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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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E. S. D.

SUPERINDUSTRIA Y COMERCIO
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 00-090.144
Solicitud de Patente a nombre de
McNEIL-PPC, INC.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad McNEIL-PPC, INC., domiciliada en Skillman, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 03 - 43,721 de junio 20, 2003, por la suma de $335.000.oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
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C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4884780	19/06/2003	6,603,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	335,000.00
		TOTAL : $	335,000.00

SON: TRESCIENTOS TREINTA Y CINCO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **00- 90144**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION** FUE PUBLICADO

EN LA GACETA DE PROPIEDAD INDUSTRIAL No **525**, DE FECHA **28** DE **FEBRERO** DE **2003**,

EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **29** DE **MAYO** DE **2003**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ____ **X** _____

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US005965166A

United States Patent [19]

Hunter et al.

[11] Patent Number: 5,965,166

[45] Date of Patent: Oct. 12, 1999

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[54] **DIRECTLY COMPRESSIBLE HIGH LOAD ACETAMINOPHEN FORMULATIONS**

[75] Inventors: **Edward A. Hunter, Glenham; Joseph A. Zelesnik, New Paltz; Bob E. Sherwood, Amenia, all of N.Y.**

[73] Assignee: **Edward Mendell Co., Inc., Patterson, N.Y.**

[21] Appl. No.: **08/964,917**

[22] Filed: **Nov. 5, 1997**

Related U.S. Application Data

[62] Division of application No. 08/558,335, Nov. 15, 1995, Pat. No. 5,733,578.

[51] Int. Cl.[6] A61K 9/14

[52] U.S. Cl. 424/489; 424/465; 424/469; 424/480; 424/490

[58] Field of Search 424/480, 489, 424/490, 469, 465

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Assistant Examiner—William E. Benston, Jr.
Attorney, Agent, or Firm—Davidson, Davidson & Kappel, LLC

[57] **ABSTRACT**

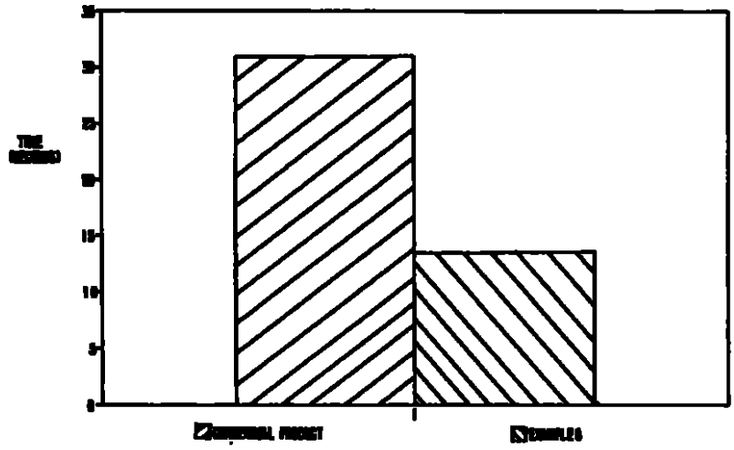
Direct compressed solid pharmaceutical dosage forms containing:

a) from about 40 to about 95% by weight acetaminophen;

b) from about 1 to about 60% by weight of a direct compression vehicle comprising microcrystalline cellulose; and

c) from about 0.01 to about 4.0% by weight of a pharmaceutically-acceptable lubricant are disclosed. The acetaminophen and direct compression vehicle are combined under high shear conditions which are sufficient to transform acetaminophen and direct compression vehicle into a homogenous granulate without degradation. In preferred aspects of the invention, the lubricant is also combined with the acetaminophen and direct compression vehicle under high shear conditions. Methods of preparing the directly compressed solid pharmaceutical dosage forms and methods of treatment with the dosage forms are also disclosed. The methods are particularly well suited for preparing directly compressed dosage forms containing high load (i.e., up to 80% or greater) amounts of acetaminophen based on the weight of the total tablet.

27 Claims, 3 Drawing Sheets



DIRECTLY COMPRESSIBLE HIGH LOAD ACETAMINOPHEN FORMULATIONS

This application is a division of application Ser. No. 08/558,335 filed Nov. 15, 1995 which application is now U.S. Pat. No. 5,733,578.

BACKGROUND OF THE INVENTION

The present invention relates to methods of preparing solid dosage forms using direct compression techniques. In particular, the present invention relates to methods of directly compressing tablets containing relatively high amounts of acetaminophen based on the total tablet weight.

In order to prepare a solid dosage form containing one or more active ingredients (such as drugs), it is necessary for the materials to be compressed into the dosage form possess certain physical characteristics which lend themselves to solid dosage form processing. Among other things, the material to be compressed must be free-flowing, must be lubricated, and, importantly, must possess sufficient cohesiveness to insure that the solid dosage form remains intact after compression.

In the case of tablets, the tablet is formed by pressure being applied to the material to be tableted on a tablet press. A tablet press includes a lower punch which fits into a die from the bottom and a upper punch having a corresponding shape and dimension which enters the die cavity from the top after the tabletting material fills the die cavity. The tablet is formed by pressure applied on the lower and upper punches. The ability of the material to flow freely into the die is important in order to insure that there is a uniform filling of the die and a continuous movement of the material from the source of the material, e.g. a feeder hopper. The lubricity of the material is crucial in the preparation of the solid dosage forms since the compressed material must be readily ejected from the punch faces.

Since most drugs have none or only some of these properties, methods of tablet formulating have been developed to impart these desirable characteristics to the material (s) which is to be compressed into a solid dosage form. Typically, excipients are added to the formulation which impart good flow and compression characteristics to the material as a whole which is to be compressed. Such properties are typically imparted to these excipients via a pre-processing step such as wet granulation, slugging, spray drying, spheronization, or crystallization. Useful direct compression excipients include processed forms of cellulose, sugars, and dicalcium phosphate dihydrate, among others.

Lubricants are typically added to avoid the material(s) being tabletted from sticking to the punches. Commonly used lubricants include magnesium stearate and calcium stearate. Such lubricants are commonly included in the final tabletted product in amounts usually less than 1% by weight.

In addition, solid dosage forms often contain diluents. Diluents are frequently added in order to increase the bulk weight of the material to be tabletted in order to make the tablet a practical size for compression. This is often necessary where the dose of the drug is relatively small.

Another commonly used class of excipients in solid dosage forms are binders. Binders are agents which impart cohesive qualities to the powdered material(s). Commonly used binders include starch, and sugars such as sucrose, glucose, dextrose, and lactose.

Disintegrants are often included in order to ensure that the ultimately prepared compressed solid dosage form has an acceptable disintegration rate in an environment of use (such as the gastrointestinal tract). Typical disintegrants include starch derivatives and salts of carboxymethylcellulose.

There are three general methods of preparing the materials to be included in the solid dosage form prior to compression: (1) dry granulation; (2) wet granulation; and (3) direct compression.

Dry granulation procedures may be utilized where one of the constituents, either the drug or the diluent, has sufficient cohesive properties to be tabletted. The method includes mixing the ingredients with a lubricant, if required, slugging the ingredients, dry screening, lubricating and finally compressing the ingredients.

The wet granulation procedure includes mixing the powders to be incorporated into the dosage form in, e.g., a twin shell blender or double-cone blender under shear mixing conditions and thereafter adding solutions of a binding agent to the mixed powders to obtain a granulation. Thereafter, the damp mass is screened, e.g., in a 6- or 8-mesh screen and then dried, e.g., via tray drying or fluid-bed drying. The wet granulating technique is rather time consuming due to its process steps and can also be considered to be relatively expensive. In addition, wet granulating has been known to reduce the compressibility of some pharmaceutical ingredients including microcrystalline cellulose.

Direct compression, on the other hand, is regarded as a relatively quick process wherein the powdered materials included in the solid dosage form are compressed directly without modifying their physical nature. Usually, the active ingredient, direct compression vehicle and other ancillary substances, such as a glidant to improve the rate of flow of the tablet granulation and lubricant to prevent adhesion of the tablet material to the surface of the dies and punches of the tablet press, are blended in a twin shell blender or similar low shear apparatus before being compressed into tablets. This type of mixing of the ingredients was believed to be essential in order to prepare pharmaceutically acceptable dosage forms. For example, *Remington's Pharmaceutical Sciences*, 16th Edition (1980), Arthur Osol, Ed., cautions artisans that the manner in which a lubricant is added to a formulation must be carefully controlled. Consequently, lubricants are usually added to a granulation by gentle mixing. At page 1556, *Remington's*, warns: "Prolonged blending of a lubricant with a granulation can materially affect the hardness and disintegration time for the resulting tablets." Further, those of ordinary skill in the art have long believed that excessive mixing of a lubricant with the granulate ingredients overcoats the granules and reduces the tablet hardness or tablet strength of the compressed tablets. Thus, for at least these reasons, high shear mixing conditions have not been used to prepare direct compression dosage forms.

Pharmaceutical manufacturers would often prefer to use direct compression techniques over wet or dry granulation techniques because of its processing time and cost advantages. Direct compression, however, is usually limited to those situations where the drug or active ingredient has a requisite crystalline structure and the physical characteristics required for formation of a pharmaceutically acceptable tablet. Often, however, one or more excipients must be combined with the active ingredient before the direct compression method can be used since many active ingredients do not have the necessary properties. Since each excipient added to formulation necessarily increases the tablet size of the final product, artisans were often limited to using direct compression techniques in formulations containing a rather

low load of active ingredient per compressed tablet. Solid dosage forms containing the drug to be administered in a relatively high load or dose (e.g., the drug itself comprises a substantial portion of the total compressed tablet weight), could only be directly compressed if the drug itself had sufficient physical characteristics (e.g., cohesiveness) for the ingredients to be directly compressed.

For example, acetaminophen, a widely used analgesic, is considered to be a high load active ingredient. Most commercial compressed tablet formulations include anywhere from 70 to 85% by weight acetaminophen per finished tablet. This high load of active ingredient combined with its rather poor physical characteristics for direct compression have not allowed pharmaceutical manufacturers to use direct compression techniques to prepare the final tablets. Previous attempts to directly compress acetaminophen with microcrystalline cellulose have failed to provide an acceptable product. The final products tend to be soft, prone to capping and otherwise not commercially desirable, i.e., difficult to swallow because of the large size. Consequently, the more time consuming and expensive wet granulation techniques must be used.

Thus, another limitation of direct compression as a method of tablet manufacturing is the potential size of the compressed tablet. If the amount of active ingredient is high, a pharmaceutical formulator may choose to wet granulate the active with other excipients to attain an acceptably sized tablet with the desired amount of acetaminophen. Usually the amount of filler/binder or excipients needed in wet granulation is less than that required for direct compression since the process of wet granulation contributes to some extent toward the desired physical properties of a tablet.

Microcrystalline cellulose, a processed cellulose, has been utilized extensively in the pharmaceutical industry as a direct compression vehicle for solid dosage forms. Microcrystalline cellulose is commercially available under the tradename EMCOCEL® from Edward Mendell Co., Inc. and as Avicel® from FMC Corp. Compared to other directly compressible excipients, microcrystalline cellulose is generally considered to exhibit superior compressibility and disintegration properties as long as it is not wet granulated prior to compression.

Thus, despite the advantages of direct compression such as reduced processing times and costs, wet granulation is widely used in the industry to prepare solid dosage forms. Currently, many skilled in the art also prefer wet granulation over direct compression because wet granulating has a greater probability of overcoming any problems associated with the physical characteristics of the various ingredients in the formulation, thereby providing a material which has the requisite flow and cohesive characteristics necessary to obtain an acceptable solid dosage form.

The popularity of the wet granulation process as compared to the direct compression process is based on at least three advantages. First, wet granulation provides the material to be compressed with better wetting properties, particularly in the case of hydrophobic drug substances. The addition of a hydrophilic excipient makes the surface of a hydrophobic drug more hydrophilic, easing disintegration and dissolution. Second, the content uniformity of the solid dosage forms is generally improved with the wet granulation method because all of the granules obtained thereby usually contain approximately the same amount of drug. Thus, segregation of the different ingredients of the material to be compressed (due to different physical characteristics such as density) is avoided. Segregation is a potential problem with the direct compression method. Finally, the particle size and shape of the particles comprising the granulate to be compressed are optimized via the wet granulation process. This is due to the fact that when a dry solid is wet granulated, the binder "glues" particles together, so that they agglomerate in the granules which are more or less spherical.

In spite of the advantages afforded by wet granulation methods, many manufacturers would nonetheless welcome the opportunity to directly compress tablets containing acetaminophen, especially those containing high loads of acetaminophen and/or microcrystalline cellulose.

Thus, there still remains a need in the industry for techniques and pharmaceutical excipients which would allow artisans to prepare direct compressed dosage forms containing relatively high amounts of acetaminophen by weight and thereby avoid the time and expense of wet granulations.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide improvements in direct compression techniques.

It is a further object of the present invention to provide a cost effective alternative to wet granulating acetaminophen formulations in order to prepare solid dosage forms containing a relatively high proportion of the drug when compared to the total weight of the dosage form.

It is a further object of the present invention to provide direct compressed acetaminophen oral solid dosage forms which disintegrate rapidly in vivo and in vitro.

A further object of the present invention is to provide direct compressed dosage forms which provide controlled release of acetaminophen without relying on fluidized bed or wet granulating techniques.

Another object of the present invention is to provide solid dosage forms which include acetaminophen and which are prepared according to the methods described herein.

In accordance with the above objects and others which will be obvious to those skilled in the art, the present invention includes a direct compressed solid pharmaceutical dosage form containing:

a) from about 40 to about 95% by weight acetaminophen;

b) from about 1 to about 60% by weight of a direct compression vehicle comprising microcrystalline cellulose; and

c) from about 0.01 to about 4.0% by weight of a pharmaceutically-acceptable lubricant. The acetaminophen and direct compression vehicle included in the direct compressed dosage form are combined under shear mixing conditions which are sufficient to transform the acetaminophen and direct compression vehicle into a homogenous granulate without degradation.

In preferred embodiments of this aspect of the invention, the solid dosage form comprises from about 60% to about 85% by weight acetaminophen and the acetaminophen is in granular form. The solid dosage forms accordingly can contain from about 10 to about 1000 milligrams of acetaminophen. In a particularly preferred embodiment, the direct compression vehicle includes microcrystalline cellulose which has been coprocessed with from about 0.1 to about 20% by weight silicon dioxide so that the microcrystalline cellulose and silicon dioxide are in intimate association with each other and provide enhanced compressibility properties for the direct compressed dosage forms. An additional

-continued

INGREDIENT	BATCH %	GRAMS PER BATCH
CSD	0.50%	2.50
SSG	1.50%	7.50
Magnesium stearate	0.40%	2.00
TOTAL	100.00%	500.00

DISCUSSION

FIG. 2 graphically provides the results for the comparison of the two step high shear mixed, direct compressed tablets of Example 8 with the high shear, then low shear mixed formulations of Examples 9 and 10 and the V-blended control formulation. The graph also provides the results for the two step high shear formulation of Example 11, which included magnesium stearate instead of sodium stearyl fumarate in the second high shear mixing step.

In each case, it can be seen that improvements in tablet hardness can be realized even if the lubricant is combined under low shear conditions. In all cases, the tablets prepared from granulations which were prepared using at least one high shear mixing step out-performed the completely V-blended control.

EXAMPLE 12

In this example, the average disintegration time for tablets prepared in accordance with Example 8 was determined and compared to that of commercially available APAP tablets sold under the Tylenol® brand. The test was carried out according to the U.S.P. guidelines using a Van-Kel disintegration apparatus. In particular, six tablets prepared according to the procedure of Example 8 as well as six Tylenol tablets were individually evaluated in the apparatus to determine disintegration time in deionized water at 37° C. without using the basket disk of the apparatus. The average disintegration time for the six tablets in each group was then calculated and illustrated as a graph which is set forth as FIG. 3.

As can be seen from the graph, the tablets prepared in accordance with the present invention had an average disintegration time of less than half of that required for the commercially sold formulation. This rapid disintegration feature illustrates an additional advantage of the formulations of the present invention.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention. It is intended to claim all such changes and modifications that fall within the true scope of the invention.

What is claimed is:

1. A direct compressed solid pharmaceutical dosage form, comprising:

(a) from about 60 to about 95% by weight acetaminophen;

(b) from about 1 to about 40% by weight of a direct compression vehicle, the direct compression vehicle comprising microcrystalline cellulose conrocessed with from about 0.1 to about 20% silicon dioxide such that the microcrystalline cellulose and the silicon dioxide are in intimate association with each other; and

(c) from about 0.1 to about 4.0% by weight of a pharmaceutically-acceptable lubricant.

2. The solid dosage form of claim 1, wherein said pharmaceutical dosage form comprises from about 60% to about 85% by weight acetaminophen.

3. The solid dosage form of claim 1, wherein said acetaminophen is in gramular form.

4. The solid dosage form of claim 1, wherein said silicon dioxide has an average primary particle size of from 1 nm to about 100 μm.

5. The solid dosage form of claim 4, wherein said, silicon dioxide has an average primary particle size of from about 5 nm to about 40 μm.

6. The solid dosage form of claim 5, wherein said silicon dioxide is derived from colloidal silicon dioxide.

7. The solid dosage form of claim 6, wherein said silicon dioxide is present in an amount ffrom about 0.5 to about 10% by weight, based on the weight of said microcrystalline cellulose.

8. The solid dosage form of claim 7, wherein said silicon dioxide is present in an amount of from about 1.25 to about 5% by weight, based on the weight of said microcrystalline cellulose.

9. The solid dosage form of claim 1, wherein said lubricant is sodium stearyl fumarate.

10. The solid dosage form of claim 1, wherein said lubricant is present in an amount of from about 0.1 to about 1.0% by weight.

11. The solid dosage form of claim 10, wherein said lubricant is present in an amount of from about 0.2 to about 0.45% by weight.

12. The solid dosage form of claim 1, wherein said silicon dioxide is colloidal silicon dioxide.

13. The solid dosage form of claim 1, wherein said amount of silicon dioxide is from about 0.1 to about 5% by weight of said dosage form.

14. The solid dosage form of claim 13, wherein said amount of silicon dioxide is from about 0.15 to about 0.9% by weight of said pharmaceutical dosage form.

15. The solid dosage form of claim 12, wherein said amount of silicon dioxide is from about 0.4 to about 0.75% by weight of said pharmaceutical dosage form.

16. The solid dosage form of claim 1, further comprising a disintegrant.

17. The solid dosage form of claim 1, wherein said disintegrant is sodium starch glycolate.

18. The solid dosage form of claim 2, wherein said direct compression vehicle is present in an amount of from about 2 to about 25% by weight of said solid dosage form.

19. The solid dosage form of claim 18, wherein said direct compression vehicle is present, in an amount of from about 5 to about 20% by weight of said solid dosage form.

20. The solid dosage form of claim 1, wherein said acetaminophen comprises at least about 75% by weight of said solid dosage form and said solid dosage form has an average tablet hardness of about 6.5 kP when said homogeneous granulate is direct compressed at a compression force of about 25 kN.

21. The solid dosage form of claim 1, wherein said pharmaceutical dosage form comprises from about 10 to about 1000 milligrams of acetaminophen.

22. The solid dosage form of claim 21, wherein said pharmaceutical dosage form comprises from about 80 to about 750 milligrams acetaminophen.

23. The solid dosage form of claim 22, wherein said pharmaceutical dosage form comprises from about 120 to about 600 milligrams of acetaminophen.

24. A method of preparing a direct compressed solid pharmaceutical dosage form, comprising the steps of:

US005773031A

United States Patent [19]

Shah et al.

[11] Patent Number: 5,773,031

[45] Date of Patent: Jun. 30, 1998

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[54] **ACETAMINOPHEN SUSTAINED-RELEASE FORMULATION**

[75] Inventors: **Shirish A. Shah**; **Chris Y. Ho**, both of Kalamazoo, Mich.

[73] Assignee: **L. Perrigo Company**, Allegan, Mich.

[21] Appl. No.: **608,839**

[22] Filed: **Feb. 27, 1996**

[51] Int. Cl.[6] A61K 9/14; A61K 47/32

[52] U.S. Cl. 424/497; 424/468

[58] Field of Search 424/490, 497, 424/468

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5,451,409	9/1995	Rencher et al.	424/468
5,489,436	2/1996	Hoy et al. .	

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9317673	9/1993	WIPO .

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Primary Examiner—Peter F. Kulkosky

Attorney, Agent, or Firm—Price, Heneveld, Cooper, DeWitt & Litton

[57] **ABSTRACT**

An orally administrable sustained-release dosage form includes particles of an active pharmaceutical ingredient which is coated with a polymeric material that is water-insoluble, but water-permeable and water-swellable, so that the sustained-release dosage form provides controlled release which is independent of certain variable physiological factors such as pH. In accordance with one aspect of the invention, the active pharmaceutical ingredient is acetaminophen and the coated acetaminophen particles are combined with uncoated acetaminophen particles to provide a combination immediate-release/sustained-release dosage form. In accordance with another aspect of the invention, the active pharmaceutical ingredient is coated with a methacrylate ester copolymer, and the coated particles are combined with uncoated particles of an active pharmaceutical ingredient to provide a combination immediate-release/sustained-release dosage form, wherein the sustained-release component provides a release rate which is substantially independent of physiological factors such as pH. The final orally administrable dosage form can be appeared as compressed tablets, capsules or pouches.

7 Claims, No Drawings

ACETAMINOPHEN SUSTAINED-RELEASE FORMULATION

BACKGROUND OF THE INVENTION

This invention relates to sustained-release pharmaceutical formulations, and more particularly to oral acetaminophen sustained-release formulations for providing extended therapeutic relief.

Many medical conditions are best treated by administration of a pharmaceutical in such a way as to sustain its action over an extended period of time. For example, this kind of pharmaceutical administration can be useful for treating chronic pain, such as that associated with rheumatic or arthritic conditions. Sustained-release dosage forms can also be used beneficially in the administration of antiarrythmics, antihypertensives and other drugs whose sustained action is important to their efficacy.

Many physiological factors influence both the gastrointestinal transit time and the release of a drug from a controlled release dosage form, and thus influence the uptake of the drug into the systemic circulation. Dosage forms should therefore be designed so that such variable factors do not compromise the efficacy and safety of the product. Ideally, such sustained-release dosage forms should release the active pharmaceutical ingredient at a controlled rate such that the amount of active pharmaceutical ingredient which is available in the body to treat the condition is maintained at a relatively constant level over an extended period of time. That is, it is desirable that active pharmaceutical ingredient be released at a reproducible, predictable rate which is substantially independent of physiological factors which can vary considerably among different individuals and even over time for a particular individual.

The release of active pharmaceutical ingredient from a controlled release dosage form is generally controlled either by diffusion through a coating, diffusion of the agent from a monolithic device, or by erosion of a coating by a process which is dependent upon enzymes or pH. Because such factors can vary from time to time for a particular individual, and can also vary from one individual to another, enzymes or pH dependent sustained-release pharmaceutical formulations do not provide a reproducible rate of release of the active pharmaceutical ingredient, and thus do not minimize intra-subject and inter-subject variation in bio-availability of the active ingredient.

Certain medical conditions are most desirably treated with dosage form which provides both immediate and extended therapeutic effect while reducing the number of doses necessary, thereby making therapy more convenient. Known examples of pharmaceutical formulations which provide both immediate and sustained-release of an active pharmaceutical ingredient are disclosed in U.S. Pat. No. 4,574,080 to Roswall et al. and U.S. Pat. No. 4,971,805 to Kitanishi et al. Each of these patents disclose a pharmaceutical formulation comprised of a quick releasing component and a slow releasing component, wherein release of the active pharmaceutical ingredient from the slow releasing component relies on a pH dependent diffusion control mechanism such as an enteric coating. Such formulations have the disadvantage of releasing the active pharmaceutical ingredient at a variable rate dependent upon the pH of the gastrointestinal fluids in which it is contacted, which can vary from subject to subject and can vary for a particular subject.

U.S. Pat. No. 4,666,703 to Kopf discloses a quick-disintegrating pharmaceutical tablet containing an active substance in a granular delayed release form comprising a pharmaceutically active substance in granular form which is coated with a mixture of a polyacrylate, such as an aqueous dispersion of an ethyl acrylate-methyl methacrylate copolymer, and ethyl cellulose, which are subsequently compressed into tablets. Kopf, however, does not provide both immediate and sustained-release of the active pharmaceutical ingredient.

Roswall et al. (U.S. Pat. No. 4,574,080) discloses a pharmaceutical orally administrable controlled release multiple-units formulation form in which individual units comprise coated cores containing an active substance which is subjected to controlled release as a result of coating the cores with a water-insoluble, but water-diffusible controlled release coating. The units include instant release particles of an active substance adhered to the surface of a controlled release coating, the particles being at least one power of 10 smaller than the coated core.

U.S. Pat. No. 5,055,306 to Barry et al. discloses a pharmaceutical tablet comprised of granules having a core including an active substance and an encapsulating coating comprising 100 parts by weight of water-swellable acrylic polymer and 20 to 70 parts of water-soluble hydroxylated cellulose derivative. The combination of water-swellable acrylic polymer and water-soluble hydroxylated cellulose derivative provides a coating having release characteristics which are pH dependent, i.e. an enteric coating.

A two layer acetaminophen tablet is available in which one layer is comprised of uncoated, quick release acetaminophen particles, and the other layer is comprised of sustained release acetaminophen. Two compression steps are required to make the tablet, and the sustained release coating is pH dependent.

SUMMARY OF THE INVENTION

The present invention comprises a mixture of polymeric coated, sustained release acetaminophen particles and uncoated, quick release acetaminophen particles pressed together in a tablet. Preferably, the coating is water permeable, but is not soluble or pH dependent.

In another aspect of the invention, other pharmaceutical agents can be substituted for acetaminophen in the foregoing mixture, using the water permeable, water-insoluble, pH independent coating. Finally, the invention alternatively encompasses acetaminophen in sustained release form per se, coated with said water permeable, water-insoluble, pH independent coating.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In accordance with a first embodiment of the invention, a sustained-release acetaminophen formulation is provided. The acetaminophen is preferably provided in a finally divided form such as small particles or granules. The acetaminophen particles preferably have an average particle size between about 180 microns to 425 microns. The acetaminophen particles may contain excipients, adjuvants or other active ingredients in minor amounts if desired, but are more preferably comprised of at least 80, 90 or 95% acetaminophen.

The sustained-release acetaminophen formulations, in accordance with the first aspect of the invention, are provided with a sustained-release coating formulation comprising a water-insoluble, water-permeable and slightly water-swellable polymer coating. The polymeric coating is not soluble in the gastrointestinal fluids and is not sensitive to

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TABLE 1-continued

TENTATIVE INGREDIENT DISCLOSURE
544XA EXTENDED RELIEF APAP 650 MG

	RAW MATERIAL	INGREDIENT	LABEL CLAIM	% OF FORMULA
8796	OPADRY W-YS-1-7003	POLYETHYLENE GLYCOL 400		0.118
8796	OPADRY W-YS-1-7003	POLYSORBATE 80, NF		0.115
3520	COMPAP WSE 95%	POVIDONE, USP		<3.305
7578R	APAP-SR	TALC #127		1.167
8796	OPADRY W-YS-1-7003	TITANIUM DIOXIDE, USP		0.462
			TOTAL	100.000

TABLE 2

TENTATIVE INGREDIENT DISCLOSURE
544XB EXTENDED RELIEF APAP 650 MG

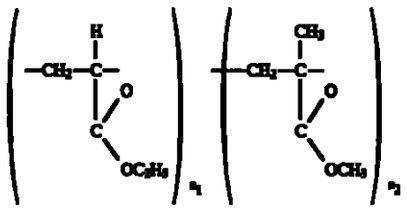
	RAW MATERIAL	INGREDIENT	LABEL CLAIM	% OF FORMULA
7578R	APAP-SR	ACETAMINOPHEN, USP	325.00 MG	41.580
3520	COMPAP WSE 95%	ACETAMINOPHEN, USP	325.00 MG	41.580
3075	CARNAUBA WAX	CARNAUBA WAX, NF		0.010
8897	CROSPOVIDONE XL	CROSPOVIDONE XL		1.970
8796	OPADRY W-YS-1-7003	HYDROXYPROPYL METHYLCELLULOSE		0.883
7578R	APAP-SR	ISONOYLPHENYLPOLYOXETHYLENE GLYCOL ETHERS		0.050
3241	MG STEARATE	MAGNESIUM STEARATE, NF		0.493
3520	COMPAP WSE 95%	MALTODEXTRIN		<2.188
7578R	APAP-SR	METHACRYLIC ACID COPOLYMERS		3.291
8871	MICROCRYSTALLINE CELLULOSE	MICROCRYSTALLINE CELLULOSE		4.855
8796	OPADRY W-YS-1-7003	POLYETHYLENE GLYCOL 400		0.118
8796	OPADRY W-YS-1-7003	POLYSORBATE 80, NF		0.115
3520	COMPAP WSE 95%	POVIDONE, USP		<2.188
7578R	APAP-SR	TALC #127		2.506
8796	OPADRY W-YS-1-7003	TITANIUM DIOXIDE, USP		0.462
			TOTAL	100.000

It will become apparent to those skilled in the art that various modifications to the preferred embodiment of the invention is described herein can be made without departing from the spirit or scope of the invention as defined by the appended claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. An orally administrable sustained-release dosage form, comprising a mixture of a pharmaceutically effective amount of uncoated acetaminophen particles and a pharmaceutically effective amount of acetaminophen particles coated with a polymeric material which is water-insoluble, said polymeric material being water-permeable, and wherein said polymeric material comprises a methacrylate ester copolymer.

2. The dosage form of claim 1, wherein said methacrylate ester copolymer has the general formula:



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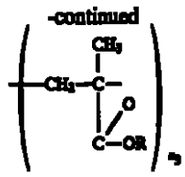

where R is an alkyl or aminoalkyl group having from 1 to about 12 carbon atoms, and wherein n_1, n_2 and n_3 are selected so that said methacrylate ester copolymer has a molecular weight of from about 100,000 to about 1,000,000.

3. The dosage form of claim 2, wherein the ratio of n_1, n_2 is from about 1:2 to about 2:1, and the ratio n_3: (n_1+n_2) is at or below about 1:15.

4. The dosage form of claim 3, wherein said methacrylate ester copolymer is substantially comprised of methylmethacrylate and ethylacrylate.

5. The dosage of claim 4, wherein said methacrylate ester copolymer has a molecular weight of about 800,000.

6. The dosage form of claim 5, wherein said acetaminophen particles have an average size of from about 180 micrometers to about 425 micrometers.

7. The dosage form of claim 6, wherein said uncoated particles and said coated particles, prior to being coated, have an average size of from about 180 micrometers to about 425 micrometers.

* * * * *

US005837729A

United States Patent [19]

Bourinbaiar

[11] **Patent Number: 5,837,729**

[45] **Date of Patent: Nov. 17, 1998**

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[54] **METHODS FOR TREATING AND PREVENTING HIV INFECTION USING ACETAMINOPHEN AND DERIVATIVES THEREOF**

[75] Inventor: **Aldar S. Bourinbaiar, New York, N.Y.**

[73] Assignee: **Metatron, Inc., Deer Park, N.Y.**

[21] Appl. No.: **638,898**

[22] Filed: **Apr. 26, 1996**

[51] Int. Cl.[6] A61K 31/24

[52] U.S. Cl. 514/535; 514/629; 514/934

[58] Field of Search 514/534, 624, 514/934

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Primary Examiner—James H. Reamer

Attorney, Agent, or Firm—Henry D. Coleman; R. Neil Sudol

[57] **ABSTRACT**

The present invention relates to the use of acetaminophen (Tylenol) and derivatives thereof which can be used to inhibit the growth, replication and elaboration of the human immunodeficiency virus (HIV). The present invention comprises in vitro as well as in vivo methods for the prevention and/or treatment of HIV infections and acquired immune deficiency syndrome (AIDS), at doses of acetaminophen or its derivatives which are effective to inhibit the replication, growth and/or elaboration of HIV.

15 Claims, 3 Drawing Sheets

METHODS FOR TREATING AND PREVENTING HIV INFECTION USING ACETAMINOPHEN AND DERIVATIVES THEREOF

FIELD OF THE INVENTION

The present invention is directed to methods of preventing and treating HIV infections using acetaminophen and pharmaceutically acceptable derivatives thereof. The present invention relates to the discovery that acetaminophen and a number of pharmaceutically acceptable derivatives, thereof may be used to inhibit the growth, replication and elaboration of HIV in humans. This invention is useful for treating and/or preventing retroviral infections such as HIV infections and the underlying immunodeficiency state known as AIDS.

BACKGROUND OF THE INVENTION

Human immunodeficiency viruses (HIV) of type 1 and 2 belong to the family of retroviruses and are considered to cause acquired immunodeficiency syndrome (AIDS). Human T lymphotropic viruses (HTLV) of type 1 and 2 are also human retroviruses and cause adult T cell leukemia and neurodegenerative diseases. Thus, there are several types of pathogenic retroviruses which can be harmful to humans. The transmission of HIV through sexual contact accounts for up to 90% of AIDS cases worldwide. This transmission is initiated by the passage of HIV across the mucosal barrier of the vagina, penis or rectum when exposed to infectious genital fluids such as semen or vaginal secretions. Increased public awareness of the sexual modes of HIV transmission has been of little consequence in reducing or curbing the AIDS epidemic. Although research activity in the area of finding effective anti-HIV agents has increased in recent years, effective compounds with anti-HIV activity that could be used to prevent transmission and/or treat HIV infections are still lacking. For example, early results with certain spermicidal agents, e.g., the nonionic surfactant, nonoxynol-9, appeared to be quite promising, but it has become clear that local toxicity of this agent is incompatible with its antiviral activity when used at an effective concentration. This shortcoming is due to the fact that the selective index (i.e., the ratio of cytotoxicity to antiviral activity as a function of drug concentration) of nonoxynol-9 (Bourinbaiar & Fruhstorfer *AIDS,* 10:14, 1996). Similar toxicity concerns have arisen with the broad use of azidothymidine (AZT).

A number of nucleoside and non-nucleoside compounds which exhibit activity against retroviral reverse transcriptase, have been posited for the treatment of AIDS, but are not without their limitations. In addition, recently introduced new drugs, such as HIV protease inhibitors, are difficult to manufacture and have shown low oral availability which requires frequent intake of large doses. Consequently, the present methods of preventing and treating HIV are limited and better alternative compounds with higher availability and selectivity must be sought.

The present inventor has discovered several classes of pharmaceutical compounds that were able to inhibit HIV replication without producing significant cytotoxicity in the host patient. Among these agents are cimetidine, mostly known as an anti-ulcer agent, and gramicidin, known as a topical antibiotic and contraceptive agent. The present inventor has also established an anti-HIV effect and the potential for AIDS therapy of several other drugs—previously used for clinical conditions unrelated to HIV

infections. Among these agents are warfarin (oral HIV protease inhibitor), coumarins, bestatin, human chorionic gonadotropin, levamisole, estrogen, progesterone, and steroid anti-inflammatory agents such as dexamethasone (see the review Bourinbaiar & Lee-Huang, *Adv. Exp. Med. Biol.* 374:71–89, 1995). Some but not all non-steroidal anti-inflammatory drugs (NSAIDs) have also been shown to be effective against HIV (Bourinbaiar & Lee-Huang, *FEBS Letters,* 360:85–88, 1995). Although indomethacin was shown to be more potent than aspirin, NSAIDs in general are quite toxic, ruling out the possibility that these drugs alone could be used as effective therapies against HIV (Bourinbaiar & Lee-Huang, *Biochem. Biophys. Res. Comm.* 208:779–785, 1995).

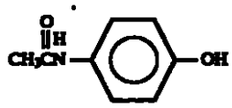
Today's world is characterized by both the exponential growth of the human population and an uncurbed epidemic of sexually transmitted AIDS. The discovery of effective anti-AIDS compounds and the development of contraceptive devices that can display anti-HIV activity in topical formulations are priority issues. In the past few years, the present inventor has spent considerable time researching compounds that might be useful in the prevention of sexual transmission of HIV and for the treatment of HIV infection. As a result, several potentially useful antiviral compounds were identified, including gramicidin, cimetidine, warfarin, coumarins, bestatin, human chorionic gonadotropin, levamisole, dexamethasone and select NSAIDs such as indomethacin, among others. It is clear, however, that the efforts in preventing the spread of HIV infections through sexual intercourse and treating AIDS will depend on the larger choice of diverse types of pharmaceutical agents with antiviral potential that could be used either alone or in combination with other active agents.

Acetaminophen, also known by brand names such as Tylenol, APAP, Panadol, Paracetamol, etc., is an over-the-counter analgesic used worldwide for more than four decades. Acetaminophen has a reputation as a generally safe and effective drug. Clinically, acetaminophen is given in a single dose of up to 1,000 mg, once a day or several times a day, with a maximum daily dose of 4,000 mg. Sensitivity reactions may occur occasionally. Overdose or consumption of acetaminophen with alcohol can cause hepatotoxicity which can be reversed by giving N-acetylcysteine to restore glutathione availability (Zimmerman, H. J., *Arch. Intern. Med.* 141:333–342, 1981).

Acetaminophen does not belong to the NSAIDs category since it has no anti-inflammatory activity. While this drug has been studied extensively as an analgesic, it was not obvious that it may have anti-HIV activity. The present inventor was the first to discover that acetaminophen and its derivatives display anti-HIV activity at non-toxic doses.

Acetaminophen was first synthesized in 1878 by reducing p-nitrophenol with tin in glacial acetic acid. Metabolic reduction of oral acetaminophen or acetaminophen prodrug forms given intravenously may result in formation of sulfate, phosphate and glucuronide active metabolites, among others, as well as other metabolites with toxic potential such as acetimidoquinone.

Acetaminophen may be represented by the following chemical formula:



Substituted acetaminophen compounds are known in the art as disclosed, for example, in U.S. Pat. No. 4,423,069, which is incorporated by reference.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention is to provide a method for suppressing HIV infection in vitro.

It is another object of the present invention to provide a method to inhibit or prevent the growth, replication or elaboration of HIV in vivo.

It is still a further object of the present invention to provide a method to prevent the transmission of HIV in vitro.

It is also an object of the present invention to provide a method to prevent the transmission of HIV during sexual intercourse.

It is still a further object of the present invention to provide a method to prevent or treat HIV infections in humans using the present compounds alone or in combination with other pharmaceutical agents having anti-HIV activity.

These and/or other objects of the present invention may be readily gleaned from the description of the present invention which follows.

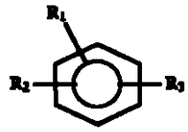
SUMMARY OF THE INVENTION

The present invention relates to a method for preventing or inhibiting HIV growth, replication and/or elaboration and spread in vitro as well as in vivo using acetaminophen and derivatives thereof alone or in combination with other pharmaceutical agents exhibiting anti-HIV activity.

More specifically, the present invention comprises a method for suppressing HIV growth, replication and/or elaboration and spread by employing anti-HIV effective doses or concentrations of acetaminophen or derivatives, thereof. In the present invention, an HIV effective concentration or dose of acetaminophen or a derivative, thereof is used to inhibit the growth elaboration and/or replication of HIV in an in vitro setting, in an in vivo setting, or in settings to treat organs and body fluids including, for example, prior to transplant procedures and transfusions or before the administration of blood components. In in vitro settings, the present compounds may be used in comparative tests to determine the potential anti-HIV activity of newly discovered agents and in diagnostic tests. In preferred methods according to the present invention which relate to the in vivo treatment of HIV infections, the present compounds are administered to a patient suffering from HIV in an amount and for a period of time which is sufficient to exert an inhibitory effect on HIV growth, elaboration and replication with one ultimate therapeutic goal being the treatment and/or prevention of AIDS. The present invention also relates to prophylactic treatments to prevent HIV infections in humans.

The present invention also relates to a method for preventing HIV infections which occur during sexual intercourse, the method comprising employing anti-HIV effective doses of acetaminophen or derivates thereof as active ingredients in topical formulations, including suppositories, lubricants, gels, films, or foams for use during intercourse. The method comprises administering a topical formulation comprising an anti-HIV effective amount of one or more pharmaceutically active agents according to the present invention into the vagina or rectum of a subject preferably before sexual intercourse (advisably, in combination with condom protection) in an amount and for a period of time sufficient to exert a protective effect against the sexual transmission of HIV.

Acetaminophen derivatives which may be used in the methods according to the present invention may be represented by the general formula:



where any one or more of R^1, R^2 and R^3 are substituted in the ortho- (o-), meta (m-) and/or +para (p-) positions of the aromatic (phenyl) core and where R^1 is a straight or branched chain C_1–C_8 alkyl, H, a halogen such as F, Cl, Br and I, trihalomethyl, such as trifluoromethyl and trichloromethyl, hydroxy, alkoxy, such as methoxy (O—CH_3), carboalkoxy (—CO_2R) such as carbomethoxy, carboxamido (—$CONH_2$), ester, aldehyde, ketone, amino (—NH_2), nitro (—NO_2), or cyano (—CN) group, or a 5- or 6-membered, saturated or unsaturated heterocyclic ring; R^2 may be any substituent defined as being a suitable substituent for R^1, a sulfate, phosphate or glucuronide, or a substituted sulfate, phosphate or glucuronide, such that R^1 may be bound to R_2; and

R^3 is any substituent defined as suitable for R^1 and R^2 and can be present with R^1 or R^2 or both R^1 and R^2.

DESCRIPTION OF THE FIGURES

FIG. 1 shows the effect of acetaminophen on reduction of productive HIV infection, as measured by p24 ELISA of MT-4 culture supernatant on day 2, is shown on the left vertical axis as nanograms of p24 per ml (ng/ml). The % values on the right axis were positioned in a fashion that allows estimation of inhibitory effect of the test drug as a function of acetaminophen concentration plotted on the horizontal axis. Complete inhibition of HIV replication was observed at a concentration of acetaminophen equivalent to 150 μg/ml or 1 mM. The experiments were repeated six times and the results of a typical experiment representing the mean of data points from three pooled wells are shown. Effect of XTT assay is shown as percent of control on the right ordinate. Note the absence of correlation between the effect of acetaminophen on cell viability and HIV replication. According to OD values of formazan dye there is no observable toxic dose-effect of acetaminophen even at the highest tested dose containing 0.5% of ethanol. The viability of MT-4 lymphocytes as tested by trypan blue exclusion was similar to control untreated cells. No toxicity was observed when control cells were grown in 0.5% ethanol.

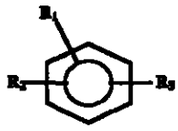
FIG. 2 shows the effect of AGB in preventing HIV transmission as measured by p24 ELISA of MT-4 culture supernatant on day 2 is shown on the left vertical axis as nanograms of p24 per ml (ng/ml). The experiments were repeated at least three times and results of a typical experiment representing the mean of data points from three pooled wells are shown. The % values on the right axis were positioned in a fashion that allows estimation of inhibitory

thereof to achieve optimal activity in combination or alone. The concentration ranges set forth herein are exemplary only and not intended to limit the scope or practice of invention. The adjustment and optimization of dosage is obvious to those of skill in the art and it is apparent that certain changes and modifications may be practiced within the scope of the appended claims.

It is to be understood by those skilled in the art that the foregoing description and examples are illustrative of practicing the present invention, but are in no way limiting. Variations of the detail presented herein may be made without departing from the spirit and scope of the present invention as defined by the following claims.

I claim:

1. A method for treating an HIV infection in a human comprising administering to said human an anti-HIV effective amount of a compound having the formula:



where any one or more of R^1, R^2 and R^3 are substituted in the ortho- (o-), meta (m-) and/or para (p-) positions of the aromatic (phenyl) core and where R^1 is a straight or branched chain C_1–C_8 alkyl, H, F, Cl, Br, I, trihalomethyl, hydroxy, alkoxy, carboalkoxy, carboxamido, ester, aldehyde, ketone, amino, nitro or cyano;

R^2 may be the same substituent as R^1, a sulfate, phosphate or glucuronide, or a substituted sulfate, phosphate or glucuronide; and

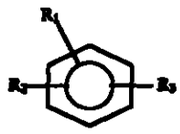
R^3 may be the same substituent as R^1 or R^2 and can be present with R^1 or R^2 or both R^1 and R^2, with the proviso that R^1, R^2 and R^3 are not all H, said compound being administered for a period of time sufficient to exert an inhibitory effect on said HIV infection.

2. The method according to claim 1 wherein said carboalkoxy is carbomethoxy.

3. The method according to claim 1 wherein said alkoxy is methoxy.

4. The method according to claim 1 wherein said trihalomethyl is trichloromethyl or trifluoromethyl.

5. A method for inhibiting the growth, replication or elaboration of HIV in humans with an HIV infection comprising administering to said humans an amount of a compound having the formula:



where any one or more of R^1, R^2 and R^3 are substituted in the ortho- (o-), meta (m-) and/or para (p-) positions of the aromatic (phenyl) core and where R^1 is a straight or branched chain C_1–C_8 alkyl, H, F, Cl, Br, I, trihalomethyl, hydroxy, alkoxy, carboalkoxy, carboxamido, ester, aldehyde, ketone, amino, nitro or cyano;

R^2 may be the same substituent as R^1 a sulfate, phosphate or glucuronide, or a substituted sulfate, phosphate or glucuronide; and

R^3 may be the same substituent as R^1 or R^2 and can be present with R^1 or R^2 or both R^1 and R^2, with the proviso that R^1, R^2 and R^3 are not all H, effective to produce a concentration range in human body fluids within the range of about 0.01 μg to about 150 μg per ml.

6. The method according to claim 1 wherein said carboalkoxy is carbomethoxy.

7. The method according to claim 1 wherein said alkoxy is methoxy.

8. The method according to claim 1 wherein said trihalomethyl is trichloromethyl or trifluoromethyl.

9. The method according to claim 1 wherein said compound is acetaminophen.

10. The method according to claim 1 wherein said body fluid is selected from the group consisting of blood, plasma, serum semen and lymph fluid.

11. The method according to claim 9 wherein said body fluid is selected from the group consisting of blood, plasma, serum semen and lymph fluid.

12. The method according to claim 1 wherein said compound is administered combination with an effective amount of at least one agent selected from the group consisting of AZT, ddC, ddI, warfarin, coumarins, bestatin, human chorionic gonadotropin, levamisole, estrogen, progesterone, dexamethasone, indomethacin, cimetidine, gramicidin and mixtures thereof.

13. A method of treating an HIV infection in a human comprising administering to said human an anti-HIV effective amount of a compound selected from the group consisting of acetaminophen and 4'-acetamidophenyl 4-guanidinobenzoate for a period of time sufficient to exert an inhibitory effect on said HIV infection.

14. The method according to claim 13 wherein said compound is acetaminophen.

15. The method according to claim 13 wherein said compound is 4'-acetamidophenyl 4-guanidinobenzoate.

* * * * *

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United States Patent [19]

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[54] ANALGESIC COMPOSITION FOR TREATMENT OF MIGRAINE HEADACHES

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[21] Appl. No.: 08/685,078

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[51] Int. Cl.[6] A61K 9/20

[52] U.S. Cl. 424/464; 424/465; 424/682

[58] Field of Search 424/44, 682, 692, 424/464.5; 514/165, 224.5, 350, 568, 728, 812

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3,865,933	2/1975	Mudge	424/195.1
4,083,951	4/1978	Gouldie et al.	424/44
4,217,340	8/1980	Tobert	424/157
5,538,959	7/1996	Mauskop	514/165

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Assistant Examiner—Kathryne E. Shelborne

Attorney, Agent, or Firm—Pennie & Edmonds, LLP

[57] ABSTRACT

Magnesium-containing analgesic compositions used for the alleviation of pain, in particular, migraine headache pain, and methods for using the same are described herein. The compositions consist essentially of an analgesic agent, a magnesium salt, a stimulant, optionally an effervescing agent, and a pharmacetically acceptable carrier or vehicle. The symptoms of migraine headache intended to be alleviated include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light physical activity, photophobia and phonophobia.

28 Claims, No Drawings

ANALGESIC COMPOSITION FOR TREATMENT OF MIGRAINE HEADACHES

FIELD OF THE INVENTION

This invention relates to magnesium-based analgesic compositions for treating migraine headaches, and methods for using the same.

BACKGROUND OF THE INVENTION

Analgesic compositions comprising magnesium salts have been used to treat a variety of ailments as well as reduce the gastric irritancy often accompanying the oral administration of such analgesic compositions. U.S. Pat. 2,801,951 to Cooper, Jr. discloses the use of an analgesic composition comprising acetylsalicylic acid, citric acid, p-ethoxyacetanilide, caffeine and $MgCO_3$ or $Mg(OH)_2/Al(OH)_3$. U.S. Pat. No. 3,865,933 to Mudge teaches the use of a mixture comprising magnesium gluconate, stramonium extract and 3-(2-methylphenoxy)-1,2-propanediol to relieve headache pain. U.S. Pat. No. 3,759,980 to Rosen et al. teaches the use of a mixture of magnesium salicylate and choline salicylate as an analgesic, anti-pyretic, anti-inflammatory and anti-rheumatic agent. U.S. Pat. No. 3,385,886 to Nicholson et al. teaches the use of phenylpropionic acid magnesium salts for the relief of pain, fever and inflammation. U.S. Pat. No. 3,359,166 to McClure teaches the use of magnesium 4-thiazolidinecarboxylate as an analgesic agent. U.S. Pat. No. 4,083,951 to Goudie et al. teaches the use of magnesium acetylsalicylate in conjunction with sodium bicarbonate as an analgesic having reduced gastric irritancy properties. U.S. Pat. No. 4,217,340 to Tobert discloses the use of a phenylbenzoic acid compound and magnesium hydroxide for treating pain and inflammation. Such compositions have employed magnesium salts for their solubility, absorption properties and buffering effects.

A deficiency of magnesium, i.e., hypomagnesemia, has been suggested to play a role in migraine headaches (B.A. Altura, *Magnesium*, 4:169 (1985); A. Mauskop et al., *Cephalalgia*, 14:241 (1994)). It had been shown that low serum ionized magnesium (IMg^{2+}) levels were found in 42 % of patients suffering migraine headaches (A. Mauskop et al., *Headache*, 33(3):135 (1993)). The magnesium salt of pyrrolidone carboxylic acid has been used to treat women with premenstrual migraine headache (F. Facchinetti et al., *Headache*, 31(5):298 (1991)). Amino-chelated magnesium compounds have been used to treat patients with classic migraine headache (K. Weaver in "Letter to the Editor," *Headache*, 30(2):168 (1990)). In addition, Mg^{2+} has been known to regulate the function of N-methyl-D-aspartate receptors (A. C. Foster et al., *Nature* (London), 329:395 (1987)), which are essential for pain transmission.

When some magnesium-based compositions are administered to patients having migraines, severe headaches or other painful conditions, the slowing of gastric motility which often accompanies these conditions delays the absorption of any medication taken orally. Such a delay in absorption is often more pronounced with tablet than with liquid medicaments. As a result, the onset of action associated with such compositions administered to migraine patients is undesirably delayed, resulting in the prolongation of pain and discomfort to the patient. Thus, there remains a need for compositions which can be used for treating migraine headaches and which are rapidly absorbed and provide rapid onset of action.

In addition, because migraine headache is believed to be, at least in part, stress-induced, patients who suffer from migraine headaches often experience other secondary pain, e.g., muscle ache, joint stiffness, eye strain and jaw problems, associated with stress-related muscle tension. Where the patient is elderly or has still other painful health conditions, the combination with migraine and such secondary pain described above can be overwhelming. Thus there is a need for compositions which can be used for treating migraine headaches which contain analgesics or other compounds known to relive pain.

Moreover, oral administration of compositions comprising magnesium salts often results in the unwanted side effect of constipation, a feeling of bloatedness and short-term loss of appetite. Thus there is a need for compositions which can be used for treating migraine headaches which contain magnesium salts and do not give produce the above-described side effects following administration.

Citation or identification of any reference in this section shall not be construed as an admission that such reference is available as prior art to the present application.

SUMMARY OF THE INVENTION

The present invention relates to a method for treatment of migraine headaches which comprises orally administering to a person in need of such treatment a rapidly absorbed magnesium- and effervescing agent-containing analgesic composition in an amount effective to relieve at least some symptoms of such headaches. Such compositions include various proportions of an analgesic agent, a magnesium salt and an effervescing agent.

Prior to ingestion, such compositions are admixed with or dissolved in water, preferably in about 2–10 ounces of water. Such compositions are ingested as their aqueous admixture or solution, preferably within 1–2 minutes of admixture or dissolution.

The invention further relates to pharmaceutical compositions for alleviating pain, consisting essentially of a therapeutically effective amount of one or more magnesium salt, stimulant, and analgesic agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is rapidly absorbed when orally administered.

The invention still further relates to pharmaceutical compositions for alleviating pain, consisting essentially of a therapeutically effective amount of one or more magnesium salt, stimulant, analgesic agent and effervescing agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is rapidly absorbed when orally administered.

The present invention may be understood more fully by reference to the following detailed description and illustrative examples which are intended to exemplify non-limiting embodiments of the invention.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, improved absorption and hence improved onset of action, as well as improved analgesia, of a preparation for treating a patient with a migraine headache can be achieved by administering to a patient with a migraine headache a magnesium-containing analgesic composition.

Such analgesic agents which can be included in the magnesium-containing analgesic compositions of the present invention include, but are not limited to, at least one or more non-opioid analgesic agent such as acetylsalicylic acid acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac,

dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, other non-steroidal anti-inflammatory drugs including salicylates, pharmaceutically acceptable salts thereof and mixtures thereof; or at least one or more opioid analgesic agent such as codeine, morphine, hydromorphine, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone, methadone, pharmaceutically acceptable salts thereof and mixtures thereof. Such pharmaceutically acceptable salts include, but are not limited to hydrochloride, hydrobromide, phosphate, sulfate, acetate, succinate, ascorbate, tartrate, gluconate, benzoate, malate, fumarate, and the like. In addition, the present compositions can contain a combination of a non-opioid analgesic agent and an opioid analgesic agent, i.e., a mixture of at least one or more non-opioid analgesic agent, and at least one or more opioid analgesic agent.

The analgesic agent(s) of the magnesium-containing analgesic compositions of the present invention are useful for relieving pain, in particular pain associated with migraine symptoms, as well as pain associated with non-migraine illnesses aggravated by migraine pain. In the former instance, it is believed that the combination of a magnesium salt and the analgesic agent(s) exert(s) a synergistic effect for relieving pain and related migraine symptoms. In addition, the analgesic agent(s) can relieve pain associated with non-migraine illnesses. Common examples include muscle ache, joint stiffness, eye strain and jaw problems associated with stress-related muscle tension, as well as pain derived from non-stress related conditions. Where the pain is less than severe, non-opioid analgesics are preferred. Preferably, the non-opioid analgesics used in the present magnesium-containing analgesic compositions are acetaminophen or ibuprofen, or mixtures thereof.

Where the patient suffering from an illness, particularly a migraine headache, has particularly severe pain, or has additional pain from a non-migraine illness such that the combination of pain is judged to be severe, it may be necessary that the analgesic component of the magnesium-containing analgesic composition include an opioid analgesic capable of provided relief from severe pain. Such a regimen is also useful where the patient has a terminal illness such that liabilities resulting from long-term administration of an opioid are outweighed by the interest in the patient's short-term comfort.

In a particular embodiment of the invention, the magnesium-containing analgesic compositions include more than one analgesic agent, i.e., at least two different non-opioid analgesic agents, at least two different opioid analgesic agents, or at least one non-opioid analgesic agent and at least one opioid analgesic agent. It is believed that combinations of non-opioid analgesic agents, or opioid analgesic agents, or both, act synergistically to relieve pain.

The magnesium component of the magnesium-containing analgesic compositions of the present invention is ionic magnesium (i.e., Mg^{2+}). Suitable sources of Mg^{2+} are magnesium salts which include, but are not limited to magnesium chloride, magnesium citrate, magnesium tartrate, magnesium oxide, magnesium carbonate, magnesium sulfate, magnesium hydroxide and mixtures thereof. It is to be understood that the present compositions can include one or more magnesium salt. Where an analgesic agent to be included in the magnesium-containing compositions is a carboxylic acid, the magnesium salt can be a magnesium salt of that analgesic agent carboxylic acid. For example, if the analgesic agent is acetylsalicylic acid, the magnesium salt can be magnesium acetylsalicylate. This is convenient in combining both important components within a single compound. When a magnesium salt of an analgesic is included in the magnesium-containing analgesic composition of the present invention, an additional analgesic may or may not be included.

It is advantageous for the compositions to be rapidly absorbed by the subject or patient following oral administration. By "rapidly absorbed" is meant that the present compositions are absorbed through the gastrointestinal tract within about 5 to about 20 minutes following ingestion.

There are a number of ways to formulate such compositions to achieve rapid absorption, and one of ordinary skill in the art would be aware of such ways. Generally, encapsulating the active ingredient or employing other forms of delaying the release of the agent into the subject should be avoided, except when such means to delay release are included in combination with a rapidly absorbed form of such agent. This could be used, for example, when the composition is intended to provide both a rapidly absorbed initial administration of the analgesic agent, followed by a delayed release of longer duration administered for continued relief of headache symptoms.

In one embodiment of a rapidly absorbable magnesium-containing analgesic composition, one or more effervescing agent is included. By "effervescing agent" is meant any compound which, upon dissolution in water, provides effervescence to the aqueous mixture or solution upon release of carbon dioxide. Such effervescing agents include, but are not limited to, alkali or alkaline earth metal carbonates, bicarbonates or mixtures thereof, including, but not limited to sodium carbonate, sodium bicarbonate, sodium glycine carbonate, calcium carbonate and magnesium carbonate. Preferably, at least one of the effervescing agents is sodium bicarbonate.

In another embodiment of the invention, the magnesium-containing compositions include one or more stimulant, such as methamphetamine, deoxamphetamine, methylphenidate, pemoline and preferably, caffeine, and mixtures thereof. Inclusion of a stimulant, inter alia, allows the present compositions to be rapidly absorbed. Without being bound to any particular theory, it is believed that such stimulants, particularly caffeine, stimulate gastric secretion and accordingly enhance absorption through the small intestine. In the case of caffeine, it is believed that magnesium cation forms a relatively stable chelate therewith, such that the caffeine serves to rapidly deliver the magnesium to the small intestine and increase its rate of absorption. Thus, the stimulant component serves to confer rapid absorption properties to the present compositions. In addition, it is believed that caffeine itself has analgesic properties (see Federal Register, 42(131):35482–35485 (1977)) which can serve to diminish the discomfort of pain, particularly pain associated with migraine headaches.

In addition to serving as a means to enhance the absorption of the present magnesium-containing analgesic compositions, the inclusion of a stimulant also serves to diminish the discomfort of constipation or a feeling of bloatedness, or relieve the temporary loss of appetite often following ingestion of opioids, which are known to be binding and are known to produce the aforementioned side effects, and counteract the gastric stasis associated with migraine headaches. In this regard, a stimulant diminishes or relieves the discomfort of these side effects by moderately stimulating peristalsis. It is within the purview of one skilled in the art to tailor the present compositions so as to provide the optimal dosage of stimulant.

Moreover, the inclusion of a stimulant serves to counteract the sedative, or in extreme cases where an analgesic is an opioid analgesic, hallucinatory effects of the analgesic. In other words, the incorporation of a stimulant improves the patient's motor coordination, alertness and overall sense of well being.

It is to be understood that the present magnesium-containing analgesic compositions can include both an effervescing agent and a stimulant, so as to further enhance the absorbability of the present compositions.

The magnesium-containing analgesic compositions further include a pharmaceutically acceptable carrier or vehicle. Such carriers or vehicles are known to those skilled in the art and are found, for example, in *Remingtons's Pharmaceutical Sciences*, 14th Ed. (1970). Examples of such carriers or vehicles include lactose, starch, dicalcium phosphate, calcium sulfate, kaolin, mannitol and powdered sugar. Additionally, when required, suitable binders, lubricants, disintegrating agents and coloring agents can be included. If desired, dyes, as well as sweetening or flavoring agents can be included.

The magnesium-containing analgesic compositions may optionally include accessory ingredients including, but not limited to dispersing agents such as microcrystalline cellulose, starch, cross-linked poly(vinyl pyrrolidone), and sodium carboxymethyl cellulose; flavoring agents; coloring agents; binders; preservatives; surfactant and the like.

The non-opioid analgesic agent(s) is (are) advantageously present in the magnesium-containing compositions at levels ranging from about 10 to about 90 wt. %, preferably about 10 to about 75 wt. %.

The opioid analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 0.5 to about 20 wt. %, preferably from about 1 to about 15 wt. %.

It is to be understood that the present compositions can contain an analgesic agent such that the analgesic agent is a mixture of one or more non-opioid analgesic agent and one or more non-analgesic agent. In such a case, the non-opiate analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 10 to about 90 wt. %, preferably about 10 to about 75 wt. %; and the opioid analgesic agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 0.5 to about 20 wt. %, preferably from about 1 to about 15 wt. %.

When added as a separate component, i.e., not as a magnesium salt of an analgesic agent, the magnesium salt(s) is (are) present in the magnesium-containing compositions at levels ranging from about 5 to about 30 wt. %, preferably from about 10 to about 30 wt. %. When a single compound of a magnesium salt of the analgesic agent is used, the amounts of such a single compound would be between about 20 and 95 wt. % of the composition.

When present, the effervescing agent(s) is (are) present in the magnesium-containing compositions at levels ranging from about 20 to about 80 wt. %, preferably from about 25 to about 75 wt. %.

The stimulant(s) is (are) present in the magnesium-containing analgesic compositions at levels ranging from about 1 to about 25%, preferably from about 5 to about 20 wt. %.

Of course, the total amounts of these components would be 100 wt. %, and those of ordinary skill in the art can vary the amounts within the stated ranges to achieve useful compositions.

The intended route of administration of the magnesium-containing analgesic compositions of the present invention is oral, wherein the composition including an effervescing agent is admixed with or dissolved in a pre-determined amount of an aqueous vehicle, such as for example water, prior to ingestion. The present compositions not including effervescing agents are not admixed with or dissolved in water prior to administration.

Compositions of the present invention which are suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets, as a powder or granules; as a solution or a suspension in an aqueous liquid or non-aqueous liquid; or an oil-in-water or water-in-oil liquid emulsion. Preferably, the compositions of the present invention is presented in liquid, capsule, or most preferably, tablet form. Such tablets may be conventionally formed by compression or molding. Compressed tablets may be prepared by compressing in a suitable machine the mixture of one or more analgesic, magnesium salt, stimulant, optionally an effervescing agent, and a pharmaceutically acceptable carrier or vehicle described above. Molded tablets may be made by molding in a suitable machine the above mixture which can optionally be moistened with an inert liquid diluent. The tablets may optionally be coated or scored, having indicia inscribed thereupon, and may be so formulated as to provide slow or controlled release of the analgesic, magnesium or effervescing compounds therein.

Such tablets can range in weight from 25–2000 mg., preferably from 100–1000 mg., and most preferably from 250–1500 mg.

Prior to ingestion, compositions comprising effervescing agents are admixed or dissolved in about 2–10 ounces of an aqueous carrier such as water, preferably about 4–8 ounces of water. The compositions of the present invention are ingested as their aqueous admixture or solution within 2 minutes, preferably within 1 minute, of their admixture with or dissolution in water, so as to maximize their effervescence and hence absorptive properties.

Compositions not comprising effervescent agents are ingested, in the case of liquid compositions, neat (undiluted), and in the case of capsules or tablets, swallowed whole, preferably with water.

The compositions of the present invention are administered shortly after the onset of migraine symptoms. Such symptoms include nausea, unilateral pain, dizziness, pulsatile pain, worsening of pain by light activity, photophobia and phonophobia.

Administration can continue every 2–6 hours, preferably every 4 hours until migraine symptoms have subsided. In patients who suffer from chronic migraine headaches, a daily administration of 1000 mg. of the magnesium-containing compositions four times per day of the present invention is advantageous.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

TABLE 1

			RESULTS	
N	Age	Sex	Severity Prior to Administration	Severity Following Administration
1	33	F	10	4
2	35	F	7	2
3	14	F	8	3
4	59	F	7	1
5	30	M	8	2

Thus for all patients included in this study, the administration of the above-described magnesium-containing analgesic composition significantly reduced the severity of migraine headaches.

EXAMPLE 10

Reduction of Migraine Symptoms Following Intravenous Administration of $MgSO_4$

Methods

Forty consecutive patients (3 men and 37 women) who presented with an acute migraine but did not have renal, cardiac or other medical problems were administered with 1 g. of $MgSO_4$ in a 10% saline solution intravenously, over 5 minutes. Patients remained in a recumbent position during the infusion and for 5 minutes after the infusion. Headache intensity was measured on a verbal 1 to 10 scale before, and 15 minutes after, the infusion. The recurrence or worsening of a headache within the following 24*h* was determined using the verbal 1 to 10 scale in a telephone interview. A greater than 50% reduction of pain intensity lasting at least 24h was considered a positive response.

Results

Of the 40 patients, 35 (87.5%) had a reduction of pain of 50% or more 15 minutes after the infusion. This included 9 patients who experienced complete relief. In 21 of these 35 patients, at least this degree of improvement or complete relief persisted for 24h or more (positive response).

Thus, the administration of magnesium salt is effective at relieving the symptoms of migraine headache.

The magnesium-containing analgesic compositions of the present invention can be used to treat patients with migraine headaches. It is to be understood that such uses are not limited to treating the symptoms of migraine headaches but rather include treating other maladies including non-migraine headache pain, muscular pain, fever associated with viral or bacterial infection, thrombotic diathesis, magnesium deficiency and gastric discomfort.

The present invention is not be limited in scope by the specific embodiments disclosed in these examples which are intended to illustrate the most preferred embodiments of the invention. Indeed, various modifications of the invention or other embodiments which are functionally equivalent to those shown and described herein will become apparent to those skilled in the art and are intended to be covered by the appended claims.

A number of references have been cited, the entire disclosures of which are incorporated herein by reference.

What is claimed:

1. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant selected from the group consisting of methamphetamine, dexamphetamine, methylphenidate, pemoline, caffeine and mixtures thereof, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam. mefamanic acid, dextromethorphan, codeine, morphine, hydromorphine, levophanol, meperidine, meptazinol, propoxyphene, yropiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

2. The composition of claim 1, wherein at least one of the one or more analgesic agent is a non-opioid analgesic agent.

3. The composition of claim 2, wherein the non-opioid analgesic agent is selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, salicylates, pharmaceutically acceptable salts thereof, and mixtures thereof.

4. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, naproxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethor-han, codeine, morphine, hydromorohine, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein at least one of the one or more analgesic agent is an opioid analgesic agent; and a pharmaceutically acceptable carrier or vehicle, wherein the composition is orally administered.

5. The composition of claim 4, wherein the opioid analgesic agent is selected from the group consisting of codeine, morphine, hydromorphine, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof.

6. A pharmaceutical composition for the alleviation of pain, associated with migraine headache consisting essentially of a therapeutically effective amount of one or more magnesium salt, one or more stimulant, and one or more analgesic agent selected from the group consisting of acetylsalicylic acid, acetaminophen, paracetamol, ibuprofen, ketoprofen, ketoconazole, indomethacin, diflunisol, na-roxen, ketorolac, dichlophenac, tolmetin, sulindac, phenacetin, piroxicam, mefamanic acid, dextromethorphan, codeine, morphine, hydromorphine, levophanol, meperidine, meptazinol, propoxyphene, propiram, buprenorphine, pentazocine, nalbuphine, butorphanol, tramadol, hydrocodone, oxycodone and methadone, pharmaceutically acceptable salts thereof, and mixtures thereof, wherein the one or more analgesic agent is a combination of a non-opioid analgesic agent and an opioid analgesic agent;

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Doctora
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO		
	Radicación	00090144
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	1032
	Folios	022

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

Los textos estudiados fueron la descripción (Folios: 3 a 11) y las reivindicaciones 1 a 14 (Folios: 48 a 52).

La presente solicitud reivindica prioridad americana N° US9.448988 de 24 de noviembre de 1999 y cumple con lo establecido en los artículos 9, 10 y 11 de la Decisión 486 de la Comisión de la Comunidad Andina.

Objeto de invención:

La presente solicitud se titula: "Método para tratar síntomas de migraña".

El objeto de la presente solicitud se refiere a al tratamiento de síntomas de migraña mediante la administración de una cantidad efectiva de acetaminofén; más específicamente, la presente solicitud se refiere al tratamiento de fonofobia y fotofobia con acetaminofén, sales farmacéuticamente aceptables del mismo o mezclas de los mismos.

Según la descripción, la migraña produce una amplia variedad de dolor y síntomas y trastornos asociados en quienes sufren de la enfermedad. Entre estos síntomas están incluidos: náusea, dolor de cabeza, dolor moderado a severo, así como también dolor incapacitante e inhabilitación total en un porcentaje de pacientes. Algunos pacientes también relatan síntomas más específicos tales como fotofobia, sensibilidad dolorosa a la luz, o fonofobia, sensibilidad dolorosa al ruido.

El tratamiento del dolor de migraña incluye tanto medicamentos para venta con receta, como medicamentos para venta sin receta o de libre acceso. entre los medicamentos de libre acceso que están disponibles actualmente está una combinación de acetaminofén/aspirina/cafeína, como que se indica en la patente de EUA N° 5972916. La combinación de ingredientes activos pueden ocasionar efectos

secundarios indeseables. Por ejemplo, es bien conocido que la aspirina ocasiona irritación estomacal y la cafeína puede ocasionar ansiedad e insomnio. Por lo tanto, existe la necesidad continua de tratamiento de migraña y de alternativas de tratamiento para los síntomas específicos de la migraña.

Lo que se reivindica como novedoso es lo siguiente: una cantidad efectiva de acetaminofén, una sal farmacéuticamente aceptable del mismo, o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fotofobia asociada con migraña.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 31/167.

Claridad de la solicitud:

El artículo 28 de la Decisión 486 de la Comisión de la Comunidad Andina 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."

De acuerdo con lo anterior, la solicitud se relaciona con un método de tratamiento y el título, pero el capítulo reivindicatorio se encuéntra encabezado en función del fármaco acetaminofén que se encuentra en una cantidad efectiva.

El artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: "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."

De acuerdo con lo anterior, las reivindicaciones están encabezadas como una cantidad efectiva de acetaminofén, lo cual no es claro si se está reclamando una cantidad de fármaco que, por lo demás, no se dice el valor de dicha cantidad, o es el fármaco en sí que se encuentra en esa cantidad. De otro lado, no se comprende si lo que se trata de reclamar es una formulación farmacéutica que contiene acetaminofén como principio activo; si este es el caso, debería decirse el vehículo en el cual se encuentra formulado dicho fármaco y no debe caracterizarse por un uso que se le va a dar a dicho fármaco.

Las reivindicaciones 9 a 12 (folios: 50 a 51) que se relacionan con las sales de acetaminofén, no son claras, puesto que no se comprende la forma de unión o enlace entre por ejemplo: cafeína con el acetaminofén para formar la sal, o la histidina con el acetaminofén; además, a lo largo de la solicitud no aparecen ejemplos de dichas sales que aclaren como se encuentran formadas. Se solicita que se explique en qué consisten tales reacciones y cuál es el producto de ellas (estructura química).

En las reivindicaciones aparecen términos que son bastante subjetivo y conllevan a ambigüedad, por lo cual le restan claridad a lo que se pretende proteger. Por ejemplo: "aproximadamente", "cantidad efectiva", "sal farmacéuticamente aceptable", etc.

Evaluación de la Unidad de Invención:

El artículo 25 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."

Según lo anterior la (s) reivindicación (es) 9 a 12 (folios: 50 y 51), que se refiere(n) a una cantidad efectiva de acetaminofén, una sal farmacéuticamente aceptable del mismo,... caracterizado porque la sal se selecciona del grupo...: sales inorgánicas,... sales orgánicas,..., mezclas de las mismas, no guarda(n) unidad de invención con las reivindicaciones precedentes, que se relacionan con con una cantidad efectiva de acetaminofén , una sal farmacéuticamente aceptable,... usados en un método para calmar o tratar la fotofobia asociada con migraña.

Determinación del estado de la técnica:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina 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.

Sólo 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: 24/11/1999, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se hizo la búsqueda de documentos relevantes en el estado de la técnica, entendiendo como estado de la técnica la definición provista en el artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina y las excepciones fijadas en el artículo 17 de la misma.

Se encontró como anterioridades (documentos cuya fecha de publicación es anterior a la fecha de presentación de la primera solicitud de patente sobre la cual se reivindica prioridad o de la fecha de presentación de esta solicitud) que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	US5965166	Directly compressible high load acetaminophen formulations	12 de octubre de 1999
2	US5773031	Acetaminophen sustained-release formulation	30 de junio de 1998
3	US5837729	Methods for treating and preventing HIV infection using acetaminophen and derivatives thereof	17 de noviembre de 1998
4	US5914129	Analgesic composition for treatment of migraine headaches	22 de junio de 1999

Evaluación de los requisitos de Patentabilidad:

El Artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina el cual establece: "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".

Se procedió a evaluar 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 de Novedad:

El artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Una invención se considerará nueva cuando no está comprendida en el estado de la técnica". "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.

Sólo 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".

Esta se evaluó por comparación entre lo solicitado y los documentos encontrados en el estado de la técnica y que se relacionan con el objeto reivindicado y de acuerdo con la definición de novedad del Artículo 16 de la Decisión 486 de la Comisión de la Comunidad Andina.

Comparando elemento por elemento el objeto de esta solicitud con lo mencionado en las anterioridades, tenemos que:

La Solicitud de Patente Colombiana No. 00090144, se refiere a:

Una cantidad efectiva de acetaminofén, una sal farmacéuticamente aceptable del mismo, o una mezcla de los mismos, como único ingrediente farmacéuticamente efectivo, usados en un método para calmar o tratar la fotofobia asociada con migraña.

La anterioridad: US5965166 (folios: 68 a 71), se relaciona con: una forma sólida de dosificación que contienen acetaminofén, celulosa microcristalina y un lubricante.

La anterioridad: US5773031 (folios: 72 a 74), trata sobre: una forma de dosificación de liberación sostenida de acetaminofén.

La anterioridad: US5837729 (folios: 75 a 78), menciona el acetaminofén o derivados del mismo empleados para hacer formulaciones para el tratamiento de VIH.

Estos documentos revelan formulaciones que contienen acetaminofén o derivados del mismo y que pueden estar en una forma de administración sólida, tal como tabletas.

83

Como se observa, el objeto de esta solicitud puede ser idéntico a lo comprendido en el estado de la técnica, con lo cual se considera que podría no cumplir con el requisito de Novedad.

Evaluación de 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".

El Nivel Inventivo se evaluó por comparación entre lo solicitado y encontrado en el estado de la técnica y que se relaciona con el objeto reivindicado y de acuerdo con la definición de nivel inventivo del Artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina.

El documento US 5837729 (folios: 75 a 78) menciona formulaciones que contienen acetaminofén o derivados del mismo, lo cual significa para una persona medianamente versada en la materia que dentro del concepto de "derivado de un compuesto" se pueden encontrar las sales del mismo.

En cuanto a la actividad, ya era conocido en el estado de la técnica el empleo de analgésicos tal como el acetaminofén para el tratamiento de la migraña (ver documento US 5914129, folios: 79 a 82), aun cuando en el documento US 5837729 se diga que se emplea acetaminofén para tratar infecciones por VIH, esto significa que dicho fármaco tiene varios usos terapéuticos que, como bien sabe el solicitante, una formulación farmacéutica no es merecedora de nueva patente por encontrársele un nuevo uso farmacéutico; por lo anterior puede decirse que la solución al problema planteado ya había sido dada con antelación a la fecha de prioridad de la actual solicitud de patente.

Como se observa, el objeto de esta solicitud podría resultar obvio para una persona del oficio normalmente versada en la materia y derivarse de manera evidente del estado de la técnica.

Evaluación de la Aplicación Industrial:

El artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que "Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios".

El objeto de la presente solicitud cumple con el requisito de Aplicación Industrial.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

88

84

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	US5965166	1 a 14	Novedad
2	US5773031	1 a 14	Novedad
3	US5837729	1 a 14	Novedad y Nivel Inventivo
4	US5914129	1 a 14	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 CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 02 FEB. 2016

CONCEPTO TÉCNICO Nº: 097	EXAMINADOR TÉCNICO Código Nº: 202005	EXAMINADOR JURÍDICO Código Nº:

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

85

RADICACIÓN: 0-80144 EDICTO No. 8867

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 13283 de 25-MAY-2006. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "METODO PARA TRATAR SINTOMAS DE MIGRAÑA".

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Jimena Escobar Uribe, o a quien haga sus veces, en su calidad de apoderada de McNeil – Ppc, Inc., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 25 MAY 2006

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME ROBLES ESCOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:30 a.m. de hoy.

Secretaria General Ad-Hoc 12-JUN-2006 Este edicto se desfija hoy 27-JUN-2006 a las cinco (5:00 p.m.)
Secretaria General Ad-Hoc
EDICTO No. 8867