on the Value of Furoxone in the Treatment of Amoebiasis", *Bombay Hospital Journal*, Vol. 10 (October, 1968), pp. 1-4; Niazi, S. P. & F. Jabeen, "Clinical Trial on Combination of Furazolidone and Iodo-chlorhydroxyquinoline (Dependal) in the Treatment of Intestinal Amoebiasis", *Journal of the Pakistan Medical Association*, Vol. 24 (April, 1974), pp. 79-83; Bhattacharjee, B. & A. K. Mukherjee, "A Clinical Trial with Furazolidone and Iodo-chlorhydroxyquinoline in Intestinal Amoebiasis", *Calcutta Medical Journal*, Vol. 69, No. 4 (1972), pp. 83-84; and Sethi, J. P. & A. Gupta, "Dependal—An Evaluation of Its Efficacy in the Treatment of Acute and Chronic Intestinal Amoebiasis", *Antiseptic*, Vol. 73, No. 10 (October, 1976), pp. 545-548.

Furazolidone commonly is administered orally either in liquid suspension or solid dosage form. Common solid dosage forms include capsules and tablets formulated to provide rapid release of the furazolidone in the intestinal tract. A sustained release dosage unit form of furazolidone in the intestinal tract. A sustained release dosage unit form of furazolidone and tylosin for the treatment of pneumoenteritis in calves is disclosed in U.S. Pat. No. 3,790,669 issued to Gale on Feb. 5, 1974. Tablets of furazolidone which may contain certain ingredients and may be film coated which are used for treatment of diseases in which various species of free-living amoeba are the aetiological agent of the disease are disclosed in U.S. Pat. No. 4,402,965 issued to Wyburn-Mason on Sept. 6, 1983.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide novel dosage unit forms of furazolidone which are use-

ful in the treatment of microbial disorders of the lower intestinal tract, especially the colon and rectum.

It is a further object of the present invention to provide such dosage unit forms which are released substantially only in the intestinal tract.

It is a still further object of the present invention to provide such dosage unit forms which result in a sustained release of furazolidone throughout a substantial portion of the entire intestinal tract, such that the furazolidone is present in the lower intestinal tract, especially the colon and rectum, at a sufficient concentration to eradicate microbial pathogens present therein.

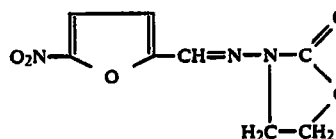
It is also an object of the present invention to provide a novel method for treating microbial disorders of the lower intestinal tract, especially the colon and rectum.

The present invention involves a pharmaceutical dosage unit form comprising:

- (a) an effective but nontoxic amount of the drug furazolidone, or its pharmaceutically acceptable salts or hydrates;
- (b) a sustained release matrix; and
- (c) an enteric coating.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel dosage unit forms of furazolidone, 3-(5-nitrofurfurylideneamino)-2-oxazolidinone having the chemical structure:



Furazolidone and a method for making it are disclosed in U.S. Pat. No. 2,742,462 issued to Gever on Apr. 17, 1956, which is incorporated herein by reference.

The present invention involves the incorporation of furazolidone in a sustained release matrix. The sustained release matrixes which are useful in the present invention are materials which are insoluble or only slightly soluble in the fluids of the intestinal tract. The preferred sustained release matrixes useful in the present invention are erodible materials which are slowly eroded from the surface of the dosage unit form as it passes through the intestinal tract. Examples of preferred materials useful in forming sustained release matrixes for the present invention include the following: carbomers, methacrylic acid/methyl methacrylate copolymers, methylcellulose, carboxymethylcellulose or its sodium salts, hydroxypropyl methylcellulose, hardened fats such as hydrogenated reposed palm kernel or other vegetable oils, fatty acids and their alkaline salts, polyvinyl chloride, polyvinyl pyrrolidone, and combinations of these materials.

Preferred pharmaceutical dosage unit forms of the present invention comprise furazolidone incorporated substantially uniformly throughout a sustained release matrix which is produced by conventional pharmaceutical tableting techniques. In producing such tablets, furazolidone is blended with one or more of the sustained release materials described hereinabove. Other excipients (pharmaceutical adjuvants) may be added to provide a tablet having the desired erodible characteristics. Excipients incorporated in the tablet may include

The first part of the report deals with the general situation of the country. It is a very interesting and informative study of the country's development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's development.

The second part of the report deals with the economic situation of the country. It is a very interesting and informative study of the country's economic development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's economic development.

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The fourth part of the report deals with the political situation of the country. It is a very interesting and informative study of the country's political development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's political development.

The fifth part of the report deals with the cultural situation of the country. It is a very interesting and informative study of the country's cultural development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's cultural development.

The sixth part of the report deals with the environmental situation of the country. It is a very interesting and informative study of the country's environmental development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's environmental development.

The seventh part of the report deals with the international situation of the country. It is a very interesting and informative study of the country's international development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's international development.

The eighth part of the report deals with the future of the country. It is a very interesting and informative study of the country's future development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's future development.

The ninth part of the report deals with the conclusion of the study. It is a very interesting and informative study of the country's development. The author has done a great deal of research and has gathered a wealth of material. The report is well written and is a valuable contribution to the study of the country's development.

one or more of the following: (1) fillers to add bulk and to improve compressibility, e.g., lactose, starches, sugars, cellulose derivatives, calcium sulfate or phosphate; (2) binders to form granules or to improve compressibility, e.g., gums, sugars, starch, cellulose derivatives, alginates; (3) lubricants to reduce friction, e.g., stearic acid, metallic stearates, high melting point waxes, talc; and (4) glidants to improve flow, e.g., starch, talc, silica.

Tablets of the present invention which incorporate furazolidone in a sustained release matrix preferably contain from about 10% to about 70% furazolidone. Such tablets preferably comprise one of the preferred sustained release materials in quantities as follows: carbomer preferably within the range of from about 5% to about 40%, more preferably within the range of from about 15% to about 30%; methacrylic acid/methyl methacrylate copolymers preferably within the range of from about 10% to about 15%; methylcellulose preferably within the range of from about 5% to about 10%; carboxymethylcellulose or its sodium salts preferably within the range of from about 5% to about 20%; hydroxypropyl methylcellulose preferably within the range of from about 35% to about 70%; hardened fats such as hydrogenated reposed palm kernel or other vegetable oils, fatty acids and their alkaline salts preferably within the range of from about 10% to about 40%; polyvinyl chloride preferably within the range of from about 15% to about 30%; or polyvinyl pyrrolidone preferably within the range of from about 10% to about 25%.

The pharmaceutical dosage unit forms of the present invention are enteric coated in order to prevent release of the furazolidone in the stomach. The enteric coating is formulated such that it dissolves after the dosage form reaches the intestines in order to expose the sustained release matrix containing the furazolidone to eroding forces in the intestines;

Enteric coating materials which preferably are used as primary ingredients in the enteric coatings of the dosage unit forms of the present invention include the following: polyvinylacetate phthalate, shellac, cellulose acetate phthalate, and polymethacrylate. Especially preferred for the dosage unit forms of the present invention are enteric coatings comprising polyvinylacetate phthalate.

The enteric coatings of the dosage unit forms of the present invention preferably are applied to the tablets comprising furazolidone and sustained release materials described hereinabove by standard pharmaceutical coating techniques. The enteric coating preferably comprises from about 5% to about 10% of the compressed tablet weight. The enteric coating typically is applied by coating the tablet with a fluid mixture comprising the enteric coating material and one or more excipients, such as polyethylene glycol and pigments, and then drying the coating.

In order to improve the uniformity and adhesion of the enteric coating, subcoats of excipients, e.g., a mixture of hydroxypropyl methylcellulose and polyethylene glycol, can be applied to the tablet and dried prior to application of the enteric coating. Polish and/or color coats may be applied to the enteric coated tablet by coating it with excipients, e.g., mixtures of hydroxypropyl methylcellulose, propylene glycol, and pigments, and drying.

The following example describes the preparation of an enteric coated sustained release dosage unit form of furazolidone of the present invention.

EXAMPLE

Ingredient Weight Per Tablet	Ingredient	Percentage
400 mg	furazolidone	57.1
105 mg	carbomer 934 ¹	15.0
35.9 mg	stearic acid	5.1
153.1 mg	sucrose	21.9
6.0 mg	zinc stearate	0.9

The ingredients in the above table are mixed according to acceptable pharmaceutical manufacturing practices. The finished blend is screened and convex, capsule-shaped tablets are compressed by direct compression using a suitable tablet press yielding tablets approximately 8 mm in width, 14 mm in length, and 6 mm in height.

The compressed tablets are coated by conventional pharmaceutical manufacturing practices using an Aeromatic fluid bed coater, model STREA-1, marketed by Aeromatic, Inc. of Towaco, NJ. A subcoat is applied to the compressed tablets by applying a 5% aqueous solution of Opadry YS-2-7013 and drying in the coater. (Opadry is supplied by Colorcon, Inc., West Point, PA, and comprises hydroxypropyl methylcellulose and polyethylene glycol.) The subcoated tablets are enteric coated by applying an aqueous solution of 12.5% Coateric Y-PA-6-2427 and 0.13% ammonium hydroxide and drying in the coater. (Coateric is also supplied by Colorcon, Inc., and comprises polyvinylacetate phthalate, polyethylene glycol, titanium dioxide, D&C yellow #10 Aluminum Lake, FD&C yellow #10 Aluminum Lake, sodium alginate and silica.) The enteric coating on each tablet is from about 35 mg to about 70 mg in weight. The enteric coated tablets are polish coated by applying a 5% aqueous solution of Opadry YS-2-7013 and drying in the coater.

Another aspect of the present invention involves a method for treating microbial disorders of the lower intestinal tract, especially the colon and/or rectum, which comprises oral administration of the pharmaceutical dosage unit forms described hereinabove. It has been determined that in the treatment of diseases affecting the colon and rectum, e.g. certain forms of shigellosis, amoebiasis, campylobacteriosis, and salmonellosis, that the administration of conventional oral dosage forms of furazolidone produces inconsistent therapeutic results. This is believed to be due to the fact that a therapeutic dose of the furazolidone orally administered by conventional means fails to reach the colon and rectum because a substantial portion is decomposed in the stomach and/or upper intestinal tract. It is believed that the pharmaceutical dosage unit forms of the present invention, when administered orally, result in the achievement of therapeutic levels of furazolidone in the colon and rectum, such that the furazolidone is able to eradicate microbial pathogens which are there.

In order to achieve clinical success in the treatment of such disorders of the lower intestinal tract with conventional dosage unit forms of furazolidone, it often is necessary to require doses of as much as 200 mg furazolidone four times a day. Such dose of furazolidone frequently is associated with side effects of nausea and vomiting. The pharmaceutical dosage unit forms of the present invention can effectively reduce such side effects by (1) reducing the daily dosage required to eradicate the pathogens and/or (2) by eliminating the release

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SUSTAINED RELEASE TABLETS BACKGROUND OF THE INVENTION

A variety of methods are known to formulate pharmaceutical compositions to provide various release patterns of the active agent from the composition. However, research continues in an effort to develop improved compositions capable of delivering pharmaceutical agents in a sustained and predictable manner.

Compositions containing active agents which exhibit low aqueous solubility are difficult to formulate in such a manner so as to promote the uniform, sustained release of the agent from the composition. The present compositions provide excellent dissolution of an active agent having low aqueous solubility from a tablet composition wherein a large percentage of the composition is the active agent itself.

SUMMARY OF THE INVENTION

The present invention relates to a sustained release pharmaceutical formulation in tablet unit dosage form which provides prolonged plasma levels of an active agent and comprises about 60.0% to about 80.0% by weight of the active agent, about 1.0% to about 15.0% by weight of a pharmaceutically acceptable excipient, about 3.0% to about 15.0% by weight of a disintegrant, about 2.0% to about 10.0% by weight of a pharmaceutically acceptable binder and about 0.5% to about 3.0% by weight of a tablet lubricant.

DETAILED DESCRIPTION OF THE INVENTION

Amounts and percentages are described in this document as weight units unless otherwise stated.

The percent of the ingredients required in the formulation of the invention, namely the active agent, the excipient, the disintegrant, the binder and the tablet lubricant, is calculated on a dry weight basis without reference to any water or other components present. Thus, these five components together constitute 100 percent of the formulation for purposes of calculating individual percentages. If additional ingredients are present in the formation, then the actual percentages for these five ingredients will change accordingly but their relative concentrations to each other will remain the same. If other ingredients are present, the sum of all of the components constitutes 100 percent of the formulation for purposes of calculating individual percentages with the exception of the film coating.

The term "unit dosage form", as employed in the specification, refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with the other ingredients of the formulation disclosed herein.

The active agents employed herein exhibit low aqueous solubility. An active agent will be present in the formulations of the invention at a concentration in the range of about 60.0% to about 80.0% by weight, preferably from about 65.0% to about 75.0% by weight. The active agents employed in the present formulations are typically those of the class commonly referred to as non-steroidal anti-inflammatories (NSAIDS). Many of these agents are weakly acidic in nature and hence typically exhibit relatively low aqueous solubility at lower pH values. The preferred active agent of this type is

fenoprofen, and especially fenoprofen calcium. However, a variety of agents may be employed in the formulation and include the salicylate derivatives such as aspirin and sodium salicylate; the pyrazolon derivatives such as phenyl butazone, oxyphenbutazone and apazone; indomethacin and sulindac; derivatives of N-phenyl anthranilic acid such as mefenamic, meclofenamic, flufenamic, tolfenamic and etofenamic acids; tolmetin sodium; propionic acid derivatives such as ibuprofen, naproxen, flurbiprofen and ketoprofen; and related compounds. Additional examples of active agents include that class of compounds which are acidic in nature and which possess the solubility characteristics described above.

The formulations of the invention will also contain from about 1.0% to about 15.0% by weight of a pharmaceutically acceptable excipient, more preferably in the range of about 5.0% to about 12.0% by weight. These excipients should be water soluble and chemically inert to the other ingredients. While the preferred excipient is lactose, a variety of other known and commonly used excipients may be used such as mannitol, glucose, fructose, xylose, galactose, sucrose, maltose, xylitol, sorbitol, as well as other pharmaceutically acceptable monosaccharides and disaccharides. Other suitable excipients would include inorganic compounds such as the chloride, sulfate and phosphate salts of potassium, sodium and magnesium, as well as calcium, lactate, gluconate and succinate salts.

The present formulation will also contain a disintegrant at a concentration in the range of about 3.0% to about 15.0% by weight, more preferably from about 5.0% to about 9.0% by weight. While a variety of disintegrants may be used in the formulation, the preferred disintegrant is starch powder. Other suitable disintegrants include the modified starches, for example, sodium carboxymethyl starch; cellulose derivatives such as microcrystalline celluloses (Avicel PH 101), or colloidal microcrystalline cellulose with carboxymethyl cellulose added as a dispersant (Avicel RC-591) and cross linked types (Ac-Di-Sol), water soluble cellulose derivatives such as methyl cellulose, sodium carboxymethyl cellulose, and hydroxypropyl methyl cellulose; alginic acid, sodium alginate, clays, cross-linked polyvinylpyrrolidone, ion exchange resins or other disintegrants which are well known to those familiar with pharmaceutical formulations. These disintegrants may be added to the formulation either in the granulation step, known as intragranular disintegrants, or after the granulation step but before the compression step, which are known as extragranular disintegrants.

The formulations of the invention will also contain a pharmaceutically acceptable binder. This binder will be present at a concentration in the range of about 2.0% to about 10.0% by weight, more preferably from about 2.0% to about 6.0% by weight. The preferred binders are pregelatinized starch and povidone. Other pharmaceutically acceptable binders include sucrose, lactose, gelatin, starch paste, acacia, tragacanth, and other gums; cellulose derivatives such as methyl cellulose, sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose, hydroxypropyl cellulose, and ethyl cellulose; microcrystalline cellulose; polyethylene glycols; corn syrup; or other binders known to those familiar with pharmaceutical formulations.

The present formulations will also contain a tablet lubricant. The lubricant will be present in the formulation at a concentration in the range of about 0.5% to

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about 3.0% by weight, preferably from about 1.0% to about 2.0% by weight. The preferred lubricants are stearic acid, in powder form, and magnesium stearate. Other suitable tablet lubricants are calcium or zinc stearate, hydrogenated vegetable oils, talc, polyethylene glycols, mineral oil or other pharmaceutically acceptable die wall lubricants.

The present formulations may also contain a surface active agent at a concentration in the range of about 0.1% to about 2.0% by weight, preferably from about 0.2% to about 1.0% by weight, and its presence is preferred. The preferred agent is sodium lauryl sulfate. However, other agents may also be employed such as DSS (dioctyl sodium sulfosuccinate), triethanolamine, polyoxyethylene sorbitan and poloxalkol derivatives, quaternary ammonium salts or other pharmaceutically acceptable surface active agents. Additionally, the lubricants and surface active agents can be combined and incorporated in the formulation as a single ingredient.

An additional disintegrant is preferably added to the present formulation following granulation of the formulation ingredients but prior to forming the tablets. This extragranular disintegrant will be present from about 0.1% to about 15% by weight, more preferably from about 1.0% to about 5.0% by weight. The extragranular disintegrant may be chosen from those described above, with the preferred extragranular disintegrant being cellulose with sodium carboxymethylcellulose.

The present formulation may also contain a hydrophobic retarding agent. This agent will be present at a concentration in the range of about 0.1% to about 15.0% by weight, more preferably from about 2.0% to about 8.0% by weight. Depending on the manufacturing method employed (discussed infra), the inclusion of this ingredient in the formulation may not be required to yield the proper release pattern. Preferably, stearic acid powder is used, but other suitable agents include purified grades of beeswax; fatty acids; long chain fatty alcohols, such as cetyl alcohol, myristyl alcohol, and stearyl alcohol; glycerides such as glyceryl esters of fatty acids like glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like; oils such as mineral oil and the like, or acetylated glycerides; ethyl-cellulose, vegetable oil derivatives, paraffin, carnauba-wax, talc; and the stearate salts such as calcium, magnesium, and zinc.

If desired, other conventional tablet ingredients such as preservatives, stabilizers, glidants, and FD&C colors may be included in the formulation. These ingredients may be included at a concentration of about 0.1% to about 2.0% by weight. Acceptable glidants or flow enhancers include such agents as colloidal silicon dioxide and talc. Coloring agents may be incorporated into the formulation by various methods but a particularly preferred procedure is the addition of appropriate dye dispersions such Opaspray, marketed by Colorcon, Inc., West Point, Pennsylvania, to the granulating solution.

The resulting tablets may be coated, if desired, with one of many readily available coating systems. Coating the tablets serves to mask the taste of the drug, make the tablet easier to swallow and, in some cases, improve the appearance of the dosage form. The tablets can be sugar coated according to procedures well known in the art, or can be coated with any one of numerous polymeric film coating agents frequently employed by formulation chemists. Representative examples of such film coating agents include hydroxypropyl methyl cellulose, carboxymethylcellulose, hydroxypropyl cellulose, methyl cel-

lulose, ethyl cellulose, acrylic resins, povidone, polyvinyl diethylaminoacetate, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methyl cellulose phthalate, acrylic latex emulsions, ethyl cellulose latex emulsions or other commercially available preparations such as Pharmacoat, manufactured by Shin-Etsu Chemical Co., Ltd., Ohtemachi, Chiyodaku Tokyo, Japan, and Opadry, manufactured by Colorcon, Inc.

The present formulations may be prepared by procedures well known by formulation chemists. However, it has been determined that the granulator employed in the manufacture of a formulation of the invention plays an important role in the release rate which the final formulation will have. For example, when using a granulator which imparts high energy to the formulation by the rapid turning of the mixing blades, the granules which are formed are typically spherical and more compact, possessing lower porosity than those produced by low energy granulators. As such, formulations prepared with a high energy granulator may require increased amounts of excipient and disintegrant in order to draw greater amounts of water into the formulation in order to promote release of the active agent. The preferred high energy granulator is the Diosna mixer available from Dierks and Sohne Maschinefabrik. In contrast, a low energy granulator may also be employed to prepare the present compositions which typically results in a formulation having a faster rate of release as compared to a formulation prepared with a high energy granulator. As such, formulations prepared with a low energy granulator will typically need less excipient and disintegrant than may be otherwise employed, and may require a hydrophobic retarding agent. While a number of low energy granulators may be employed, the preferred low energy granulators are planetary mixers such as a Pony mixer and especially a Hobart mixer.

A particularly preferred formulation of the invention is as follows:

Ingredient	Percent by Weight
fenoprofen calcium	about 67.0% to about 72.0%
pharmaceutically acceptable excipient	about 5.0% to about 12.0%
disintegrant	about 5.0% to about 9.0%
pharmaceutically acceptable binder	about 2.0% to about 6.0%
tablet lubricant	about 1.0% to about 2.0%
surface active agent	about 0.2% to about 1.0%

A more highly preferred formulation of the present invention may be represented by the following:

Ingredient	Percent by Weight
fenoprofen calcium	about 70.0%
lactose	about 10.0%
starch powder	about 7.0%
cellulose with sodium carboxymethylcellulose	about 3.0%
pregelatinized starch	about 3.0%
povidone	about 3.0%
stearic acid	about 1.0%
magnesium stearate	about 0.5%
sodium lauryl sulfate	about 0.25%

The formulations of the invention will have a prolonged in vitro release rate. The in vitro test used to measure release rate of the active agent from a formula-

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oralmente ingeribles tal como tabletas y complementos alimenticios con amplia aceptación reguladora y altamente productiva.

Clasificación Internacional de Patentes (IPC.): A61K 009/036

3. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Una vez revisado el capítulo reivindicatorio esta dependencia encuentra:

- Reivindicación 12: Se requiere al solicitante hacer la conversión de unidades de viscosidad al sistema internacional e unidades (pascales).

4. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 2004/03/31

Teniendo en cuenta la fecha indicada se realizó la búsqueda en el estado de la técnica de documentos relacionados con la solicitud encontrándose los siguientes documentos más relevantes:

Nº	Documento	Título	Fecha de publicación*
D ₁	US 4668517	FURAZOLIDONE DOSAGE FORM	1987/05/26
D ₂	US 4753801	SUSTAINED RELEASE TABLETS	1988/06/28

5. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La presente Solicitud de Patente reivindica:

Reivindicación 1: Sistema de recubrimiento de película entérico que comprende una dispersión de etilcelulosa y un formador de poro sustancialmente gastroinsoluble.

Dicho sistema de recubrimiento de película entérico está afectado por los siguientes documentos del Estado de la Técnica:

D₁ que enseña furazolidona de liberación sostenida con cubierta entérica para ser liberado en el tracto intestinal, las matrices son materiales que son insolubles o ligeramente solubles en los fluidos del tracto intestinal. Comprende: derivados de celulosa y alginatos entre otros componentes.

El presente documento es propiedad de la Universidad de la Habana y no debe ser
reproducido, distribuido o utilizado sin el consentimiento escrito de la institución.

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THE UNIVERSITY OF CHICAGO

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1. The first step is to identify the problem or issue that needs to be addressed. This involves gathering information and understanding the context of the problem.

1. The first group of people who are interested in the study of the history of the United States are the people who are interested in the history of the United States. This group of people is interested in the history of the United States because they want to know more about the country they live in. They want to know about the people who lived in the United States and about the events that happened in the United States. They want to know about the things that made the United States what it is today.

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D₂ que enseña tabletas de liberación sostenida en unidad de dosificación que comprende un ingrediente activo con baja solubilidad acuosa, desintegrantes, lubricantes, ligantes, preservativos, agentes retardantes hidrofobitos, estabilizadores, colorantes, etc y entre estos componentes se encuentran la etilcelulosa y los formadores de poro gastroinsolubles como el alginato de sodio (Ver folios: 80 y siguientes).

TABLA 1		
CARACTERÍSTICAS REIVINDICADAS	D ₁	D ₂
Sistema de recubrimiento de película entérico	SI folio 77 (abstract), folio 78 (ln 5, 22, 44, 45), folio 79 (cl 5, ln 31-33)	SIMILAR Folio 80 (abstract)
Dispersión de etilcelulosa	SIMILAR Folio 78 (ln 53), folio 79 (cl 5 ln 3)	SI Folio 81 (cl 2 ln 37, 41, 62-63); folio 85 (cl 3 ln 44 cl 4 ln 1)
Formador de poro gastroinsoluble	SI folio 79 (cl 5 ln 6)	SI Folio 81 (cl 2 ln 37, 44)

La solicitud **difiere con D₁** en que especifica que **utiliza etilcelulosa** pero esta diferencia no parece conceder un efecto técnico inesperado.

El efecto técnico logrado por esta diferencia es una migración mas efectiva del ingrediente activo mediante el cambio del patrón de desintegración y un sistema de recubrimiento con mayor viscosidad (folios 46-47).

El problema técnico objetivo de la invención podría redefinirse en: “como lograr una migración mas efectiva del ingrediente activo mediante el cambio del patrón de desintegración y un sistema de recubrimiento con mayor viscosidad”.

Por tanto, la solicitud, tal como se reivindica, es obvia, porque el experto medio en la materia enfrentado al problema de como lograr una migración mas efectiva del ingrediente activo mediante el cambio del patrón de desintegración y un sistema de recubrimiento con mayor viscosidad y conociendo el estado de la técnica haría lo que dice en D1 pero utilizando específicamente etilcelulosa tal como lo enseña D2 logrando así, por medio de prácticas rutinarias de laboratorio optimizar la formulación para lograr el sistema de recubrimiento tal como esta reivindicado.

En conclusión, no se considera que la presente solicitud merezca reconocimiento de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D ₁	US 4668517	1-19	NIVEL INVENTIVO
D ₂	US 4753801	1-19	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 60 días contados a partir de la fecha de 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 N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
19 MAR. 2010

CONCEPTO TÉCNICO No. 510	EXAMINADOR TÉCNICO Código No. 202087
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