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78

SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

MINISTERIO DE DESARROLLO ECONOMICO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicación: 00015153 00000001
Fecha (AMP): 2002-11-23 12:39:01
Trámite: 002 PATENTES D 1 REGISTRO SUB PETICION
Dependencia: 2023 DIVISION DE NUEVAS CREACIONES

Ref.: SOLICITUD DE PATENTE

EXPEDIENTE N° 00015153

FECHA SOLICITUD: MARZO 2, 2000

PATENTE: COMPOSICIONES DE BETAHISTINA DE LIEBRACIÓN CONTROLADA

SOLICITANTE: FARMACEUTICI FORMENTI S.P.A.

DILIA RODRÍGUEZ D'ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial N°. 517 de fecha Junio 27 de 2.002, se proceda con el estudio de fondo.

Para tal fin me permito anexar la tasa correspondiente.

Agradezco continuar con el presente trámite.

Señor Jefe,

DILIA RODRÍGUEZ D'ALEMAN

RCH/srr

p. 302



Handwritten signature/initials

Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA : COMERCIO
Radicación : 00015153 00000003 Folios: 2
Fecha (AME): 2002-11-26 15:33:08
Trámite : 002 PATENTES D : REGISTRO/ 528 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 000176087-2

RECIBO OFICIAL DE CAJA : 02 - 76,747
FECHA : NOVIEMBRE 18 DE 2002

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VAL. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	4801705	18/11/2002	1,914,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	112 PTC CAP-1 EXAMEN DE PATENTIBILIDA	318,000.00
TOTAL :			\$ 318,000.00

CON: TRESCIENTOS DIEZ Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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2005-01-20
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302

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctora
Dilia María Rodríguez
Apoderada

Oficio N° 11879

REFERENCIA	Radicación	00 15153
	Trámite	002
	Evento	001
	Actuación	430
	Folios	017

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 00 15153, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

- . Descripción: folios 4-6
- . Ejemplos: folios 6-14
- . Capítulo reivindicatorio estudiado: folios 15-16
- . Se reivindica prioridad, presentada en Italia, el 05.03.99, bajo el número MI99A000454

Objeto de la invención

Según las reivindicaciones 1 a 11 de la presente solicitud, se refiere a formulaciones sólidas orales de liberación controlada de betahistina que se obtienen por un proceso de granulación por fusión con un componente graso y luego mezclar el granulado obtenido con un polímero hidrofílico y excipientes convencionales.

Clasificación internacional de patentes A 61 K 9/22 // 31/44 // 31/13

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Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 05.03.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
1	WO 9818610	"Incorporación y encapsulación de partículas de liberación controlada"	07.05.98
2	FR 2432313	"Nueva forma galénica de betahistina y su procedimiento de obtención"	29.02.80

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, 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 la NOVEDAD

El artículo 16 de la decisión 486 dispone *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9818610 se relaciona con composiciones de liberación controlada que contienen betahistina que contienen:

- un material plastificable como los ésteres de celulosa
- un componente para controlar la rata de liberación como ceras o ácidos grasos
- excipientes

La solicitud francesa FR 2432313 revela formas de liberación controlada de betahistina que contiene:

- excipientes
- ésteres de celulosa, derivados de ácido acrílico
- ácido esteárico

Comparando elemento por elemento, las composiciones de la anterioridad citada son iguales a las de las reivindicaciones 1-9 y pueden afectar la novedad de la presente solicitud.

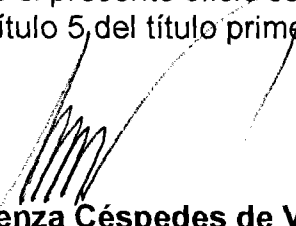
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En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9818160	1-9	Novedad
2	FR 2432313	1-9	Novedad

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 5 del título primero de la Circular Única N° 10 de 2001


Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 20 MAR 2025

CONCEPTO TÉCNICO Número 0008	EXAMINADOR TÉCNICO Código 202024
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PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : B29C 47/04, B01J 13/04, A01N 25/26		A1	(11) International Publication Number: WO 98/18610
			(43) International Publication Date: 7 May 1998 (07.05.98)
(21) International Application Number: PCT/US97/18984			(81) Designated States: AU, CA, JP, NO, PL, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(22) International Filing Date: 27 October 1997 (27.10.97)			
(30) Priority Data: 60/029,038 28 October 1996 (28.10.96) US 60/052,717 16 July 1997 (16.07.97) US			
(71)(72) Applicant and Inventor: VAN LINGERICH, Bernhard, H. [DE/US]; 18005 33rd Place North, Plymouth, MN 55447 (US).			
(74) Agent: HOLLANDER, Barry, I.; Fisher, Christen & Sabol, Suite 300, 1019 19th Street, N.W., Washington, DC 20036 (US).			
(54) Title: EMBEDDING AND ENCAPSULATION OF CONTROLLED RELEASE PARTICLES			
(57) Abstract Controlled release, discrete, solid particles which contain an encapsulated and/or embedded component such as a heat sensitive or readily oxidizable pharmaceutically, biologically, or nutritionally active component are continuously produced without substantial destruction of the matrix material or encapsulant. A release-rate controlling component is incorporated into the matrix to control the rate of release of the encapsulant from the particles. The additional component may be a hydrophobic component or a high water binding capacity component for extending the release time. The plasticizable matrix material, such as starch, is admixed with at least one plasticizer, such as water, and at least one release-rate controlling component under low shear mixing conditions to plasticize the plasticizable material without substantially destroying the at least one plasticizable material and to obtain a substantially homogeneous plasticized mass. The plasticizer content is substantially reduced and the temperature of the plasticized mass is substantially reduced prior to admixing the plasticized mass with the encapsulant to avoid substantial destruction of the encapsulant and to obtain a formable, extrudable mixture. The mixture is extruded through a die without substantial or essentially no expansion and cut into discrete, relatively dense particles. Release properties may also be controlled by precoating the encapsulant and/or coating the extruded particles with a film-forming component.			

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rate of release of agent increases.

The present invention provides a controlled release particulate composition which contains a hydrophobic component for controlling the release of an encapsulated and/or embedded active component from a plasticized matrix.

5 High water binding capacity agents may also be used to delay or control the release of the encapsulant from the matrix. Furthermore, in the process of the present invention the amount of plasticizer is high to facilitate plasticization of the matrix material at low shear and is then reduced prior to adding the encapsulant to facilitate subsequent forming and to reduce post extrusion drying. The controlled
10 release or delayed release composition may be produced without substantial expansion of the matrix material to thereby avoid production of a low density product which prematurely or too rapidly releases the encapsulant or the embedded component. The products may be produced using low shear mixing to avoid decomposition of the matrix material and encapsulant or active component.
15 However, even though low shear mixing is utilized, substantial plasticization of the matrix material and at least substantially uniform distribution of the active component are achieved. Edible products produced in accordance with the present invention for delivering pharmaceutically or nutritionally active components may be consumed or swallowed without chewing so that the products
20 may reach the digestive tract without substantial enzymatic hydrolysis in the mouth. In addition, in embodiments of the invention, the substantially spherical shape and high density of the products reduce or prevent substantial surface related destruction of the active components upon exposure of the particles to air, oxygen, light, or water. Timing of the release of the embedded or encapsulated
25 component so that it is delayed until the product reaches the stomach and/or the intestine may be controlled by the use of varying amounts and types of hydrophobic components or high water holding capacity components in the plasticized matrix. The processes of the present invention may be used for the continuous production of an edible composition for delivering pharmaceutically or
30 nutritionally active components, or for the production of an agricultural product for the controlled release of biocides, herbicides, fertilizers, growth stimulators,

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83DETAILED DESCRIPTION OF THE INVENTION

An active component is encapsulated and/or embedded in a plasticizable matrix component or material in an continuous process to produce discrete, solid particles. Release of the active component from the matrix is delayed or controlled over time so that the active component is delivered when and where it is needed to perform its intended function. The release of the active component from the matrix may be controlled by an additional ingredient or additive which affects the hydrophobicity of the matrix or particle, the water binding capacity of the matrix or particle, the solubility or porosity of the matrix material or particle, or the glass transition (T_g) of the matrix material or particle. Pretreatment of the encapsulant, process conditions, and the final shape of the discrete particles may also be used to control the release of the active component from the matrix material. The continuous process of the present invention advantageously at least substantially uniformly distributes, embeds, or encapsulates the active component in the matrix material. The active components may be dispersed in the matrix material on a microscopic or molecular level. Active components which are dispersed on a molecular level may provide a higher bioavailability when released, as compared to their crystalline forms. The active components may be encapsulated or embedded either in a solid form or liquid form. The encapsulants and encapsulated products of the present invention may be edible such as pharmaceutically or biologically or nutritionally active components, or flavors or fragrances or they may be inedible compositions such as a detergent, herbicide, fungicide, pesticide, insecticide, or rodenticide, and the like. Release of the encapsulant from the matrix material may also be controlled by the use of a film or coating upon the encapsulant and/or upon the discrete, solid matrix-encapsulated particles.

The matrix material may be a plasticizable biopolymer such as a carbohydrate, such as a starch or cyclodextrin, or polymer such as polyvinylpyrrolidone or other non-hydrophobic polymers such as copolymers of N-vinylpyrrolidone (NVP) and vinylacetate, polyvinyl alcohol, cellulose esters, cellulose ethers, and polyethylene glycol. Exemplary starches which may be used

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in the present invention are native or modified starches derived from corn, wheat, rice, potato, tapioca, or high amylose starch. Sources of starch which may be used also include flours from grains such as corn, wheat, durum wheat, rice, barley, oat, or rye, and mixtures thereof.

5 Additional matrix components which may be used include carbohydrates which have a lower molecular weight than starches. The lower molecular weight matrix components tend to dissolve more readily than does the starch and increase the penetrability or porosity of the matrix. As a result, access by the dissolution medium, such as water or acid, to the encapsulant is increased thereby permitting quicker release of the encapsulant from the matrix material. Examples of
10 carbohydrates other than starch which may be used are sugars, such as mono- and di-saccharides, and starch hydrolyzate products such as dextrans or syrups with dextrose equivalent values (DE values) ranging from about 2 to about 99, or from about 5 to 98, and mixtures thereof.

15 The matrix material is used in an effective encapsulating amount. In embodiments of the present invention, the matrix material content, such as the starch content of the particles may be at least about 40% by weight, for example from about 60% by weight to about 95% by weight, based upon the weight of the final product.

20 The plasticizer or softener which may be used to lower the melt temperature or glass transition temperature (T_g) of the matrix material and facilitate plastification is preferably water but may be an aqueous-based composition such as a sugar solution, alcohol, sorbitol, polyethylene glycol, polypropylene glycol, silicone, hexanol, pentanol, dimethylsulfoxide (DMSO),
25 hexane, or an oil. The amount of plasticizer, such as water, should be sufficient to substantially reduce the melt or glass transition temperature of the plasticizable material such as starch so that it may be admixed with the other ingredients at a sufficiently low temperature and under sufficiently low shear conditions so as to avoid substantial mechanical or thermal destruction of the plasticizable material or
30 matrix material. Exemplary amounts of plasticizer, such as water, may range from about 20% by weight to about 50% by weight, preferably from about 35% by

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weight to about 45% by weight, most preferably about 40% by weight based upon the weight of the plasticizable material or matrix material such as starch.

5 The additional ingredients which may be used to control the release properties of the final product may be a hydrophobic agent for slowing down the rate of release of the encapsulant. Exemplary of components which may be added to affect the hydrophobicity of the matrix include fats, oils, waxes, fatty acids, emulsifiers, such as mono- or di- glycerides, synthetic polymers such as polyolefins such as polyethylene or polypropylene, polyvinyl chloride, polyvinyl acetate and derivatives thereof, paraffin, and modified starches from plant sources
10 that possess hydrophobic properties that are obtained via either physical or chemical modification, and mixtures of hydrophobic components. Plant lipids or synthetic lipids with melting points up to about 65°C may, for example, be employed as a hydrophobic agent. The hydrophobic components increase the hydrophobicity of the matrix and help to prevent or delay penetration of water or
15 gastric juice into the matrix by repelling water or aqueous acids, thereby delaying the release of the encapsulant into the surrounding media.

Additional components which may be used to delay or prevent a fast release of the encapsulant from the matrix are components or agents which have a high water binding capacity. The agents may have a water binding capacity or
20 water holding capacity which is greater than the water binding capacity of the matrix material, such as starch. The high water binding capacity component may bind water which penetrates the particles, or prevent the water from dissolving the matrix, thereby preventing or delaying the release of the encapsulant from the matrix. Exemplary of high water binding capacity agents which may be used in
25 the present invention are protein from animal sources such as gelatin, casein, and protein from sources such as wheat, soy, corn, or other grains, and hydrocolloids such as carrageenans, alginates, xanthan gum, gum arabic, guar flour or guar gum, agar, tragacanth, karaya, locust bean gum, pectin, soluble fiber, insoluble fiber and the like. Exemplary proteins from grains which may be used are gluten, vital
30 wheat gluten, zein, and soy protein concentrate. The proteins from plant sources may also be used to increase the tolerable addition of lipids within the matrix

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composition and thereby indirectly increase the hydrophobicity of the matrix. The high water binding capacity components may be used alone or mixtures thereof may be employed.

5 The additional components or ingredients used to control the rate of release of the encapsulant may be used in amounts up to about 70% by weight, preferably from about 5% by weight to about 50% by weight, most preferably from about 10% by weight to about 35% by weight, based upon the weight of the matrix material, such as starch.

10 Active components which may be encapsulated or embedded in the matrixes in accordance with the present invention include pharmaceutical compositions or compounds, nutraceutical compositions or compounds, nutritional components, or biologically active components, flavorants, fragrances, detergents or surface-active compositions. The pharmaceutical compounds or compositions may, for example, include antibiotics, analgesics, vaccines, antiinflammatory
15 agents, antidepressants, anti-viral agents, anti-tumor agents, enzyme inhibitors, formations containing zidovudine, macromolecular polypeptides, aromatic nitro and nitroso compounds and their metabolites useful as anti-viral and anti-tumor agents, HIV protease inhibitors, viruses, and steroids, mixtures thereof, and the like.

20 Nutraceutical components may include components which promote health or prevent disease or enhance well-being such as antioxidants, phytochemicals, hormones, vitamins such as Vitamin C and Vitamin E, pro-vitamins, minerals, microorganisms such as bacteria, fungi, and yeast, prebiotics, probiotics, trace elements, essential and/or highly unsaturated fatty acids such as omega-3 fatty
25 acids, and mid-chain triglycerides, nutritional supplements, enzymes, pigments, oligopeptides, dipeptides, and amino acids.

Biologically active components which may be encapsulated include agriculturally useful compositions to either prevent infestation such as herbicides, pesticides, insecticides, rodenticides, fungicides, mixtures thereof, and the like or

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hydrochloride, triflupromazine, trihexyphenidyl hydrochloride, trimeprazine
tartrate, trimethadione, trimethobenzamide hydrochloride, trimethoprim,
trioxsalen, tripelennamine, triprolidine, trisulfapyrimidine, tropicamide, trypsin,
tryptohan, tuberculin, tyloxapol, tyropanoate sodium, tyrosine, tyrothricin,
5 thyrothricin bethamethasone, thiotic acid, sotalol, salbutamol, norfenefrine,
silymarin, dihydroergotamine, buflomedil, etofibrate, indometacin, urea, valine,
valproic acid, vancomycin hydrochloride, vasopressin, verapamil, vidarabine,
vinblastine, vincristine, vitamins, warfarin, yellow fever vaccine, zinc acetate,
zinc carbonate, zinc chloride, zinc gluconate, beta acetyl digoxin, piroxicam,
10 haloperidol, ISMN, amitriptylin, diclofenac, nifedipine, verapamil, pyritinol,
nitrendipin, doxycycline, bromhexine, methylprdnisolone, clonidine, fenofibrate,
allopurinol, pirenepine, levothyroxin, tamoxifen, metildigoxin, o-(beta-
hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, paracetamol,
naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, tramadol,
15 bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol,
enalaprilhydrogen maleate, bezafibrate, ISDN, gallopamil, xantinol nicotinate,
digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam,
diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam,
flunarizin, erythromycin, metoclopramide, acemetacin, ranitidin, biperiden,
20 metamizole, doxepin, dipotassium chloroazepate, tetrazepam, estramustine
phosphate, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamide,
cefactor, etilfrine, cimetidine, theophylline, hydromorphone, ibuprofen,
primidone, clobazam, oxaceprol, medroxyprogesterone, flecainid, pyridoxal 5
phosphate glutamate, hymechromone, etofylline clofibrate, vincamine,
25 cinnarizine, diazepam, ketoprofen, flupentixol, molsimine, glibornuride,
dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine,
glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine,
thioridazine, betahistine, L-tryptophan, murtol, bromelaine, prenylamine,
salazosulfapyridine, astemizol, sulpiride, benzerazide, dibenzepine, acetylsalicylic
30 acid, miconazol, nystatin, ketoconazole, sodium picosulfate, coltyramine,
gemfibrocil, rifampicin, fluocortolone, mexiletin, amoxicillin, terfenadrin,

92



5 mucopolysaccharide polysulfate, triazolam, mianserin, tiaprofenic acid,
amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, L-
aspartate, penbutolol, piretanide, aescin amitriptyline, cyproterone, sodium
valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine,
10 magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine,
methyldopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin,
medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, prajmalium
bitartrate, lipid derivatives of phosphonatides, amphiphilic polymers, adenosine
derivatives, sulfated tannins, monoclonal antibodies, and metal complexes of
15 water soluble texathyrin.

The amount of the active component or encapsulant which is incorporated
into the products of the present invention may be such so as to provide or deliver
an effective amount, such as a pharmaceutically effective amount or a
nutraceutically effective amount of the active component at its intended location,
15 such as the small intestine. Exemplary amounts of the active component or
encapsulant which may be encapsulated or embedded into the matrix may be from
about 1% by weight to about 85% by weight, preferably from about 3% by weight
to about 50% by weight, based upon the weight of the matrix ingredient, such as
starch.

20 Film-building or film-forming substances which may be used to coat the
encapsulants prior to incorporation into the matrix include commonly used coating
materials such as zein, pectin, shellac, gelatin, fats, oils, waxes, emulsifiers, native
or modified starch, chitosan, chitin, and mixtures thereof. The film-building or
film-forming substance may also be used to coat the extruded, particulate product.
25 Pretreatment of the encapsulant by coating it with a film forming substance such
as a high melting fat or wax, or with an emulsifier such as glycerin monostearate,
or the like, tends to prevent unwanted interaction between an encapsulant and the
matrix. The encapsulants and the extrudate particles may be coated with film-
forming amounts of the substances in aqueous or alcoholic solutions, or
30 oleaginous compositions.

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most preferably at least about thirty-six months. In embodiments of the present invention, the drying may be performed using conventional drying equipment using drying temperatures which do not adversely affect the thermal stability of the encapsulants. Exemplary drying temperatures may range from about 10°C to about 90°C, preferably from about 20°C to about 60°C. The drying may be conducted to achieve a moisture content of less than about 30% by weight, preferably less than about 12% by weight, for example, from about 6% by weight to about 9% by weight. In embodiments where no starch or substantially no starch is used as a matrix material, the moisture content may be less than about 6% by weight.

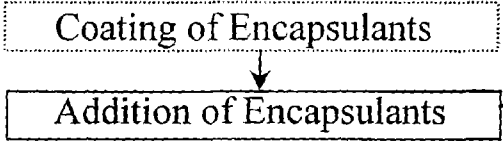
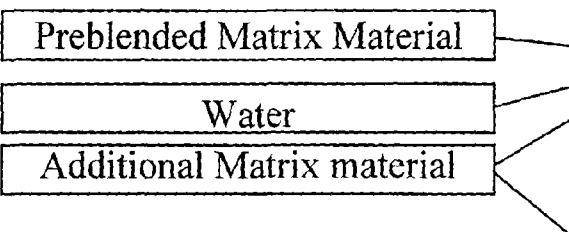
In embodiments where film-building substances or coatings are applied to the particles or pellets, conventional spray nozzles may be located close to the die or for spraying an aqueous or alcoholic solution of the film-building substances onto the cut pieces as they fall downwardly from the extruder die. In other embodiments, the film-building substances may be applied after drying of the pellets. For example, the film-building substances may be applied using spray nozzles, conventionally known fluid bed coating apparatus, or other conventional coating apparatus and methods. If the application of the film-building substances increases the moisture content above a shelf stable level, the water or other volatile media may be removed from the surface of the particles by additional drying.

In embodiments of the present invention, the extruded pieces or pellets may be compressed in conventional tablet presses to obtain compressed versions of the extruded pellets.

In other embodiments of the present invention, the mixture may be extruded through a sheeting die into a sheet. The extruded sheet may then be cut or molded into individual pieces, such as tablets, or disks, using a rotary die or rotary cutter, or reciprocating cutter or counterrotating drums conventionally known as agglomeration drums or tableting drums.

The products of the present invention comprise discrete particles which may be spherical, lens-shaped, or flat discs having diameters of from about 0.5

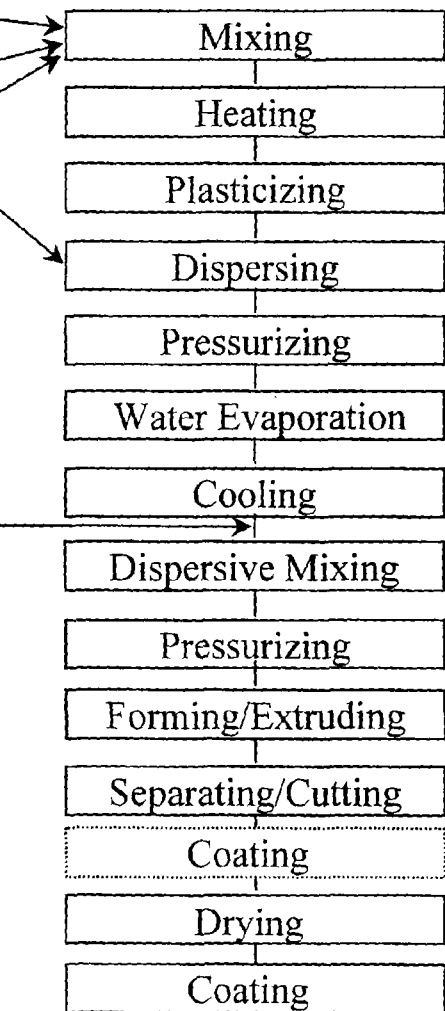
FIG. 1



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9/6

Extruder Apparatus



RÉPUBLIQUE FRANÇAISE.

INSTITUT NATIONAL
DE LA PROPRIÉTÉ INDUSTRIELLE

PARIS

(11) N° de publication :

2 432 313

(A n'utiliser que pour les
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A1

**DEMANDE
DE BREVET D'INVENTION**

(21)

N° 78 22665

(54)

Nouvelle forme galénique de la bétahistine et son procédé d'obtention.

(51)

Classification internationale. (Int. Cl 3) A 61 K 9/56//31/44.

(22)

Date de dépôt 1er août 1978, à 13 h 42 mn.

(33) (32) (31)

Priorité revendiquée :

(41)

Date de la mise à la disposition du
public de la demande

B.O.P.I. — «Listes» n. 9 du 29-2-1980.

(71)

Déposant : FOULHOUX Pierre, résidant en France.

(72)

Invention de :

(73)

Titulaire : *Idem* (71)

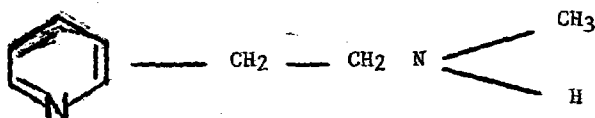
(74)

Mandataire : P S I S.A.R.L., 42, rue de Paradis, 75010 Paris.

La présente invention concerne une nouvelle forme galénique de la bétahistine et/ou ses dérivés, son procédé d'obtention et les médicaments comprenant cette forme.

On sait que la bétahistine, de formule

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10 a une structure proche de celle de l'histamine et on l'utilise, le plus souvent, sous forme de sels (chlorhydrate et méthane sulfonate notamment), pour le traitement des syndromes de Ménière en l'administrant par voie orale sous forme de comprimés, l'action de ces substances jusqu'à présent observée étant spécifique des troubles de pressions intra-labyrinthiques, cochléaires ou vestibulaires, d'ordre micro-circulatoires.

15 Toutefois, l'administration de la bétahistine sous sa forme actuelle présente des inconvénients limitant son utilisation thérapeutique aux traitements précités.

En premier lieu, le produit est très hygroscopique de sorte que sa stabilité et sa solubilité interdisent pratiquement son utilisation sous la forme de gélules.

20 En outre, on a constaté que la forme de comprimés provoque un nombre significatif d'intolérances, en particulier gastriques, ce qui ne permet pas son utilisation pour une catégorie importante de malades d'une part, et d'autre part, qui limite singulièrement son utilisation pour des traitements à long terme.

25 De plus, avec les formes classiques, après chaque administration, c'est-à-dire trois ou quatre fois par jour, on constate une succession d'augmentations et de diminutions rapides des taux plasmatiques, l'organisme étant soumis alternativement à des sur-dosages et des sous-dosages.

30 Enfin, les inconvénients des formes classiques n'ont pas permis jusqu'à présent le traitement de troubles circulatoires généraux, traitements nécessitant une administration prolongée, qui est au contraire possible avec la nouvelle forme galénique d'administration de la bétahistine et/ou de ses dérivés tel qu'on le démontre ci-après, cette nouvelle forme permettant la libération régulière du médicament dans l'organisme pendant des périodes suffisamment longues pour autoriser simplement la prise journalière de deux unités.

35 La présente invention a pour objet une nouvelle forme galénique à libération programmée retardée de la bétahistine et/ou ses dérivés et est remarquable en ce qu'elle est constituée par des microgranules comprenant une âme neutre constituée d'un grain d'un excipient inerte comprenant au moins deux composants du type appartenant à la classe constituée par le saccharose, l'amidon, le talc, la
40 la silice desséchante, le lactose et l'acide stéarique, ce grain neutre étant

muni d'une première couche comprenant la bétahistine et/ou ses dérivés puis d'une seconde couche extérieure constituée par une enveloppe microporeuse comprenant au moins un polymère naturel et/ou synthétique appartenant à la classe constituée par la gomme laque, la gomme arabique, la gélatine, l'éthylcellulose, l'acétophtalate de cellulose, le triacétate de cellulose, le polyoxyéthylèneglycol, les méthacrylates, le copolymère styrène - acrylonitrile et la polyvinylpyrrolidone et enveloppes successives.

En particulier, l'enveloppe microporeuse peut être formée de gomme laque selon une proportion en poids variant entre 2 et 10 % et l'excipient inerte peut être un mélange comprenant de 40 à 80 % en poids de saccharose et de 10 % à 40 % en poids d'amidon.

Selon une forme de réalisation avantageuse de l'invention, la première couche peut comprendre de 1 à 20 % en poids de bétahistine et/ou ses dérivés, de 0,01 à 0,5 % en poids d'acide stéarique, de 5 à 15 % en poids de talc et de 2 à 10 % en poids de silice desséchante. En outre, l'âme neutre peut comprendre des adsorbats de bétahistine et/ou ses dérivés.

L'invention a également pour objet un procédé d'obtention de la nouvelle forme galénique remarquable en ce qu'on prépare au préalable des microgranules neutres tamisés et séchés, qu'on projette sur ces microgranules une solution dans l'alcool absolu de bétahistine et/ou ses dérivés, qu'on enrobe ensuite lesdits microgranules pour réaliser la première couche en un ou plusieurs enrobages, puis qu'on forme l'enveloppe microporeuse par enrobage à l'aide dudit polymère en solution dans un solvant.

De plus, la présente invention a pour objet des médicaments comprenant la nouvelle forme d'administration de la bétahistine et/ou ses dérivés, notamment les chlorhydrates et le méthane sulfonate, sous forme de microgranules actifs mélangés à des microgranules neutres non enrobés afin d'obtenir une concentration prédéterminée en bétahistine et/ou ses dérivés, cet ensemble de microgranules étant présenté sous forme de gélules, de comprimés, de suppositoires, de sirop, de granulés ou de poudre.

L'ensemble des caractéristiques et avantages de l'invention seront mieux compris par l'homme de l'art en se référant à la description qui va suivre de modes de réalisation particuliers pris à titre d'exemples non limitatifs de la nouvelle forme galénique, de son procédé et de ses applications thérapeutiques, en particulier en relation avec les contrôles pharmacologiques et cliniques effectués en utilisant la nouvelle forme galénique.

EXEMPLE DE PREPARATION DE LA NOUVELLE FORME GALENIQUE

On indique ci-après l'exemple de fabrication correspondant à 100 gélules dosées à 12 mg de méthane sulfonate de bétahistine.

40 a) Formule de fabrication

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.Méthane sulfonate de bétahistine..... 1,200 kg
 .Saccharose - amidon - gomme laque
 talc - silice desséchante - acide
 stéarique 22,800 kg
 5 .Alcool éthylique absolu q.s.

b) Procédé de préparation

On granule de l'amidon de maïs et du saccharose puis on tamise et on turbine longuement les grains de façon à les rendre parfaitement sphériques. On tamise à nouveau et on sèche parfaitement.

10 Dans un mélangeur en acier inoxydable, on projète sur les âmes neutres ainsi obtenues une solution alcoolique de méthane sulfonate de bétahistine.

On réalise ensuite la première couche en incorporant à ces microgranules les autres excipients à l'exception de la gomme laque puis on recommence la pulvérisation de méthane sulfonate de bétahistine, cet enrobage étant recommencé plusieurs fois avec tamisage et séchage si nécessaire entre chaque couche.

Lorsque la première couche contenant le principe actif est terminée, on réalise la couche extérieure microporeuse, en projetant sur les granules la gomme laque en solution dans l'alcool éthylique absolu.

20 On sèche ensuite soigneusement en éliminant l'alcool éthylique restant, on tamise à nouveau et on contrôle comme ci-après le titre des microgranules obtenus avant de mettre en gélules, après avoir ajusté éventuellement le titrage par addition et homogénéisé avec des microgranules neutres pour arriver au titrage désiré de 12 mg de méthane sulfonate de bétahistine.

MESURE DE LA LIBERATION DU METHANE SULFONATE DE BETAHISTINE

25 La caractéristique des pores de l'enveloppe extérieure est choisie de façon à assurer une libération retardée de méthane sulfonate de bétahistine théorique.

30 . 1ère heure : libération inférieure à 40 %
 . 4ème heure : libération inférieure à 75 %
 . 8ème heure : libération supérieure à 80 %.

Pour contrôler cette caractéristique, on utilise un appareil à délitement dans lequel on met en contact une quantité de microgranules correspondant à environ 50 mg de principe actif avec des liquides artificiels, l'appareil permettant de maintenir une agitation constante et une température constante de 35 37° C $\pm$ 5° C. Les liquides artificiels sont des solutions tamponnées à pH successifs utilisées selon le schéma ci-dessous :

	Solutions	Temps de libération	pH	Résultats	
				Théoriques	Réels
	25 ml liquide gastrique	1 heure (1ère heure)	1,5	< 40 %	31 %
40	25 ml liquide intestinal	1 heure (2ème heure)	4,5	> 40 %	45 %