

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

MINISTERIO DE INDUSTRIA Y COMERCIO
 EXPEDIENTE N° 06 78456 - 00001-0000
 2020-02-26 15:06:05 Dep. 2020 NUECREACIONE
 Tra. 2 PATENTES Eve: 1 REGDEPOSITO
 Act. 538 PETICION Folios: 2

Referencia : Expediente N° 06 78456

Asunto : PETICIÓN DE EXAMEN DE PATENTABILIDAD a la solicitud de patente de Invención titulada "COMPOSICIÓN FARMACÉUTICA SÓLIDA QUE INCLUYE EN COMBINACION UN AGENTE REGULADOR DE LA MOTILIDAD INTESTINAL Y UN AGENTE ANTIPLATULENTO".

Solicitante : PROCAPS S.A.

REINALDO PINILLA MORENO, identificado como aparece al pie de mi firma, en mi condición de apoderado de la sociedad PROCAPS S.A., sociedad legalmente constituida y domiciliada en ciudad de Barranquilla, Colombia, por orden expresa de mi poderdante y estando dentro del término de ley, me permito solicitar respetuosamente se practique el EXAMEN DE PATENTABILIDAD a la solicitud de la referencia, conforme lo indica el Artículo 44 de la Decisión 486 de la CAN.

Para tal efecto anexo a la presente, el comprobante de pago por un valor de \$420.000.00, referido a la cancelación de la tasa por concepto de examen de patentabilidad de una solicitud de patente de invención.

Ruego a usted tome nota de lo anterior y proceda de conformidad.

Atentamente,


 REINALDO PINILLA MORENO

C.C. 80'425.609

T.P. 91563 del C.S.J.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 16,760
FECHA : FEBRERO 26 DE 2008

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***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GYNO PHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	83556	30/01/2008	1,882,000.00
GYNO PHARM S.A.	CONSIGNACION	BANCO DE BOGOTA	062754387	2131825	15/02/2008	1,596,000.00

***** CONCEPTO *****

NT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
	TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-78456

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **579** DE

FECHA **31 DE AGOSTO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE NOVIEMBRE DE 2007**

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



US005248505A

United States Patent [19]

Garwin

[11] **Patent Number:** 5,248,505[45] **Date of Patent:** Sep. 28, 1993**[54] METHOD FOR TREATING
GASTROINTESTINAL DISTRESS**[75] **Inventor:** Jeffrey L. Garwin, Paoli, Pa.[73] **Assignee:** McNeil-PPC, Inc., Milltown, N.J.[21] **Appl. No.:** 852,355[22] **Filed:** Mar. 17, 1992**Related U.S. Application Data**

[63] Continuation of Ser. No. 430,707, Nov. 1, 1989, abandoned.

[51] **Int. Cl.:** A61K 9/24; A61K 31/74;
A61K 31/695; A61K 31/54[52] **U.S. Cl.:** 424/472; 424/78.01;
424/475; 514/63; 514/161; 514/188; 514/327;
514/278; 514/456; 514/819; 514/820; 514/867;
514/330[58] **Field of Search** 514/63, 188, 161, 278,
514/228, 441, 456, 819, 820, 867; 424/78.01,
472, 475**[56] References Cited****U.S. PATENT DOCUMENTS**

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Primary Examiner—Frederick E. Waddell*Assistant Examiner*—K. Weddington

[57]

ABSTRACT

This invention relates to a pharmaceutical composition for treating gastrointestinal distress comprising an effective amount of an antidiarrheal composition, e.g. loperamide, and an antifatulent effective amount of simethicone and methods of treating gastrointestinal distress comprising administering such pharmaceutical compositions.

16 Claims, No Drawings

1600 mg.; bismuth subsalicylate with a dosage range from about 120 mg. to 1200 mg; diphenoxylate HCl with a preferred dosage range from about 0.7 mg. to 10 mg.; polycarbophil with a preferred dosage range of about 150 to 2000 mg.; and calcium polycarbophil with a preferred dosage range of about 150 to 2000 mg. Compatible mixtures of these antidiarrheal compositions and their pharmaceutically acceptable salts can also be included in a pharmaceutical composition of the invention.

Loperamide is the most preferred antidiarrheal active for use in the pharmaceutical composition of the invention. Loperamide as a component of the present invention includes pharmaceutically acceptable salts of loperamide such as loperamide HCl. Loperamide acts by slowing intestinal motility and by normalizing water and electrolyte movement through the bowel. Further, loperamide inhibits peristaltic activity by a direct effect on circular and longitudinal muscles of the intestinal walls. Loperamide in man thus prolongs the transit time of the intestinal contents and reduces the daily fecal volume and increases the viscosity and bulk density and thus diminishes loss of foods and electrolytes.

Dosage ranges chosen for the loperamide component of the composition of the present invention depend upon the age and weight of the Patient. A preferred adult dose given initially for the treatment of gastrointestinal distress is 4 mg. followed by 2 mg. after each unformed stool until diarrhea is controlled. A preferred ratio of simethicone to loperamide is in the range of from about 100 to 1 to about 10 to 1. Loperamide acts in the intestines and is therefore preferably enteric coated so that it will pass through the stomach and be released in the small intestines. While enteric coating is preferred, it is not essential since loperamide will not be absorbed or metabolized in the stomach but will eventually pass through into the small intestines in any event.

Other ingredients both active and inactive can be added to the combination antidiarrheal/antiflatulence compositions of the invention. For example, flavoring compositions are desirably added to chewable and liquid dosage forms. The composition of the invention can also be provided in an oral solid dosage form.

Antispasmodic and anticholinergic compositions and their pharmaceutically acceptable salts may, for example, be added to the compositions of the invention. Examples of antispasmodics include phenobarbital, dicyclomine HCl, belladonna alkaloids, and atropine. Further, various digestive enzymes such as lipase, amylase and protease may also be provided as additional components in combination with the compositions of the invention to reduce and relieve gastrointestinal distress.

A method of treating gastrointestinal distress is also provided in accordance with the present invention. The method comprises administering a combination pharmaceutical composition in accordance with the invention to a patient having the symptoms of gastrointestinal distress which is a combination of diarrhea and flatulence, including discomforts associated with flatulence which may include bloating, pain, and uncomfortable fullness. The method comprises treating the patient with an effective amount of an antidiarrheal composition and an antiflatulent effective amount of simethicone. The antidiarrheal is preferably selected from the group consisting of loperamide, attapulgit, bismuth subsalicylate, polycarbophil, calcium polycarbophil and mixtures thereof. More preferably, the antidiarrheal

composition is loperamide in a dosage range of about 0.5 to 8.0 mg. combined with from about 20 to 125 mg. of simethicone.

EXAMPLES

The invention will now be illustrated by examples. The examples are not intended to be limiting of the scope of the present invention but read in conjunction with the detailed and general description above, provide further understanding of the present invention and an outline of a process for preparing the compositions of the invention.

EXAMPLE I

Bi-layer Loperamide HCl 2 mg./Simethicone 80 mg., Chewable Tablet

Ingredients	mg/tablet
SIMETHICONE LAYER	
dicalcium phosphate, NF	784.000
colloidal silicon dioxide, NF	40.000
simethicone, USP	80.000
aspartame, NF	5.000
flavors	16.056
stearic acid, NF	18.879
Layer Total	943.935
LOPERAMIDE LAYER	
loperamide HCl, USP	2.000
sucrose, NF	12.000
mannitol, USP	565.120
aspartame, NF	2.820
flavors	9.060
stearic acid, NF	6.000
colloidal silicon dioxide, NF	3.000
Layer Total	600.000
Bi-layer Tablet Total	1543.935

Manufacturing Instructions

A. Simethicone Granulation

Combine dicalcium phosphate, colloidal silicon dioxide, simethicone, aspartame, flavors and stearic acid. Mix using an appropriate mixer (e.g., PK Blender) for 10 minutes.

B. Loperamide Granulation

Granulate loperamide HCl with sucrose and a portion of the mannitol using an appropriate fluid bed granulator (i.e., Glatt GPCG-3).

Dry blend stearic acid, colloidal silicon dioxide, aspartame, flavors and the remaining mannitol with the above granulation. Mix for 10 minutes in an appropriate mixer (e.g., PK Blender).

C. Compression

Compress the loperamide and simethicone granulations as separate layers using a bi-layer tablet press (e.g., Stokes Versa Press).

EXAMPLE II

Bi-layer Loperamide HCl 2 mg./Simethicone 80 mg. Swallowable Caplet

Ingredients	mg/tab
SIMETHICONE LAYER	
dicalcium phosphate, NF	784.000
colloidal silicon dioxide, NF	40.000
simethicone, USP	80.000
sodium starch glycolate, NF	80.360
stearic acid, NF	20.090
Layer Total	1004.450

Recent Advances in Pharmacotherapy

The irritable bowel syndrome

Stephen M. Collins, MD

The irritable bowel syndrome (IBS) is an extremely common disorder. It is believed to occur usually after emotional stress and perhaps because of behavioural and dietary factors. There is definite evidence of disturbed gastrointestinal function associated with IBS; however, a diagnostic marker remains elusive. The current trend is to diagnose IBS on the basis of the patient's history and the findings at physical examination and after minimal investigation. The physician-patient relationship remains the most important factor in the management of IBS. Long-term benefit may be achieved with the use of dietary fibre supplements or stool-bulking agents. The evaluation of currently available drugs is difficult because of the placebo effect. Drug therapy should be aimed at specific symptoms and used mainly during the initial phase of treatment.

Le syndrome dit du côlon irritable est très fréquent. On l'attribue ordinairement aux tensions affectives; peut-être est-il lié aux certains facteurs du comportement et de l'alimentation. Bien qu'il se manifeste par de nets troubles fonctionnels, on ne dispose pas de critère indiscutable pour en faire le diagnostic. Celui-ci s'appuie donc actuellement sur l'anamnèse et l'examen clinique; il n'exige pas une exploration poussée. Le traitement du côlon irritable repose avant tout sur le rapport entre le malade et son médecin. On peut obtenir une amélioration durable par l'emploi des produits diététiques à base de fibres ou de ceux qui augmentent le

volume du bol fécal. Il est difficile, vu l'effet placebo, de juger de l'efficacité des médicaments actuellement disponibles. On n'y aura recours qu'en les dirigeant contre des symptômes précis et surtout en début de traitement.

There is no uniformly accepted approach to the treatment of the irritable bowel syndrome (IBS); some advocate drug therapy,¹ and others believe drugs play a small part in its management.² This controversy reflects a general ambivalence to this disorder on the part of many physicians. Is it largely an expression of psychoneurotic behaviour, or is it an organic disease of the gastrointestinal tract?³ The observation that the symptoms reported by patients with IBS are experienced but not reported by as much as 14% of the population has led to further uncertainty about the nature of the syndrome.^{4,5} People with IBS account for approximately 10% of the patients who visit family physicians and for at least 50% of those who are referred to gastroenterologists;⁶⁻⁸ therefore, these people have an enormous socioeconomic impact on our society.⁹

Although many preparations are available,¹⁰ few have been proven to be effective, and doubts about the nature of IBS undermine any attempts to rationalize, implement and evaluate different forms of therapy. In addition, the heterogeneity of IBS and the natural history, which is characterized by frequent relapses and remissions, compound the problem. Finally, attempts to evaluate IBS therapy have been substantially constrained because of a placebo rate that may exceed 60%.

I have reviewed what is known about the pathophysiologic features of IBS and have attempted to use this information to rationalize existing therapeutic options. I have emphasized the principles, rather than the specifics, of therapy and the treatments that have been shown to be effective in adequately designed studies, although this information is often unavailable. In addition,

Dr. Collins is an associate professor of medicine and director of the Intestinal Diseases Research Unit, McMaster University, Hamilton, Ont.

Reprint requests to: Dr. Stephen M. Collins, Rm. 3N5C, McMaster University Health Sciences Centre, 1200 Main St. W, Hamilton, Ont. L8N 3Z5

I have provided data from my experience in managing patients with this common and difficult problem.

Pathogenesis

Psychologic factors

The evidence that IBS is primarily, or even exclusively, a behavioural problem has been based on several observations. As a group, IBS patients exhibit more symptoms of affective disorders, such as anxiety and depression, than do normal subjects,¹¹⁻¹⁴ and the symptoms are often precipitated by stressful events.¹⁵ Furthermore, psychotherapy¹⁶ and hypnotherapy¹⁷ have been shown to lessen the symptoms significantly in some patients. Although psychotropic drugs may help, the effect is not necessarily an exclusively psychotropic one, because many of these agents directly affect the gastrointestinal tract.

Symptoms experienced by patients with IBS may be experienced but not reported by up to 14% of the general population.^{18,19} In addition, balloon distension of the rectum produces pain at lower distension volumes in patients with IBS than in control subjects.^{20,21} These findings suggest that the former group present because of general intolerance of pain. However, Cook and associates,²² using electrocutaneous stimulation, found that patients with IBS were actually less likely than healthy subjects to report pain from a noxious stimulus. In fact, the patients exhibited a level of tolerance that was similar to that of patients with Crohn's disease. That people with IBS are intolerant of pain due to rectal distension may reflect local changes within the gastrointestinal tract that are part of the pathogenic features of the disease.

Not all patients with IBS exhibit psychoneurotic behaviour or perceive emotional stress as a precipitating factor; in some, symptoms are triggered by gastrointestinal infection (postinfectious IBS).¹⁵ These observations have led physicians to consider the existence of gastrointestinal dysfunction in IBS.

Altered gastrointestinal motility

Several groups have identified changes in the gastrointestinal motility of patients with IBS. Although the condition may involve any part of the gastrointestinal tract interest has traditionally been focused on colonic motility. Unfortunately, the colon is a highly complex and variable organ in terms of its motility apparatus,²³ and the identification of abnormalities in this region has been elusive. Three groups have shown an increased incidence of low-frequency electrical slow-wave activity (3 cpm) in the sigmoid region,²⁴⁻²⁶ but this finding has not been confirmed by others.^{27,28} Changes in electrical spiking activity have been

found²⁸ and appear to have some bearing on the dominant pattern of altered bowel habit (i.e., diarrhea or constipation). Patients with IBS who have constipation have been found to have slow transit of the luminal contents, whereas those with diarrhea have rapid transit.²⁹ In addition, patients with constipation generally have increased motility, predominantly noncontractile, in the sigmoid colon, unlike those with diarrhea, who exhibit generally decreased activity in this region.³⁰⁻³² In the small intestine, where motility patterns are more predictable, abnormalities have been found in short- and long-term studies.^{33,34} The occurrence of abdominal pain has been correlated with specific bursts of motility in the small intestine³⁵ and with arrival of the luminal contents at the cecum.²⁹

The motility apparatus of the gastrointestinal tract in patients with IBS is unduly sensitive to exogenous and endogenous stimuli. Some patients have significant increases in colonic motor activity after the administration of cholecystokinin³⁶ or parasympathomimetic agents.³⁷ Some patients, particularly those with predominant constipation, exhibit a prolonged colonic motor and electrical response after a meal.³⁸ In addition, bile acids have been shown to induce greater increases in colonic motility in some patients with IBS than in control subjects.³⁹ These abnormal responses to such ubiquitous stimuli may be the basis for gastrointestinal symptoms and food intolerance in many of the patients.

Alterations in other gastrointestinal functions

Abnormalities of gastrointestinal function have not been restricted to the motility apparatus. The intestinal epithelium of patients with predominant diarrhea has been reported to become secretory after bile-acid infusion.⁴⁰ In a double-blind study patients who reported intolerance to specific foods showed increased concentrations of fecal prostaglandin E₂ when challenged with those foods.⁴¹ This interesting finding remains controversial,⁴² but it raises questions about the nature of IBS and whether it reflects a variety of pathophysiologic processes, especially since entities such as isolated lactase deficiency⁴³⁻⁴⁵ and idiopathic bile-salt malabsorption⁴⁶ may also mimic IBS.

Conclusion

Behavioural abnormalities and changes in gastrointestinal function have been identified in patients with IBS. I believe that IBS is an exclusive disorder of neither the brain nor the gastrointestinal tract but, rather, the gut-brain axis, through which chronic stress and other behavioural factors affect gastrointestinal function and through which stimuli from the abnormally responsive gastrointestinal tract are transmitted to the brain. The extent to which behavioural and gastrointestinal

37

factors contribute to the syndrome, as well as the affected site within the gastrointestinal tract, vary substantially between patients.

Management

Physician-patient relationship

The physician-patient relationship is the major determinant of the outcome of therapy in IBS, and its importance cannot be overemphasized.^{47,48} In addition to having a serious and sympathetic attitude to the patient's symptoms, the physician should try to make a confident and positive diagnosis. Traditionally the diagnosis of IBS has involved exclusion of organic disease and often exhaustive investigations of gastrointestinal structure and function. This approach is not only costly, time-consuming and potentially hazardous to the patient but also undermines the patient's confidence in the physician.

The trend now is toward a positive diagnosis, based largely on features obtained from the patient's history and the absence of evidence of organic disease from physical examination and minimal investigation.^{49,50} Highly characteristic symptoms of IBS include abdominal pain or discomfort, gas, and constipation or diarrhea, or alternating episodes of each.⁴⁷ Tenesmus and the presence of mucus in the stool are also common. In attempting to reach a positive diagnosis the physician should focus on the multiplicity and duration of symptoms (2 years or more), as well as the absence of fever, weight loss, anemia or blood in the stool. Sigmoidoscopy is helpful, not only because it permits visualization of the rectal mucosa and the consistency of the stool but also because air insufflation may sometimes reproduce the symptoms. A routine blood count helps to exclude anemia and leukocytosis; screening of the stool for blood, fat globules and leukocytes may also be helpful, particularly in cases of persistent diarrhea.

Consideration of further investigation should, in most cases, depend on specific symptoms such as fever and weight loss, the discovery of an abnormality at physical examination or the results of screening tests. In patients more than 40 years of age with a strong family history of gastrointestinal cancer or evidence of cancerphobia, endoscopic or radiologic studies may be indicated. The "shot-gun" approach to the diagnosis of IBS — extensive investigation of the upper and lower gastrointestinal tract, the pancreatobiliary systems and the retroperitoneal area — is now generally unacceptable.⁴⁷

The patient's history is important not only in establishing a positive diagnosis but also in identifying factors that may influence subsequent management. It is necessary to identify any evidence of anxiety or depression, to determine tactfully the sources of these problems and to probe any "hidden agenda" that reflects psychosocial problems.⁴⁷

The patient's eating habits must be evaluated for fibre content, meal frequency and evidence of intolerance to specific foods (although patients with IBS commonly provide a litany of offending foods). The physician should then identify the major symptoms as potential targets for therapy.

In some patients, particularly those whose symptoms have been precipitated by a stressful event or who fear a more serious illness, a confident diagnosis supplemented by an explanation of the basis of the symptoms is sufficient. To all patients the physician must stress that IBS is a common, chronic problem, associated with relapses and remissions, and temper their expectations of treatment by advising them that deterioration may occur under adverse conditions and that an adjustment of lifestyle is necessary in the long term.

For many patients with IBS reassurance alone is insufficient, and further therapy is required. I use dietary management, with or without stool-bulking agents, as the main strategy for long-term treatment. Drug therapy should be reserved for severe or refractory symptoms and viewed as a temporary measure while patients adapt to their new diet, alter their lifestyle and generally modify their expectations of treatment.

Dietary measures

The widely held belief that the gastrointestinal tract tolerates regular eating habits better than irregular ones seems intuitively correct and may provide a starting point for further dietary advice: the sensible elimination of particularly troublesome foods and the evaluation of any suggestion of lactose intolerance. Intolerance to food because of immunologically based hypersensitivity is uncommon and difficult to diagnose but should be considered if the patient has other manifestations of atopy.

Dietary fibre deficiency is assumed to play some role in the pathogenesis of IBS, but evidence of this is indirect.⁵¹ In animal studies low-residue diets have been associated with disturbances in gastrointestinal motility,⁵² and in subjects with IBS fibre supplements have been associated with alterations in colonic motility.⁵³ Most gastroenterologists believe that fibre helps to relieve several IBS symptoms, particularly constipation, but results of clinical trials have been mixed. Some placebo-controlled studies have shown a significant clinical improvement;^{53,54} however, others have shown no benefit.^{55,56} These discrepancies may be explained by differences in the types of fibre supplements, the short duration of most studies, the heterogeneous patient populations and the failure to control the spontaneous intake of fibre.

The most widely used natural fibre is bran, and the therapeutic daily dose is from 10 to 25 g. Bran should be introduced gradually in anticipation of side effects and problems with compliance.

The latter may be minimized if a dietitian counsels the patient about alternative sources of fibre and imaginative ways of incorporating fibre into the diet. Side effects such as increased bloating, flatulence, abdominal pain and diarrhea usually occur within the first month; thus, therapy should be continued for at least 3 months for proper evaluation. Preparations that contain simethicone often help to reduce symptoms of gas that occur during the introduction of fibre. If bran is poorly tolerated, stool-bulking agents such as those containing psyllium are often useful. Results of adequately controlled clinical trials of these agents are conflicting,^{57,58} but as with bran their use is promoted largely on the basis of clinical experience. Heaton⁵⁹ has written an excellent review of this topic.

Drug therapy

Drug therapy for IBS is controversial. Some believe that it is of little use and potentially dangerous, because it may reinforce the pattern of learned illness behaviour that is common among IBS patients.⁶⁰ To disregard these concerns is irresponsible. However, I believe that to dismiss drug therapy undermines the credibility in the origin and severity of the symptoms and overlooks extensive evidence that the gastrointestinal tract is abnormal. An assessment of the relative importance of behavioural factors and gastrointestinal dysfunction in each patient is a matter of clinical judgement. An open-minded, balanced and individualized approach to drug therapy is essential. Although some patients respond merely to reassurance and adjustments of lifestyle, others require pharmacotherapy, at least temporarily.

Many drugs are available to treat IBS symptoms, but few have been shown in adequately controlled trials to be superior to placebos.¹⁰ The potential value of placebo therapy has recently been addressed.⁴⁷ However, the evaluation of drug therapy has been difficult because of the syndrome's heterogeneity, variability and susceptibility to ubiquitous influences and because of the absence of objective markers to monitor therapy. We are only beginning to understand the pharmacologic complexities of gastrointestinal motility⁶¹ and the relation between motility patterns and symptoms. Without such knowledge we cannot easily rationalize therapy. In light of these problems and uncertainties, drug therapy cannot be dismissed simply because of a current lack of hard evidence of efficacy.

Drug therapy should be aimed at specific symptoms rather than be used to achieve a global improvement in the patient's condition.

Constipation: The principle underlying the treatment of constipation is to increase fecal mass; in IBS this is best achieved with the use of fibre or bulk-forming agents, particularly in patients with hard stools. In those with severe constipation I generally use nonirritant laxatives, such as lac-

tulose, in liberal dosages to induce soft bowel movements before fibre therapy is started. I usually discourage the use of irritant laxatives; however, some patients acquire a strong attachment to these widely available drugs — an attachment that is sometimes difficult to break with the more gentle but less explosive nonirritant laxatives.

Abdominal pain: Abdominal pain may result from distension of the gastrointestinal tract by gas or stool or from contraction of its smooth muscle. In the case of distension the restoration of a normal bowel habit should eventually decrease the pain. The use of antifatulent drugs, including those that contain simethicone, may be beneficial in the short term if the pain is associated with gas and distension.

Antispasmodic drugs are used to reduce cramping pain, which is believed to be caused by muscle contraction; these drugs may directly inhibit smooth muscle contraction, block neuromuscular cholinergic transmission or have a combined effect. Mebeverine hydrochloride has been the most widely studied antispasmodic agent in controlled trials, and the evidence generally supports its use.⁶²⁻⁶⁴ Other drugs include dicyclomine hydrochloride^{65,66} and prefinium.⁶⁷ The carminative peppermint oil has been proven to be beneficial when used in an enteric-coated form,⁶⁸ but a more recent study did not confirm this.⁶⁹ Attention has also been drawn to the use of calcium-channel blockers; however, recent evidence has suggested that the side effects outweigh any benefits.⁷⁰

Narcotic-based analgesics should be avoided at all costs because of the risk of dependence and the possible development of a pseudo-obstructive syndrome.⁷¹

Diarrhea: Some patients present with persistent diarrhea that does not respond to fibre. These patients should always be screened for lactase deficiency with the use of a lactose tolerance test and for malabsorption of idiopathic bile salt with radiolabelled bile acid breath tests.⁷² Even in the absence of bile-acid malabsorption it is worth trying cholestyramine, since studies have shown that the motor³⁹ and secretory⁴⁰ mechanisms of the affected gastrointestinal tract are more sensitive than those of normal tracts to bile acids.⁷³

The opiate class of antidiarrheal drugs includes codeine phosphate, diphenoxylate hydrochloride and loperamide hydrochloride. Each has been shown to be superior to placebos in the treatment of chronic idiopathic diarrhea.⁷⁴ Loperamide is the best tolerated and is particularly beneficial in patients who also complain of urgency.⁷⁵ In those with alternating episodes of diarrhea and constipation I treat the constipation and emphasize the use of fibre or stool-bulking agents, because treatment of the diarrhea may induce severe constipation.

Prokinetic agents: Some patients with IBS have dyspeptic symptoms that suggest involvement of the proximal gastrointestinal tract. They may complain of bloating, postprandial fullness,

epigastric discomfort, nausea or vomiting. There is usually no evidence of peptic ulcer disease, but some patients may have delayed gastric emptying.^{76,77} Prokinetic drugs such as metoclopramide hydrochloride and, more recently, domperidone have been shown to accelerate gastric emptying;⁷⁸ however, the evidence is conflicting.⁷⁹⁻⁸¹ The mechanism of action of domperidone is not fully understood, but its effects are unlikely to be based exclusively on its ability to antagonize the peripheral effects of dopamine.⁷⁸ The precise role of domperidone in the management of IBS awaits further resolution of its pharmacologic effects on gastrointestinal motility.

Trimebutine maleate has enjoyed popularity in Europe for the treatment of various functional gastrointestinal symptoms.⁸²⁻⁸⁴ An opiate ligand, it has a complex pharmacologic profile that cannot be predicted on the basis of the actions of commonly used opiates such as codeine and morphine.⁸⁵ Trimebutine alters colonic myoelectrical activity⁸⁶ and shortens the transit time in constipated patients.⁸⁴ Its precise role in the management of IBS, like that of domperidone, awaits a clearer profile of its pharmacologic properties and a better understanding of the pharmacologic control over gastrointestinal motility.

Psychologic symptoms: The rationale for the use of psychotropic drugs has been based on the observation that depression and psychoneurosis are more common in patients with IBS than in healthy people.¹¹⁻¹⁴ The results of studies of the efficacy of antidepressants are conflicting,^{11,87-91} and interpretation is particularly difficult when such drugs are used in combination with other agents. The same is true of anxiolytic drugs, which also are often combined with an antidepressant or antispasmodic agent.⁹²⁻⁹⁴ In addition, many antidepressant and anxiolytic agents directly affect the gastrointestinal tract; this further confounds the analysis of their efficacy in IBS. Nevertheless, if there is strong evidence of affective illness the use of these drugs seems appropriate, at least temporarily. I am reluctant to advocate their use for primary long-term treatment of gastrointestinal symptoms in a chronic benign disorder like IBS.

Prognosis

IBS is characterized by episodes of relapse and remission, the frequency of which may be influenced by emotional stress and dietary factors. One study showed that most patients remained symptomatic after 1 year.⁹⁵ A more recent study has given a somewhat better prognosis, the condition of 68% of the patients substantially improving after 5 years. Much of this improvement was attributed to the long-term use of fibre or stool-bulking agents.⁹⁶ IBS is seldom, if ever, cured, but changes in lifestyle as well as in expectations of therapy contribute substantially to a better outcome.

Prospects

We need to be innovative in our evaluation of drug therapy for IBS. The previously described problems that are related to the heterogeneity and variability of IBS are not easily addressed by conventional clinical trials and are likely to yield false-negative results. It may be worth while to consider the "n of one" study design, which involves repeated placebo-controlled examinations in one patient.^{97,98} It allows individualization of the study according to each patient's symptoms and minimizes problems due to the heterogeneity of IBS. It also decreases the patient sample size without compromising statistical significance.

Ultimately one may expect to see the development of more specific drugs for correcting motility disturbances associated with IBS. Recent evidence has indicated that there is substantial heterogeneity in muscarinic and cholecystokinin receptors within the gastrointestinal tract.⁹⁹⁻¹⁰¹ Because there is evidence of increased sensitivity to these agents,^{36,37} drugs may be developed to block them at strategic sites within the motility apparatus. If we are to improve our pharmacotherapy of IBS, however, the first challenge is to understand better the pharmacologic features of gastrointestinal motility, to approach how they might be affected by stress or dietary factors and to clarify the relation between symptoms and motility in various regions of the gastrointestinal tract.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
✓ REINALDO PINILLA MORENO

ASUNTO	Radicación	06-78456
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	NO 10308
	Folios	3

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☒

Vía PCT (fase nacional) ☐ Cap. I ☐ Cap. II ☐

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:

1. Documentos estudiados

<u>Descripción:</u>	Folios: 12 a 21	(como se radicó inicialmente)
<u>Reivindicaciones:</u>	Folios 22 a 26	(como se radicó inicialmente)

2. Objeto de la Invención

Titulo de la invención: "COMPOSICIÓN FARMACEUTICA SOLIDA QUE INCLUYE EN COMBINACIÓN UN AGENTE REGULADOR DE LA MOTILIDAD INTESTINAL Y UN AGENTE ANTIFLATULENTO"

Problema Técnico Planteado: la necesidad una composición farmacéutica para el tratamiento y regulación en seres vivos de la motilidad digestiva o intestinal y la flatulencia en combinación que no presente las desventajas del arte previo en relación con la velocidad de disolución de los antidiarreicos, antiperistálticos y bloqueantes de H2. (folios 14 y 15)

Solución: una composición farmacéutica sólida que incluye un agente regulador de la motilidad digestiva y un agente antiflatulento un facilitador de la fluidez, uno o más lubricantes, por lo menos un diluyente, por lo menos un desintegrante y al menos un aglutinante.

IPC: A61K 9/20, A61K 31/695

3. De la solicitud de Patente

a. Reivindicaciones (artículo 30 D 486)

La Reivindicación 1 carece de concisión, debido a que se presenta un número demasiado alto de alternativas posibles dentro de la misma. Los elementos que constituyen las composición se divulgan por su función dentro de la misma lo que no limita el número de sustancias de las que puede estar conformada la composición.

Las reivindicaciones mencionadas no cumplen con el requisito de concisión o sustento por la descripción de acuerdo al art. 30 de la Decisión 486.y/o art.22 Tratado PCT.

4. Determinación del Estado de la Técnica

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

Fecha de presentación de la solicitud nacional. 2006-08-10

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

Nº	Documento	Título	Fecha de publicación*
D1	US5248505	METHOD FOR TREATING GASTROINTESTINAL DISTRESS	28-08-1993
D2	CMAJ, VOL. 138, FEB 15, 1988. Pp 378-313	RECENT ADVANCES IN PHARMACOTHERAPY	1988

5. Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

la reivindicación 1 reclama una composición farmacéutica sólida caracterizada porque comprende: a) Por lo menos un agente regulador de la motilidad; b) Al menos un agente antiflatulento; c) por lo menos un facilitador de la fluidez; d) uno o más lubricantes; e)Por lo menos un diluyente; f) por lo menos un desintegrante; g) al menos un aglutinante.

El estado de la Técnica más cercano es D1 que divulga una composición que comprende Loperamida que es un modulador de la motilidad intestinal (col. 3 líneas 15-16) y simeticona como agente antiflatulento y los demás excipientes reclamados en la composición.(ejemplo 2).

La solicitud se diferencia de D1 en que al parecer el agente regulador de la motilidad preferido es trimebutina.

El Efecto Técnico que logra la diferencia es el mismo que D1 ya que la solicitud carece de información técnica que permita evidenciar alguna ventaja o efecto técnico sorprendente.

El Problema Técnico Objetivo de esta solicitud es identificar una composición alternativa que comprenda un modulador de la motilidad intestinal y un antiflatulento.

D2 discute los diversos métodos de tratamiento del síndrome de colon irritable y las terapias con medicamentos que se pueden utilizar, la cuales incluyen el uso de antiespasmódicos, antidiarreicos, y agentes procinéticos entre los que se destaca el uso de la trimebutina maleato (página 313) como agente promotor de la motilidad intestinal, el cual es un ligando opiáceo útil para tratar este tipo de desórdenes. Igualmente se menciona el uso de simeticona en las preparaciones farmacéuticas para reducir los síntomas de la producción de gas por el consumo de fibra (pág. 312).

En consecuencia, a partir de la información contenida en D1 y D2 y con los conocimientos técnicos comunes, un experto en la materia puede lograr las composiciones de la presente solicitud, intercambiando loperamida por otro agente promotor de la motilidad intestinal como la trimebutina de D2, y llegar a las composiciones sólidas reclamada.

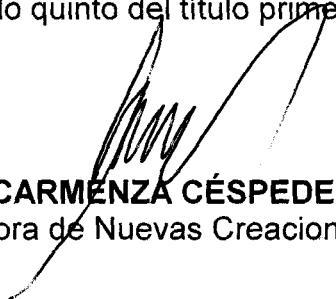
6. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US5248505	1-26	Nivel Inventivo
D2	CMAJ, VOL. 138, FEB 15, 1988. Pp 378-313	1-26	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 notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista, de fecha 2 AGO. 2010

CONCEPTO TÉCNICO No. 2595	EXAMINADOR TÉCNICO Código No. 202073
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